Human and Environmental Exposure Assessment

Report of the National Nanotechnology Initiative Workshop
February 24–25, 2009

nanoEHS

About the Nanoscale Science, Engineering, and Technology Subcommittee

The Nanoscale Science, Engineering, and Technology (NSET) Subcommittee is the interagency body responsible for coordinating, planning, implementing, and reviewing the National Nanotechnology Initiative (NNI). The NSET is a subcommittee of the Committee on Technology of the National Science and Technology Council (NSTC), which is one of the principal means by which the President coordinates science and technology policies across the Federal Government. The National Nanotechnology Coordination Office (NNCO) provides technical and administrative support to the NSET Subcommittee and its working groups in the preparation of multiagency planning, budget, and assessment documents, including this report. More information is available at http://www.nano.gov.

About the National Nanotechnology Initiative

The National Nanotechnology Initiative is the Federal nanotechnology R&D program established in 2000 to coordinate Federal nanotechnology research, development, and deployment. The NNI consists of the individual and cooperative nanotechnology-related activities of 25 Federal agencies that have a range of research and regulatory roles and responsibilities. The goals of the NNI are fourfold: (1) to advance a world-class nanotechnology research and development program; (2) to foster the transfer of new technologies into products for commercial and public benefit; (3) to develop and sustain educational resources, a skilled workforce, and the supporting infrastructure and tools to advance nanotechnology; and (4) to support responsible development of nanotechnology.

About the Nanotechnology Environmental and Health Implications Working Group

The NSET Subcommittee and its Nanotechnology Environmental and Health Implications (NEHI) Working Group provide leadership in establishing the NNI environmental, health, and safety research agenda and in communicating data and information related to the environmental and health aspects of nanotechnology between NNI agencies and with the public. NNI activities support the development of the new tools and methods required for the research that will enable risk analysis and assist in regulatory decision making.

About this Report

This document is the report of a workshop held February 24–25, 2009. This was the first in a series of four workshops sponsored by the NSET Subcommittee to inform the NNI's long-range planning efforts for environmental, health, and safety research. Any ideas, findings, conclusions, and recommendations presented in this report are those of the workshop participants. This report was designed, assembled, and edited by NNCO staff.

About the Cover

Cover design is by Kathy Tresnak of Koncept, Inc. Book design is by staff members of the National Nanotechnology Coordination Office (NNCO). *Central image left*: A researcher is loading the tray with carbon nanofibers. *Central image right*: an air sample taken from the researcher's personal breathing zone; the image was generated by transmission electron microscopy (courtesy of the National Institute for Occupational Safety and Health). *Cover background*: a false-color scanning tunneling microscopy image revealing the atomic-scale electronic perturbations caused by a lattice defect in bilayer graphene (courtesy of Joseph Stroscio, National Institute of Standards and Technology, http://cnst.nist.gov).

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Human and Environmental Exposure Assessment

Report of the National Nanotechnology Initiative Workshop

February 24–25, 2009, Bethesda, MD

Part I of IV in the 2009–2010 NNI Environmental, Health, and Safety Workshop Series

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Acknowledgments

The many individuals listed below dedicated considerable time and expertise to make the NNI Human and Environmental Exposure Assessment Workshop a reality and to write and produce this report.

Workshop Organizing Committee:

- Vladimir Murashov, Chair (NIOSH)
- Michele Conlon (EPA)
- Charles Geraci (NIOSH)
- Aleksandr Stefaniak (NIOSH)
- Paul Schulte (NIOSH)
- Treye Thomas (CPSC)
- Paul Wambach (DOE)

The committee planned, organized, and ran this workshop and wrote and reviewed the report chapters.

Workshop Presenters: William Halperin (University of Medicine & Dentistry of New Jersey), Robert Herrick (Harvard University), Paul Lioy (Rutgers University), David MacIntosh (Environmental Health & Engineering, Inc.), and Susan Woskie (University of Massachusetts, Lowell) shared their expert perspectives with workshop participants on the state of the science in nanotechnology-related human and environmental exposure assessment and contributed their written remarks to the report.

AAAS Fellows: Joe Cresko, Katya Delak, Jane Dennison, Jessica Eisner, Meghan Radtke, Gina Schatteman, and José Zambrana, Jr., took substantive notes at the workshop breakout sessions and contributed significantly to the drafting of this report.

Support Staff: Staff members of the National Nanotechnology Coordination Office (NNCO) executed the planning and organization of the workshop and production of the report. In particular Liesl Heeter supported the organizing committee, handled workshop logistics along with Halyna Paikoush, and was series editor of the report. Kristin Roy formatted the report, and Pat Johnson copyedited it.

Host: The Consumer Product Safety Commission hosted the two-day event, and the staff, led by Alicia Walker, provided indispensable logistical and technical support.

Sponsor: The members of the National Science and Technology Council's Subcommittee on Nanoscale Science, Engineering, and Technology (NSET) sponsored the workshop and reviewed the draft report before its publication. The members of the NSET Subcommittee's Nanotechnology Environmental and Health Implications (NEHI) Working Group were particularly involved in planning and realizing the workshop and in vetting the report.

Thanks are due to all the participants in the February 24–25, 2009 workshop, held in Bethesda, MD. The substance of the workshop depended upon the thoughtful engagement of the speakers, moderators, and participants whose presentations and discussions at this workshop provide the foundation for this report.

Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and workshop participants and do not necessarily reflect the views of the United States Government or the authors' parent institutions.

Preface

Since its inception, the National Nanotechnology Initiative (NNI) has funded research on potential environmental, health, and safety (EHS) effects of nanoscale science, engineering, and technology to support the responsible development of novel nanoscale materials and product functionalities. This report summarizes discussions that took place during the NNI Workshop on Human and Environmental Exposure Assessment held February 24–25, 2009, in Bethesda, MD, a topical workshop convened to determine the state of the science in exposure assessment as it relates to nanotechnology. This workshop led off a series of four nanotechnology-related EHS workshops organized by the Nanotechnology Environmental and Health Implications (NEHI) Working Group of the National Science and Technology Council's Nanoscale Science, Engineering, and Technology (NSET) Subcommittee. The purpose of the EHS workshop series was to assess ongoing progress and to identify gaps and barriers with respect to the research needs and goals identified in the NNI's 2008 *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research*. The proceedings from this series of workshops will be used to help inform the NNI as it adaptively manages its EHS research strategy.

The participants in the workshop on Human and Environmental Exposure Assessment identified the vital role that exposure assessment plays in the nation's ability to properly address the environmental, health, and safety aspects of nanomaterials. Assessing the potential health risks of nanomaterials will involve adequately characterizing the toxicity potential of nanomaterials and the exposures that the population and the environment may experience. The complexity of nanomaterials requires development and implementation of new approaches to assessing exposures and thus requires new vision and input from those involved in exposure science. Novel exposure assessment approaches should be developed in concert with the increasing interest in, understanding of, and mitigation of potential hazards.

Workshop participants stressed that there are two areas of exposure science in particular that require attention. The first is metrology: developing tools to characterize and measure relevant attributes of engineered nanomaterials, including particle size, number, and surface area. The second is the life cycle analysis of engineered nanomaterials in consumer goods, including their transformation and degradation throughout the development, use, and ultimate disposal of products. This information will be necessary to assess the exposure potential in occupational settings and of the general population and the environment throughout the life cycles of engineered nanomaterials. Better characterization of nanomaterials will in turn help to inform the hazard characterization studies by providing information on relevant exposure metrics, exposure scenarios, and exposure potential.

The ultimate goal is the safe, responsible, and sustainable development of engineered nanomaterials. The emerging area of nanotechnology provides new opportunities for scientists from a variety of disciplines, including exposure science, to advance the science of assessing the behaviors of these novel materials in multiple environments. It is important for funding agencies and manufacturers of nanomaterials to specifically allocate resources for this endeavor and to encourage hazard assessments to be conducted in tandem with exposure assessments, so that they can result in meaningful information to manage any possible health risks of nanomaterials. The long-term viability of nanomaterials and public acceptance of nanotechnology will depend on ability to adequately assess the potential health risks due to exposures from nanomaterials throughout their life cycles.

On behalf of the NSET subcommittee, we thank the workshop co-chairs and the other members of the organizing committee for planning this workshop and leading the preparation of this report. Our sincere thanks also go to all the speakers, moderators, and participants for their manifold contributions to the workshop and to this report.

Sally S. Tinkle
Co-Chair
NSET Subcommittee

Travis M. Earles
Co-Chair
NSET Subcommittee

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NNCO

About the 2009–2010 NNI Series of EHS Workshops and Reports

From February 2009 to March 2010, the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the National Science and Technology Council sponsored a four-part series of workshops to solicit stakeholders' input on the National Nanotechnology Initiative (NNI) strategy to address potential environmental, health, and safety (EHS) implications of nanotechnology research, development, and deployment:

- Human and Environmental Exposure Assessment
  February 24–25, 2009, Bethesda, MD
  Website: http://www.nano.gov/events/meetings-workshops/exposure
- Nanomaterials and the Environment, & Instrumentation, Metrology, and Analytical Methods
  October 6–7, 2009, Arlington, VA
  Website: http://www.nano.gov/events/meetings-workshops/environment
- Nanomaterials and Human Health, & Instrumentation, Metrology, and Analytical Methods
  November 17–18, 2009, Arlington, VA
  Website: http://www.nano.gov/events/meetings-workshops/humanhealth
- Risk Management Methods, & Ethical, Legal, and Societal Implications of Nanotechnology (Capstone Meeting), March 30–31, 2010, Arlington, VA
  Website: http://www.nano.gov/events/meetings-workshops/capstone

The interagency NSET Subcommittee's Working Group on Nanotechnology Environmental and Health Implications (NEHI) led the organization and management of the workshop series, with active participation from stakeholders in academia, industry, nongovernmental organizations, and the general public. Three NNI EHS documents released by the NEHI Working Group for public review provide a backdrop to the 2009–2010 EHS workshops; all are available at http://www.nano.gov/.

1. *Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials* (2006) evaluated the state of the science, and grouped EHS research into five categories: (1) Instrumentation, Metrology, and Analytical Methods; (2) Nanomaterials and Human Health; (3) Nanomaterials and the Environment; (4) Human and Environmental Exposure Assessment of Nanomaterials; and (5) Risk Management Methods. It also described principal research needs within each category.

2. *Prioritization of Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials: An Interim Document for Public Comment* (2007) was intended to elicit comments from the public, the scientific community, and other stakeholders on how the NSET Subcommittee proposed to approach prioritization of environmental, health, and safety research needs.

3. *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* (2008) incorporated input from the 2007 prioritization document. The 2008 strategy describes an adaptive management approach for interagency efforts to address EHS implications of nanotechnology, including identifying priority research needs, assessing existing research, analyzing strengths and weaknesses, and periodically updating and revising the strategy. It provides information to agencies that conduct and fund research on nanotechnology. It informs those agencies on critical research needs, and it facilitates collaborative research activities to address those critical research needs.

As part of its adaptive management of the NNI interagency nanotechnology-related EHS research strategy ("NNI EHS strategy"), the NSET Subcommittee's objectives are to review the state of the science, identify critical gaps, and inform the updating of the strategy, taking into account research advances made in the United States and abroad and the evolving needs of regulatory decision makers. The goals of the NNI EHS strategy are to support nanotechnology risk assessment and risk management, to advance EHS research, and to develop adequate and timely EHS guidelines and regulations so that nanotechnology R&D is sustainable and of long-term benefit to the nation and the world. All four EHS workshops and their proceedings inform the 2011 update of the U.S. Federal Government's NNI EHS strategy.

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Executive Summary

Exposure assessment is an integral component of the risk assessment and management framework. Knowledge of both exposure to nanomaterials and the potential hazards they may induce allows for evaluating risk and establishing appropriate measures to mitigate risk. However, because nanotechnology is relatively new, very little exposure data for engineered nanomaterials have been reported in the scientific literature. This paucity of exposure data is hindering the development of nanotechnology safety and health guidelines, which in turn, can create uncertainty about the viability of nanotechnology-enabled products and about future liabilities. Therefore, addressing gaps in our knowledge of exposures to nanomaterials will not only help to ensure the safety and health of people and the environment but also will have a positive effect on nanotechnology product development and introduction in the marketplace.

Recognizing the importance of this research area, the NSET Subcommittee's Nanotechnology Environmental and Health Implications (NEHI) Working Group identifies exposure assessment as one of five priority categories for environmental, health, and safety (EHS) research. The working group described this research area as characterizing exposures to nanomaterials among workers, other populations, and environments by measuring and modeling exposure levels and by monitoring indicators of biological responses through the product life of a nanomaterial (see *Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials*, http://www.nano.gov/NNI_EHS_research_needs.pdf).

This report presents state-of-the-science assessments and provides recommendations for paths forward in addressing critical exposure assessment research gaps, based on discussions that took place during the February 2009 National Nanotechnology Initiative Workshop on Human and Environmental Exposure Assessment (http://www.nano.gov/events/meetings-workshops/exposure). It will act as a resource for agencies that conduct and fund research on nanotechnology, to inform those agencies about critical research needs and to facilitate collaborative research activities.

This report is structured around five priority research needs within the exposure assessment category that were identified in the 2008 NNI interagency EHS Research Strategy (*Strategy for Nanotechnology-Related Environmental, Health, and Safety Research*, http://www.nano.gov/NNI_EHS_Research_Strategy.pdf). Thus, the report has five sections corresponding to the five priority exposure assessment research needs:

- Characterize exposure among workers
- Identify population groups and environments exposed to engineered nanoscale materials
- Characterize exposure to the general population from industrial processes and industrial and consumer products containing nanomaterials
- Characterize health of exposed populations and environments
- Understand workplace processes and factors that determine exposure to nanomaterials

In addition, this report has a section that addresses needs not previously identified and a section addressing implementation issues.

Research Need 1: Characterize Exposure Among Workers

Identifying workers who may be exposed to engineered nanomaterials and characterization of those exposures is inconsistent and, in most cases, inadequate. Even though the number of workers involved in the research, production, distribution, and use of engineered nanomaterials continues to grow, there are only a few evaluations of these population groups. Methods for measuring incidentally produced nanomaterials such as welding fumes and diesel exhaust have been developed; however, existing methods were not designed to account for particle size. The development and commercialization of direct-read personal exposure monitors is hindered by the lack of established standards for exposure limits. Existing emission measurement protocols are unable to quantify the actual engineered nanomaterials or to characterize short-duration tasks. In the absence of nanomaterial-specific methods of exposure assessment, the health and safety practitioner has to rely on qualitative approaches to evaluate the potential exposure experience of a worker group.

The challenges of establishing exposure registries for workers potentially exposed to engineered nanomaterials include (1) the need for developing clear hazard categories for engineered nanomaterials, (2) identifying a funding mechanism to manage monitoring of job and worker migration, and (3) developing novel techniques to follow these evolving technologies, dynamic industries, and mobile workers. These challenges can be successfully addressed, provided additional investments are made.

Key Points

Although investment in this research need by the U.S. Government and various national and international organizations has been increasing, a lack of tools for adequate exposure assessment of workers involved in the research, production, distribution, and use of engineered nanomaterials remains a major barrier to evaluating risk and recommending risk-appropriate exposure mitigation programs. Therefore, more effort and investment should be directed toward expanding currently available emission assessment techniques to allow for feasible exposure assessments of engineered nanomaterials in the workplace. Given the breadth of nanomaterial types and forms, in the short term, these efforts should focus on the few nanomaterials such as common metal oxides, metals, and carbon nanotubes that are presently, or are about to be, used in commercial products. In the longer term, new tools should be developed through national and international surveys to support effective characterization of the worker population potentially exposed to nanomaterials.

Nanotechnology Terminology Used in this Report

Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modeling, and manipulating matter at this length scale. —*NNI Strategic Plan,* December 2007 (available at http://www.nano.gov/NNI_Strategic_Plan_2007.pdf)

Usage Note

Throughout this report, the expression *engineered nanomaterials* is used to describe non-naturally occurring nanomaterials, which best reflects remarks made at the time of the workshop and is the expression still in use among the EHS community. Since the workshop, the International Standardization Organization (ISO) has adopted core terminology, including specific definitions for *engineered* and *manufactured* nanomaterials (ISO/TS 80004-1:2010, available at http://cdb.iso.org/).

Research Need 2: Identify Population Groups & Environments Exposed to Engineered Nanoscale Materials

The information needed to strategically design research studies about populations likely to be exposed to engineered nanomaterials is growing at a rapid pace. Increased participation in voluntary reporting programs such as the EPA Nanomaterial Stewardship Program and others will improve the ability to discern geographic areas where engineered nanomaterials may be emitted into the environment, consumed as ingredients of products, and disposed of in solid waste or wastewater.

New information on consumer product use patterns, obtained through population-based surveys or other means, would help to refine understanding of population subgroups most likely to be exposed to certain engineered nanomaterials. These data sets could be combined with additional data about patients, such as their places of work, to look for worksite-related patterns of health or environmental problems associated with nanotechnology.

Understanding environmental and consumer exposures is hindered by the paucity of data about the fate of engineered nanomaterials in the environment. Through agglomeration, aggregation, chemical transformation, etc., engineered nanomaterials may significantly change from their initial manufactured states. Additionally, the challenges of detecting and characterizing nanomaterials multiply the complexity of evaluating exposure to, and potential risk from, engineered nanomaterials.

Key Points

There is a need to collect and analyze information about nanomaterial manufacturing, processing, and direct use in consumer products to discern geographic areas where engineered nanomaterials may be emitted into the environment, consumed as ingredients of products, and/or disposed of in solid waste or wastewater. Population-based surveys should be conducted to obtain information on use patterns for consumer products, which would help to refine the understanding of population subgroups more likely to be exposed to certain nanomaterials. Research should also focus on identifying potential subpopulations of organisms that are more susceptible to engineered nanomaterial exposure than others. In the long term, more quantitative assessments of those population groups most likely to be exposed to engineered nanomaterials will become available, once exposure assessment models to characterize human and environmental exposures are developed and validated.

Research Need 3: Characterize Exposure to the General Population from Industrial Processes and Industrial and Consumer Products Containing Nanomaterials

Analytical methods necessary for conducting exposure measurements in the general population do exist, but they are not always widely available as commercial methods. There are still many questions regarding which analytical methods are fully validated for these types of studies, how to determine the composition of a nanomaterial, and how to characterize and detect nanomaterials in biological matrices.

The main challenge in this area is a lack of data quantifying exposures of the general population to engineered nanomaterials. More studies are needed to look at emissions and human contact during normal use of products and after wear and tear have degraded the products, and to look at human contact during repeated applications of products containing nanomaterials. The transformation of nanomaterials during transport in the environment and in human bodies is poorly understood; overcoming this knowledge gap is another major challenge.

Key Points

In order to assess nanomaterial exposures to the general population from industrial processes and consumer products, further studies are necessary to characterize and detect engineered nanomaterials in biological matrices and to understand their transformations during transport in the environment and in human bodies. More studies should be conducted looking at emissions and human contact during normal use and after wear-and-tear have degraded a product, and at human contact during repeated exposures. In the long term, engineered nanomaterials exposure assessment models should be developed. Existing models developed for traditional chemicals could be modified to serve this purpose. To facilitate this process, critical exposure descriptors need to be identified.

Research Need 4: Characterize the Health of Exposed Populations and Environments

There is limited information on occupational health surveillance for workers exposed to nanomaterials. Some companies and government laboratory workers handling nanomaterials are included in existing health surveillance programs as a matter of practice or due to exposure to other hazards. There are no known health surveillance programs related to exposures of the general population to anomaterials, and the advisability of such an effort for the general

population has not been determined. Should such health surveillance programs be determined to be useful, there are ongoing health surveillance programs developed for other hazards that would be leading candidates for expansion to include engineered nanoscale materials.

Because the responsibilities and roles for health and environmental surveillance are distributed across industry, government, academia, and nongovernmental organizations, they are vulnerable to parochial interests, creating barriers to an integrated approach. Federal public health agencies can play an important role in collecting and providing access to information created through taxpayer-funded work. There are no fundamental barriers to beginning useful programs with the recognition that these will need to adapt as the industry changes and as knowledge increases about the health and environmental effects of manufacturing and using engineered nanomaterials. Evidence of an ongoing commitment to fund such projects would help recruit and build the community of researchers studying the health and environmental risks associated with nanotechnology.

Key Points

Because at this time there are no adverse health endpoints uniquely associated with engineered nanomaterials, having workplace health surveillance programs specific to engineering nanomaterials is not recommended. Rather it is recommended to continue the general health surveillance programs already covering some workers handling nanomaterials, who are included in general health surveillance programs as a matter of practice or due to their exposure to other hazards. The advisability of conducting health surveillance programs related to the general population and engineered nanomaterials has not been determined. The benefits and feasibility of initiating nanotechnology workers' health surveillance programs and general population health surveillance programs should be reassessed as more nanotechnology-related health effects information is generated. Over the long term, if such health surveillance programs are determined to be justified, the mechanisms to support and conduct such programs will need to be established.

Research Need 5: Understand Workplace Processes and Factors that Determine Exposure to Nanomaterials

To date, only limited job-level determinants of exposure have been evaluated and reported in the literature. A need exists to understand the processes and factors that determine exposure to nanomaterials in the workplace. As progress continues to be made in the near term on existing research topics (developing exposure classifications of nanomaterials, developing exposure classifications for processes, and developing predictive models of workplace exposure), a concomitant shift toward addressing emerging state-of-the-science research topics is necessary and should be initiated in the near future. Key near-term research opportunities include the development of internationally harmonized and validated protocols for exposure surveys, sample collection, and analysis and reporting. Importantly, there are also opportunities to clarify whether the metrics of engineered nanomaterial characteristics used in toxicology studies correlate with the metrics that can be measured in the field, and for toxicity testing to inform exposure assessment with regard to which nanomaterials are hazardous.

Existing international bodies such as the International Organization for Standardization (ISO), the Organisation for Economic Co-operation and Development (OECD), and the United Nations (UN) may provide a framework for development and validation of needed internationally harmonized protocols for exposure assessment, whereas industry has a role to play in product stewardship.

Key Points

Further studies should be conducted to understand processes and factors that determine exposure to engineered nanomaterials in the workplace. In the near term, exposure classifications of nanomaterials and processes should be developed. Near-term research opportunities include the development of internationally harmonized and validated protocols for exposure surveys, sample collection and analysis, and reporting through existing international frameworks such as the ISO, OECD, and UN. Over the long run, comprehensive predictive models should be developed for workplace exposures covering a broad range of engineered nanomaterials and processes.

Emerging Trends and Cross-Cutting Issues

Studies of ultrafine air pollutants have established a working hypothesis that the hazards of nanoscale materials are related to their size, shape, and solubility. Research on the health implications of nanotechnology has generally been supportive of this theory. However, there will be exceptions, with some percentage of new engineered nanoscale materials having effects that cannot be predicted based on current knowledge. Nanotechnology increasingly provides material scientists with tools that enable them to engineer a wide range of new materials for specific applications, a fact that exacerbates existing deficiencies in abilities to predict and test for hazards during the development of new materials. A systematic and driven approach toward understanding the effects of nanotechnology on health is necessary. Until new knowledge provides the tools for better predictions and faster and more efficient testing, health and safety research in nanotechnology will depend, in part, on observations aimed at detecting effects as soon as possible. The ability to detect effects early could further be advanced if standard identification of relevant health concerns or standard desirable data sets could be defined.

Another significant impediment to nanotechnology health and safety research is the diversity of materials that constitute nanotechnology. Possible approaches to tackling this impediment include grouping nanomaterials based on physico-chemical traits of the material and creating computer models of interactions of nanomaterials with different biological components, based on mechanistic toxicology studies.

A key goal for the development of nanotechnology databases is the ability to share knowledge and integrate efforts worldwide. With the possibility looming for health issues related to nanotechnology, the need for standards-compliant databases appears to be most acute for regulators. Consequently, it is in the best interest of the government to develop functional and usable standards. A critical need is a clear identification of a minimum data set that must be included in a database where correlations to health or environmental effects may be made in the future. Existing exposure databases for conventional chemicals could be used to collect data on engineered nanomaterials because there are cross-cutting issues. However, such databases should be modified to include nanotechnology-specific descriptors. Informatics is a viable mechanism for enabling an efficient exchange of information and could prove advantageous for communicating good practices and protocols. Centralizing available information resources requires confidence in the quality of information, global coordination, and allocation of dedicated resources to maintain such information clearinghouses.

Environmental monitoring in facilities that produce engineered nanomaterials or use them in the manufacture of consumer products can provide a significant portion of the data necessary to enable the nanotechnology community to understand health and safety concerns. In order to make rapid inline monitoring a reality in nanomaterial manufacturing, novel technological capabilities are required, but currently, it is not financially feasible to use commonplace tools in nanotechnology research for this type of monitoring. In the long run, personal exposure monitors in the workplace for nanomaterials should be developed to allow for the accurate characterization of exposures in the workplace.

A roadmap for a comprehensive source-to-receptor exposure assessment throughout the life of nanotechnology-enabled products and materials is needed to provide the framework for effective national and global collaborative stakeholder research efforts. Such a roadmap will further the prioritization of nanomaterials, populations, and techniques for exposure assessment studies and, therefore, will facilitate proactive risk assessment and risk management. Roadmap development and execution should be conducted in coordination with major international standards-setting organizations.

Key Points

There is an urgent need to define a standard set of desirable data to identify relevant health concerns. In the long term, this data set would assist with predicting and testing for hazards during new material development and, therefore, with reducing product risk at the nanomaterial/nanotechnology-enabled product design stage. A global nanomaterial exposure and hazard database should be developed and should include such a standard data set.

Support should be given to the development and maintenance of a global information clearinghouse for communicating good practices and protocols.

A roadmap for a comprehensive source-to-receptor exposure assessment throughout the life of nanotechnology-enabled products and materials should be developed and executed in coordination with major international standards-setting organizations to provide a framework for effective national and global collaborative stakeholder research efforts. Over the long term, such a roadmap will promote prioritization of engineered nanomaterials, populations, and techniques for exposure assessment studies, and, therefore, will facilitate proactive risk assessment and risk management.

1. Introduction

Background

Exposure assessment is an integral component of the risk assessment and management framework. Knowledge of both exposure and hazards allows for evaluating risk and establishing appropriate measures to mitigate risk. However, because nanotechnology is relatively new, very little exposure data for engineered nanomaterials have been reported in the scientific literature. This paucity of exposure data is hindering the development of nanotechnology safety and health guidelines, which in turn, can create uncertainty about the viability of nanotechnology-enabled products and about future liabilities. Therefore, addressing gaps in our knowledge of exposures to nanomaterials will not only help to ensure the safety and health of people and the environment but also will have a positive effect on nanotechnology product development and introduction into the marketplace.

Recognizing the importance of this research area, the NSET Subcommittee's Nanotechnology Environmental and Health Implications (NEHI) Working Group identifies exposure assessment as one of five priority categories for environmental, health, and safety (EHS) research.

About the Workshop

The National Nanotechnology Initiative (NNI) Workshop on Human and Environmental Exposure Assessment was held February 24–25, 2009, at the Consumer Product Safety Commission headquarters in Bethesda, MD. It was sponsored by the NSET Subcommittee, which implemented the workshop under the auspices of its NEHI Working Group.

The National Institute for Occupational Safety and Health (NIOSH), in recognition of its research on exposure assessment for workers, played a leading role in organizing this workshop. This was the first workshop in the 2009–2010 four-part NNI environmental, health, and safety workshop series aimed at furthering development and adaptation of the U.S. Federal Government strategy to responsibly and proactively address potential EHS implications of nanotechnology research and development.

This workshop on exposure assessment addressed one of the five priority EHS research categories for engineered nanoscale materials that were identified in the 2008 *NNI Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* ("NNI EHS strategy") (*1*). The workshop focused on the research needed to fully characterize exposures to nanomaterials among workers, other populations, and environments by measuring and modeling exposure levels and by monitoring indicators of biological responses throughout the product life cycles of nanomaterials. More than 165 scientists and other stakeholders from national and international government, academia, industry, labor, the public, and other sectors participated in person at the workshop. An additional 25 viewers joined from other locations via webcasts of the plenary sessions.

The workshop was organized around six expert presentations, held in plenary sessions, that gave state-of-the-science overviews for each of the five Human and Environmental Exposure Assessment research needs identified in the 2008 *EHS Research Strategy* (p. 33) plus one on emerging needs. The speakers and their topic areas are listed below, along with links to the original presentations in PDF format, as provided on the workshop website, http://www.nano.gov/events/meetings-workshops/exposure:

- **Research Need 1**: "Characterize exposures among workers," Dr. Robert Herrick, Harvard University
- **Research Need 2**: "Identify population groups and environments exposed to engineered nanoscale materials," Dr. David MacIntosh, Environmental Health & Engineering, Inc.
- **Research Need 3**: "Characterize exposure to the general population from industrial processes and industrial and consumer products containing nanomaterials," Dr. Paul Lioy, Rutgers University
- **Research Need 4**: "Characterize the health of exposed populations and environments," Dr. William Halperin, University of Medicine & Dentistry of New Jersey
- **Research Need 5**: "Understand workplace processes and factors that determine exposure to nanomaterials," Dr. Susan Woskie, University of Massachusetts, Lowell
- **Emerging Needs**: "Emerging Needs in Human and Environmental Exposure Assessment," Dr. Paul Schulte, NIOSH

These six presentations served as catalysts for general open-floor discussions by workshop participants and for more focused discussions in the breakout sessions. They were webcast (and archived on the workshop website) to facilitate broader public participation.

Following the expert presentations, six concurrent breakout sessions were held on both Day 1 and Day 2, one session each for the five Human and Environmental Exposure Assessment research needs and one session for identifying emerging trends. The various sessions also addressed implementation issues. During the first day, breakout sessions focused on collecting information: where the science is in addressing research needs, where the science will need to be in five years, and whether the current research needs are framed correctly. Discussions on the second day of the workshop centered on identifying paths forward in closing critical research gaps identified in the first-day breakout sessions. Specific technical questions for each of the breakout sessions helped focus the discussions. Following the breakout sessions, participants shared findings and conclusions from their respective sessions in a general plenary session, allowing for feedback from all participants.

About the Report

This report summarizes the principal findings of the presentations and discussions that took place during the February 2009 NNI workshop on Human and Environmental Exposure Assessment. The report is the principal output of the workshop; however, additional materials related to the workshop, including presentation slides and video recordings, are available on the workshop website.

Chapters 2–6 of this report each focus on one of the five research needs listed above. Each chapter begins with an expanded, written version of the invited expert's remarks and then summarizes the plenary and breakout session discussions on individual exposure assessment research and development needs. Any ideas, findings, conclusions, and recommendations presented in the speakers' remarks are those of the contributing authors.[1]

Chapters 7 and 8 summarize workshop discussions to identify emerging and cross-cutting research needs, and implementation issues. The appendixes provide supporting information about the workshop: the agenda (Appendix A), the list of participants (Appendix B), and a list of abbreviations and acronyms used in the report (Appendix C).

References

1. *NNI Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* (NSTC/NSET, Washington, DC, 2008; http://www.nano.gov/NNI_EHS_Research_Strategy.pdf).

1 The October 2010 special issue **16**(4) of the *International Journal of Occupational and Environmental Health*, entitled "Human and Environmental Exposure Assessment for Nanomaterials," is dedicated to the topic of exposure assessment for engineered nanomaterials, based on the speakers' presentations (see http://www.ijoeh.com/index.php/ijoeh/issue/view/78).

2. *Research Need 1:* Characterize Exposures Among Workers

Guest Speaker/Co-Chair: **Robert F. Herrick (Harvard University)**
Government Co-Chair: **Charles Geraci (NIST)**
Rapporteur: **Jane Dennison (AAAS Fellow)**

Introduction

Key Points

Although investment in this research need by the U.S. Government and various national and international organizations has been increasing, a lack of adequate tools to assess exposures of workers involved in the research, production, distribution, and use of engineered nanomaterials remains a major barrier to evaluating risk and recommending risk-appropriate exposure mitigation programs. Therefore, more effort and investment should be directed at expanding currently available emission assessment techniques to allow for accurate exposure assessment for engineered nanomaterials at concentration levels close to safe and attainable and/or feasible in the workplace. Given the breadth of nanomaterial types and forms, in the short term, these efforts should focus on the few nanomaterials that are presently, or are about to be, in commercial products, such as common metal oxides, metals, and carbon nanotubes. In the longer term, new tools should be developed through national and international surveys to support effective characterization of the worker population potentially exposed to nanomaterials.

Participants

In addition to the co-chairs, rapporteur, and NNCO representative, 19 individuals participated in one or both of the Research Need 1 breakout sessions. Participants included six representatives of private business (BASF, Concurrent Technologies Corp., Evonik Degussa, Kanebo Cosmetics, PPG Industries, Washington CORE); six representatives of U.S. military departments (Defense Logistics Agency, U.S. Navy National Medical Center and Bureau of Medicine and Surgery, and U.S. Army Center for Health Promotion and Preventive Medicine); two representatives of foreign governmental organizations (Health Canada and Japan Institute of Occupational Safety and Health); one state government representative (the Massachusetts Division of Occupational Safety); and one representative each from DOE (Argonne National Laboratory), EPA, NIOSH, and NIST. These participants came from the fields of occupational safety and medicine, industrial hygiene, toxicology, chemistry, and environmental, health, and safety (EHS) management, among others. The Research Need 1 and Research Need 5 ("understand workplace processes and factors that determine exposure to nanomaterials") groups combined on Day 2 of the workshop to discuss cross-cutting exposure issues pertinent specifically to workers.

Invited Presentation

Characterize Exposure Among Workers

Robert F. Herrick, Department of Environmental Health, Harvard University

Background

Within this research need, there are two broad topics: develop qualitative and quantitative exposure survey protocols, and explore utility and feasibility of exposure registries. These are discussed separately, including the sets of specific questions that we were asked to address.

As a preliminary step to addressing the state of the science on Research Need 1, "characterize exposure among workers," two measures of the level of scientific activity around worker exposure research were identified. The first is Table 1.1 from the National Research Council's *Review of Federal Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* (*1, 2*).

In 2006, five of 246 (approximately two percent) of the Federally funded projects deemed directly relevant to EHS issues addressed human and environmental exposure assessment (receiving 1.6 percent of the total funding).

Table 1.1 NNI Evaluation of Federal Grant Awards in FY 2006 that are Directly Relevant to EHS Issues*

Category	Number of Projects	$ Invested (Millions), FY 2006
Instrumentation, Metrology, and Analytical Methods	78	26.6
Human Health	100	24.1
Environment	49	12.7
Human and Environmental Exposure Assessment	**5**	**11**
Risk Management Methods	14	3.3
TOTAL	246	67.8

* Source: 2008 *NNI Strategy for Nanotechnology-Related Environmental, Health, and Safety Research,* pp.11, 20, 26, 33, 38 (2).

A related metric that provides some insight into the state of the science on worker exposures is a tally of the peer-reviewed publications on the topic, as gauged by searching the PubMed and ISI Web of Science databases. Table 1.2 presents the results of searching these resources (January 28, 2009), using first the broad term "nanoparticles," then restricting the search to articles that included consideration of nanoparticle analysis, measurement, and exposure.

Table 1.2 Comparison of Article Topics Related to Nanoparticles

Search Term	PubMed Citation	ISI Web of Science Citations
nanoparticles	20416	75479
nanoparticles analysis	5208	9748
nanoparticles measurement	514	1951
nanoparticles exposure	21	1246

The results of these searches confirm what would be predicted from the data on research funding. There is very little investment being made in research on human exposure assessment to nanomaterials, and the result is that the research need on characterizing worker exposures is largely unmet.

Develop Qualitative and Quantitative Survey Protocols

Within this broad topic, the first question to be addressed is, "How can potentially exposed groups of workers be systematically identified?"

This can be approached from two directions, both of which are founded upon existing agency capabilities. The first is to link with the EPA Nanoscale Materials Stewardship Program (NMSP), as described in the EPA concept paper for the Nanoscale Materials Stewardship Program under TSCA (*3*). This program is described as being intended to help EPA assemble existing data and information from manufacturers and processors of existing chemical nanoscale materials; identify and encourage use of risk management practices in developing and commercializing nanoscale materials; and encourage the development of test data needed to provide a firmer scientific foundation for future work and regulatory/policy decisions. The types of data being collected in the program include exposure information, specifically, self-reports on descriptions of the activities (i.e., bag dumping, tote filling, unloading drums, sampling, cleaning, etc.) in which workers may be exposed to nanomaterials and the agents involved in production and processing of nanomaterials; descriptions of any protective equipment and engineering controls used to protect workers; the physical form(s) of the chemical substance (e.g., solid: crystal, granule, powder, or dust) and percentage of the chemical substance (if part of a mixture) at the time of exposure; estimates of the maximum number of workers involved in each activity for all sites combined; and estimates of the maximum duration of the activity for any worker in hours per day and days per year.

This report could be significantly enhanced by the addition of information on the job titles and other descriptive information that would allow linkage with the work histories derived from workers' personnel records in these facilities. The information in the EPA report would not include personal identifiers; rather it should be developed in consultation with the reporting companies to reflect the terminology that the companies use to describe workers in their personnel systems. For example, the goal would be to have sufficient information in the NMSP reporting system so that within a group of workers with job titles like "process operator" or "lab technician," it would be possible to identify and separate those who work with nanomaterials from those who do not. Information such as this would enhance the value of the NMSP for exposure and medical surveillance in the future.

The second approach to systematically identifying potentially exposed workers is to conduct a national survey of potential occupational exposures in nanotechnology. This could follow the well-established model of the National Occupational Exposure Survey (NOES) (http://www.cdc.gov/noes/) (*4*). This would be done first as an inventory, primarily qualitative, to build a database of descriptive information. The survey could be designed to describe and characterize potential exposures associated with the unit processes throughout the life cycle, including nanomaterial R&D, manufacturing, downstream applications incorporating engineered nanomaterials into other products, and destruction and disposal, including process wastes.

The second question within the topic is, "Can existing public health geographical information systems (GIS) and infrastructure be used for effective sharing of nanotechnology occupational safety and health data including exposure data?"

It appears that the answer is probably not, based upon an overview of the current applications of these approaches. These approaches have been used for hazard surveillance in traffic-related studies, at hazardous waste sites, and for other air and water contamination-related exposures. The application of these approaches to occupational nanomaterial exposures raises issues of confidentiality, trade secrets, and site access that would be very difficult to address. The recommendation is, therefore, that these public health GIS- and infrastructure-based approaches not be considered a priority for investigation of occupational nanomaterial exposures.

In response to the question, "Can personal exposures to nanomaterials be measured?" the answer is not yet, but soon.

The hierarchy of exposure measures ranks personal real-time monitoring as the most informative, followed by personal time-weighted averages, area concentration measurements representative of personal exposures, and categorical exposure classifications. As summarized in Table 1.3, instrumentation and measurement technology is rapidly developing, and while these measurement devices are not small and portable enough to be worn in a worker's breathing zone, they are approaching that degree of miniaturization. Until then, it is possible to apply the existing measurement technologies to make measurements that are representative of personal exposures, while devising strategies to capture the biologically relevant characteristics of exposures.

Table 1.3. Examples of Instruments & Techniques Allowing Characterization of Nanoparticle Aerosols*

Parameter	Instruments	Remarks
Mass and granulometric distribution	Cascade impactors	Berner or micro-orifice cascade impactors allow gravimetric analysis of stages finer than 100 nm during individual assessment.
	TOEM (Tapered Oscillating Element Microbalance)	The tapered oscillating element microbalance preceded by a granulometric selector determines the mass concentration of nano-aerosols
	ELPI (Electrical Low-Pressure Impactor)	The electrical low-pressure impactor allows real-time detection according to size of the active surface concentration and gives a granulometric distribution of the aerosol. If the charge and density of the particles are known or assumed, the data then can be interpreted in terms of mass concentration. The samples at each stage then can be analyzed in the laboratory.
	SMPS (Scanning Mobility Particle Sizer™)	Real-time detection according to the size of the particle number concentration gives a granulometric distribution of the aerosol. Knowledge of the shape and density of the particles then allows estimating of the mass concentration.
Number and granulometric distribution	CNC (Condensation Nucleus Counters)	Condensation nucleus counters allow particle number concentration measurements in real time within the particle diameter detection limits. Without a granulometric selector, the CNC is not specific to the nanometric field. P-Trak offers screening with an upper limit of 1000 nm. TSI model 3007 is another example.
	SMPS	The SMPS allows real-time detection according to the electrical mobility diameter (related to size) of the particle number concentration.
	Electron microscopy	Offline electron microscopic analysis can provide information on granulometric distribution and on the aerosol's particle number concentration.
	ELPI	Real-time detection according to size and active surface concentration gives a granulometric distribution of the aerosol. If the charge and density of the particles are known or assumed, the data then can be interpreted in terms of particle number concentration. The samples at each stage then can be analyzed in the laboratory.
Specific surface area and granulometric distribution	Diffusion chargers	Commercially available diffusion chargers allow real-time measurement of the active surface of the aerosol and have a response in relation to the active surface
	ELPI	The ELPI allows real-time detection of the aerodynamic diameter according to size and active surface concentration. The samples at each stage then can be analyzed in the laboratory.
	Electron microscopy	Electronic microscopy analysis can provide information on the surface of particles in relation to their size. Transmission electron microscopy provides direct information on the projected surface of the particles analyzed, which can be linked to the geometric surface for certain forms of particles.
	SMPS	The SMPS allows real-time detection according to the electrical mobility diameter (related to size) of the particle number concentration. Under certain conditions, the data can be interpreted in terms of specific surface area.
	Parallel use of SMPS and ELPI	The differences in the aerodynamic diameter and electrical mobility measurements can be used to deduce the fractal size of the particles, thus allowing a particle surface estimate.

* Source: C. Ostiguy, B. Roberge, L. Ménard, C.-A. Endo. 2008. *Best Practices Guide to Synthetic Nanoparticle Risk Management*. Report R-599 Chemical Substances and Biological Agents Studies and Research Projects (IRSST, Montreal, Canada, 2008; http://www.irsst.qc.ca/files/documents/PubIRSST/R-599.pdf), 23.

The last two questions within the topic can be addressed together: they are, "Are there adequate emission measurement protocols—with what limitations?" and "How can emission measurements be translated to personal exposures?"

The 2006 NIOSH document *Approaches to Safe Nanotechnology* (http://cdc.gov/niosh/topics/nanotech/safenano/) (*6*) proposes a stepwise approach to measure emissions:

- Identify potential sources of emissions
- Conduct particle concentration sampling
- Background measurements
- Area sampling
- Conduct filter-based area and personal air sampling

This approach, called the Nanoparticle Emission Assessment Technique (NEAT) has the limitation that it is intended to qualitatively determine the release of engineered nanomaterials in the workplace. It is intended for the initial evaluation of workplaces where engineered nanomaterials are manufactured or used. The information gained from this qualitative assessment can provide the basis for more comprehensive and quantitative approaches.

As for translating the results of qualitative emission measurement, or emission modeling approaches, to personal exposures, the EPA *Nanotechnology White Paper* (*7*) provides some cautionary guidance. This document concludes that the models used by EPA's Office of Pollution Prevention and Toxics (OPPT) to assess environmental fate and exposure are, for the most part, designed to provide estimates for organic molecules with defined and discrete structures. They are not designed for use on inorganic materials; therefore, they cannot be applied to inorganic nanomaterials. In addition, many models derive their estimates from structural information and require that a precise structure of the material of interest be provided. Since many of the nanomaterials in current use, such as quantum dots, ceramics, and metals, are solids without discrete molecular structures, it is not possible to provide the precise chemical structures that these models need.

There are, however, a few published reports of nanoparticle emission measurements and modeling. The scenarios investigated include high-speed machining, cooking, laser ablation, and vehicle exhaust. In addition, the NNI identifies one project, "Experimental and Numerical Simulation of the Fate of Airborne Nanoparticles from a Leak in a Manufacturing Process to Assess Worker Exposure," Award # 0646236 from the NSF to the University of Minnesota-Twin Cities.[1] To date, this project does not appear to have produced any peer-reviewed publications.

Explore Utility and Feasibility of Exposure Registries

The second broad topic is to "explore utility and feasibility of exposure registries." Within this topic, there are two specific questions to be addressed: "Are exposure registries feasible?" and "What are the limitations?"

The answer to the feasibility question is that not only are exposure registries feasible, they are necessary, and essential for the NNI to achieve its goal of supporting the responsible development of nanotechnology. The answers to the previous questions about survey protocols are complementary to the broader need to characterize and document occupational exposures. Hazard surveillance for engineered nanoparticles is an

1 "The toxicity of nanoparticles has received increased attention in the recent years. Toxicologists proposed to determine the total airborne nanoparticle surface area as a health relevant measure in order to assess worker exposure. If there is a leak in nanoparticle production equipment, nanoparticles can be emitted in large quantities. Between the leak and the point of human exposure they undergo physical or chemical reactions that can change the particle properties, including number and surface area concentrations, morphology, or chemical composition. In this project the PI proposes to measure the fate of nanoparticles, emitted through a leak in a nanoparticle production process into a workplace environment. Dr. Pui will particularly focus on changes of the nanoparticle surface area" (from the Research.gov (http://www.research.gov) webpage on this project, Federal Award ID Number 0646236).

essential component of any occupational health surveillance effort and is used for defining the elements of the risk management program. Hazard surveillance should include the identification of work tasks and processes that involve the production and use of engineered nanoparticles, and should be viewed as one of the most critical components of any risk management program. A National Nanomaterial Exposure Survey would provide the foundation for developing an exposure registry. A well-documented registry of workers potentially exposed to nanomaterials would direct research and medical surveillance, and inform risk management and policy decisions (*8*).

The creation of exposure registries for nanomaterials would not pose any unique problems or raise issues about limitations that have not been resolved in the registries that have been created for workers exposed to other hazards such as beryllium, ionizing radiation, 2-naphthylamine, or World Trade Center dust, and residents exposed to trichloroethylene, benzene, and dioxin (*8*). The complexity of the engineered nanomaterials industry, however, would make the cooperation of industry essential in preparing and maintaining such a registry.

Concluding Comments

The research need of characterizing exposures among workers presents a number of challenges that can be successfully addressed; however, there is very little investment being made in research on human exposure assessment related to nanomaterials. The result is that the research need on characterizing worker exposures is largely unmet.

References

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2. *The National Nanotechnology Initiative Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* (NSTC/NSET Subcommittee, 2008; http://www.nano.gov/NNI_EHS_Research_Strategy.pdf), pp. 11, 20, 26, 33, 38).

3. U.S. Environmental Protection Agency, *Concept Paper for the Nanoscale Materials Stewardship Program under TSCA* (EPA HQ-OPPT-2004-0122-0058; http://www.regulations.gov/search/Regs/contentStreamer?objectId=090000648025bc79&disposition=attachment&contentType=pdf).

4. National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, *Exposure Assessment Methods: Research Needs and Priorities*. (DHHS [NIOSH] Publication 2002-126, Washington, DC, 2002; http://cdc.gov/niosh/docs/2002-126/2002-126.pdf).

5. C. Ostiguy, B. Roberge, L. Ménard, C.-A. Endo, *Best Practices Guide to Synthetic Nanoparticle Risk Management. Report R-599 Chemical Substances and Biological Agents Studies and Research Projects* (IRSST, Montreal, Canada, 2008; http://www.irsst.qc.ca/files/documents/PubIRSST/R-599.pdf).

6. National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH* (NIOSH Draft 9-30-05, 2005; http://www.cdc.gov/niosh/topics/nanotech/pdfs/Approaches_to_Safe_Nanotechnology.pdf).

7. U.S. Environmental Protection Agency, *Nanotechnology White Paper* (EPA Publication 100/B-072/001, 2007; http://www.epa.gov/OSA/pdfs/nanotech/epa-nanotechnology-whitepaper-0207.pdf).

8. P. Schulte *et al*., Sharpening the focus on occupational safety and health in nanotechnology. *Scandinavian Journal of Work, Environment, and Health* **34**(6), 471–478 (2008).

State of the Science

A majority of the workshop participants said that the state of the science for identifying workers who may be exposed to engineered nanomaterials and the methods for characterizing those exposures was quite varied and, in most cases, deficient. The pace at which these new materials are being researched and developed is very rapid, and many are being rapidly commercialized. The effort to identify exposed worker groups becomes even more complex with the realization that the engineered nanomaterial is, in and of itself, not always the final product. The nanomaterial is almost always used by a third party to create a nanotechnology-enabled product. The extent of this business area and the number of workers involved is undoubtedly growing, but there are few good evaluations of the extent of this secondary market. Efforts are underway at the Federal level by EPA to gather information through the Nanoscale Material Stewardship Program, but the information has been slow in developing. State-level programs, such as one launched by California, may yield more information and provide better insight into the scope of the research, production, distribution, and use of engineered nanomaterials.

Most of the participants recognized that a lot is known about measuring ultrafine particulates, such as welding fume and diesel exhaust, and that experience should be used as a starting point when assessing engineered nanomaterial exposures. While some of the methods for measuring these specific environmental contaminants are intended to be quantitative in nature, they were not designed to account for one of the fundamental parameters that must be addressed, namely particle size. The challenge is further compounded when considering that there is little organized information available on the actual scope of production of engineered nanomaterials. In the absence of nanomaterial-specific methods, the health and safety practitioner has to rely on a variety of approaches to evaluate the potential exposure experience of a worker group. Very often, the initial challenge is identifying the points in a process or a material handling task that can lead to an actual exposure. Most of the discussion centered on the use of qualitative approaches because of the lack of specific methods or a lack of access to advanced techniques that could be used to assess exposures.

The current state of hazard communication was identified as being very deficient. All of the participants agreed that the current practice of relying on Material Safety Data Sheets (MSDS) to communicate what might be known about the hazards of nanomaterials is not productive. Many stated that relying on the MSDS resulted in handling practices that were determined, after the fact, as inappropriate for the material. Developing better, more effective methods of communicating current hazard information and risk management guidance was identified as a key priority.

Challenges

The Research Need 1 group stated that there was very little information available that would help them in identifying where they might be faced with worker exposures and how to characterize the magnitude of the exposures. Very little has been published that would provide guidance specific to engineered nanomaterials. The literature on ultrafine material exposure methods has been used as a starting point for assessing nanomaterials.

The challenges presented in Research Need 1 are described as follows:

How can potentially exposed groups of workers be systematically identified?

The focus of the discussion was limited to engineered nanomaterials rather than incidental nanomaterials that can be created through material treatment processes such as sanding or from incidental processes such as combustion, vehicle exhaust, or electric motor discharge. When evaluating techniques for systematically identifying groups of workers, one important consideration is whether the approach should be based on quantities used or produced, or on what might be known about the toxicity of the material. Should all engineered nanomaterials be treated as highly hazardous until it has been demonstrated otherwise? Since many of the currently produced nanomaterials already are in some state of commercialization or are the nanoscale form of an existing material, should existing practices be reevaluated?

Another key issue is the classification of engineered nanomaterials and how to track them. Little is known about the actual extent of production and use of

nanomaterials. There have been a couple of industry surveys and reports (ICON, Lux, NanoBusiness Alliance), but it is still difficult to have a good understanding of the scope of the nanomaterial industry in the United States. The EPA, through the 1976 Toxic Substances Control Act (TSCA) and the Premanufacture Notice Program, is developing some classifications for nanomaterials. It also has launched a volunteer Nanoscale Material Product Stewardship program, which has met with limited success. The interplay between the various issues identified above and the pros and cons of using a product stewardship approach are discussed below.

One difficulty is that neither the health and safety specialists nor the workers know which nanomaterials they are working with, because materials are not labeled or typically described as engineered nanomaterials on Material Safety Data Sheets. Product stewardship leaders need to know the identity and characteristics of materials, and the manufacturers need to have a robust system in place to communicate pertinent hazard information to workers and customers. A main barrier to the EPA product stewardship model (http://www.epa.gov/osw/partnerships/stewardship/) is the issue of trade secret information and whether a nanomaterial is considered a "proprietary ingredient or confidential business information." One suggestion made during the discussion was that the question of whether the material in question was, or contained, a nanomaterial could be posed and answered with a simple yes or no, without mention of composition.

Product stewardship programs have important advantages because they will track materials through their life cycles, which is important for engineered nanomaterials because they themselves are seldom the final product but often lead to intermediate products and then go to secondary users with possibly other intermediate steps before becoming incorporated into a final product. The production of the nanomaterials is just a starting point, so there is a need to track them throughout their life cycles to gain a better understanding of potential worker exposures. Stewardship program advantages also show up when products are decommissioned, e.g., torch cutting on a piece of equipment that may lead to exposure if there is no recognition that a material used in manufacturing the equipment has an engineered nanomaterial that could be released. The issue of destructive treatment, recycle, reuse, and destruction of engineered nanomaterial-containing products is full of unknowns and is an additional research area that needs to be pursued.

A good point of discussion centered on how to systematically start the process of developing a product stewardship program for an engineered nanomaterial. If a material is discovered in a laboratory, then the process could begin there, or it could begin during pilot projects or other scale-up processes, as long as the materials meet the definition of engineered nanomaterials. The free, unbound engineered nanoparticle is certainly the focus of attention, and agglomerates and aggregates of those particles should be considered when identifying the engineered nanomaterials. Worker classification schemes would have to be matched up with the broad definition of engineered nanomaterials and would have to be adjusted as more is learned about the materials. One seemingly logical starting point for a systematic identification and tracking process would be the premanufacture notice, at least for materials being introduced into commerce in the United States.

Individual organizations may choose to enact their own internal processes for tracking workers who may be exposed to engineered nanomaterials. For example, the Department of Defense (DOD) uses an exposure system that tracks individual workers with chemicals. Would it be feasible to track engineered nanomaterials using material classifications that include physical and chemical characteristics such as particle size (to determine whether they are respirable), primary particle and agglomerated/aggregated particle size, chemical composition, and other parameters? One corporate example was given where the program began with definitions: *nano-objects* (ISO definition: [1] "material with one, two or three external dimensions in the nanoscale"), *nano-composites* (nanomaterials bound in a resin matrix, with different categories depending on how the engineered nanomaterials was incorporated), and *nano-agglomerates* that accommodate the behavior of the primary material. In the example, the engineered nanomaterials are then assigned categories based on risk assessments considering inherent toxicology. If

1 ISO TC 229 Core Terms (ISO/TS 80004-1:2010, available at http://cdb.iso.org/)

data are not available for an engineered nanomaterial, then data from the "large" micro-sized form is used to develop hazard information by analogy. The result is the construct of an internal "nano-registry." The example stressed the importance of coming up with a scheme that makes sense for the materials being worked with, the conditions of the task or process, the amount used, and the frequency of use.

A lack of selection criteria compounds the challenge of using a traditional risk assessment model that relies on clear definition of the material, hazard assessment of the materials, identifying the workers at risk, evaluating their exposures, and characterizing their risk. Relative risk must also be factored into the process; for example, in R&D labs, researchers are working with small amounts of material compared to manufacturing processes that work with materials on a much larger scale. Certainly it would be preferable to base risk management criteria on reliable health-effects information. Another example was given of a company that uses the threshold limit value (TLV) that is based on micron-sized particles and then factors into its risk management program the practice that assumes that engineered nanomaterials will be more toxic. However, this information does not make it into the company's product data sheet because the engineered nanomaterials are encapsulated in liquid.

The participants agreed that it is the manufacturer of the engineered nanomaterials that is in the best position to develop and communicate risk information to the users of the materials, even in the absence of complete toxicology data. Until better guidelines for MSDS content are developed, it would be helpful for the scientific community to develop some clear categories of engineered nanomaterials. The issue of physical hazards of engineered nanomaterials has not been fully explored, e.g., engineered nanoparticles can be more reactive and more explosive or flammable at a lower temperature than the larger form of the same material.

The value of the EPA product stewardship program as a useful resource—especially since it is voluntary—is still evolving. At one point, EPA reached out to a large number of companies and received roughly 20 responses. However, as companies recognize the need to develop and communicate good, reliable risk management information, their confidence and comfort levels will become higher, and more companies might opt to participate. The issue of product liability was identified as a big incentive to voluntarily report. In addition, insurance companies are categorizing companies that work with engineered nanomaterials as having new or uncharacterized risk. Participation in a product stewardship program may help mitigate the perception of risk and eventually lower insurance costs. Perhaps groups of workers who work in companies manufacturing engineered nanomaterials can systematically be identified through insurance companies. This would be particularly useful for higher-volume operations and commercial labs, but a lot of worker exposure may still be at the R&D level in research institutions. On the commercial side, companies do not want to spend time and money on health and safety concerns before the decision is made to commercialize a new engineered nanomaterial and will likely default to general practices. Commercialization of a new material is key to progress in identifying nanotechnology workers.

Opportunities

Can existing public health geographical information systems (GIS) and infrastructure be used?

There is no evidence that geographical information systems work in this context. GIS is good for community epidemiology and public health campaigning but may be difficult to use for tracking groups of workers. There was some discussion about the feasibility of adding data to an existing GIS database or using data with the U.S. map of nanomaterial companies (http://www.nanotechproject.org/maps/mappage.html) from the Woodrow Wilson Institute. This workshop is a starting point that should help NNI agencies prioritize further research in this area.

Can personal exposures be measured?

The participants felt that there are several methods that could be used to measure fine particles, but the challenge is to detect and measure actual engineered nanomaterial emissions and to be specific for the engineered nanomaterials of interest. The group also recognized that exposure measurement methods are difficult to validate, and for ultrafine particles, the methods are not standardized, and there are no

reference materials. However, it was recognized that several existing exposure measurement techniques have utility, particularly particle counting and size distribution; they are good starting points. However, neither is highly useful for personal monitoring.

Two approaches published in 2009 were identified and discussed in the breakout session: the Nanoparticle Emission Assessment Technique described in the appendix to the NIOSH document *Approaches to Safe Nanotechnology* (*1*), and the emission measurement guidance developed by the Organisation for Economic Co-operation and Development (OECD) (*2*). Both approaches focus on an initial effort to measure particle count and size distribution. The NIOSH and OECD reports suggest a tiered approach starting with measuring emission using a condensation particle counter (CPC). The next level up in the process would involve choosing an analytical method based on knowledge of material, access to instrumentation, and whether there are any engineered nanomaterial-specific methods available. The method chosen may not be specific for the nanoscale form of a material, but if it has been validated for a primary element used in the engineered nanomaterials, the challenge would be to demonstrate sample collection eminency for the nanoscale form. For continuity with historical exposure studies, these types of methods could be used to go forward. For example, if a particular engineered nanomaterial is made from a metal that is well-characterized with an existing TLV and a validated sampling and analytical method, that should be used as a starting point.

Recent research reports by Luz and a survey by the International Council on Nanotechnology (ICON) at Rice University indicate that half of engineered nanomaterials being produced are metals and metal oxides. There are exposure limits for most of them—either permissible exposure limits (PELs) set by the Occupational Safety and Health Administration (OSHA) of the U.S. Department of Labor or TLVs set by the American Conference of Governmental Industrial Hygienists (ACGIH)—which are based on a variety of processes and operations, including welding.

The question posed during the workplace exposure assessment sessions is whether current sampling devices are adequate to develop an accurate indication of exposure to engineered nanomaterials. Current sampling equipment such as the personal cascade impactor allows for size discrimination no smaller than a particle with the equivalent diameter of 180 nm (*3*). Therefore, these sampling devices would not discriminate between nanoparticles, nanofibers, and nanoplates with an equivalent diameter less than 180 nm. However, they would detect nanomaterial particles with larger equivalent diameters, such as long nanofibers or large nanoplates and larger agglomerates and aggregates of nanoparticles.

Reportedly, if there were enough demand, an instrument manufacturing company could develop instrumentation for personal sampling that would conceivably have three stages covering nanomaterial particles with equivalent diameters less than 100 nm and would go up to the particle size of 10 μm. For accurate exposure assessment, both sensitivity and specificity are important. The type of instrumentation developed would depend on the relevant exposure metric, which would be dictated by the most biologically relevant metric. Particle number, size, size distribution, mass, and surface area are all being evaluated as possible exposure metrics. For now, an effective approach is to combine particle counting (number and size distribution) with elemental analysis if applicable. An additional confirmatory analysis can be obtained using transmission electron microscopy (TEM) to confirm the presence of the engineered nanomaterials of interest. In its field investigations, NIOSH performs TEM analysis on air samples from each process evaluated in order to get detailed information on the nature of the particles sampled and their elemental composition, and to gain a better understanding of background contributions. Specific to worker exposure monitoring, setting an exposure limit is important because without one, companies will be reluctant to conduct personal monitoring and may rely only on qualitative process-emission monitoring. Without personal exposure monitoring, there will not be enough demand for instrument manufacturers to develop appropriate direct-reading monitors.

Additional discussion on this topic concerned the potential for biological monitoring. Lead in blood is measured today in exposed workers; is it reasonable

to look for engineered nanomaterials in blood or urine? Is it possible that there is a biomarker for engineered nanomaterials exposure? Lung fluid is used to deagglomerate engineered nanomaterials in toxicology experiments, so is there too much emphasis on the free primary particle? If available active surface area is a key indicator of biological activity, is there a difference between particles or agglomerates/aggregates that are 55 nm, 95 nm, or 105 nm? A lot of focus is being placed on first-generation materials with unique properties because of their physical characteristics. Is there a need to start focusing now on more complicated second- and third- generation materials? Right now, high-production-volume materials are first generation. In the manufacturing of nanoscale formulations of pharmaceuticals or drug actives carried by engineered nanomaterials, companies should assume high danger and use containment such as glove boxes, isolators, or clean rooms. One participant stated that because of the difficulty of doing exposure assessment, companies do not need to employ sophisticated methods, but should monitor simple particle release and then follow the precautionary principle to mitigate exposures, and in that way manage the risk. Local exhaust device efficiencies should be monitored, but work is needed to identify and demonstrate the proper flow and capture velocities needed. One approach discussed was to monitor particle concentration levels and compare to background burden, making sure that hoods and other local exhaust controls were effectively lowering concentrations. Respiratory protection was briefly discussed from the perspective of action that might be taken in the absence of exposure monitoring. One company stated that it uses full-face respirators for all nanomaterials during the transfer and open handling of the materials. The group noted that NIOSH had recently published a study on the performance of N-95 and P-100 respirators to protect against a nanoscale aerosol challenge.

Are there adequate emission measurement protocols? What are the limitations?

The group discussed the suggestion that existing methods could be used for evaluating and measuring exposures, even if they do not differentiate engineered nanomaterials of interest. The challenge is to develop a comfort level with existing industrial hygiene exposure assessment methods as they are applied to engineered nanomaterials. NIOSH suggests first determining particle number and size distribution at various processing points and during a variety of tasks associated with the handling and manipulation of engineered nanomaterials. An initial assessment must be conducted prior to the start up of any active engineered nanomaterial processing so that the indoor background particle contribution can be evaluated. Obtaining ultrafine ambient measurements outdoors may not be helpful because facilities that filter their air do not experience the same levels or fluctuations as are found outdoors. The exposure assessment can be expanded to include methods specific for particles and elements, depending on the engineered nanomaterials being produced or handled. For example, the sampling and analytical method for silver (NIOSH Method 7300) could be employed for nanoscale silver. The method could be enhanced by using a size-selective inlet, such as a personal cyclone, to collect only the respirable fraction of particles. Elemental analysis would provide a quantitative indication of exposure. TEM analysis of companion filter samples could then be performed as the next level of evaluation to show that the particles are the engineered nanomaterials of interest. The next step in any assessment would be quantification of the actual engineered nanomaterial; that may not yet be possible. This approach has merit if the process being evaluated has a strong emission source or allows for long sampling time because of the sensitivity and detection limits of current analytical methods and direct-reading instruments. Short duration tasks, often only 15 minutes in length, make it difficult to collect enough material on an integrated sampler to allow detection or reliable quantification of the engineered nanomaterials.

There was some discussion regarding the commentary published in *Nature (4)* in 2006 dealing with the grand challenges of nanotechnology and whether we can get to some of these goals more quickly by going through the NNI research strategy and prioritization process. NIOSH has an agency-level strategic plan of research and is looking for ways to prioritize its work (via its Board of Scientific Counselors review of the NIOSH Nanotechnology Strategic Plan). Discussions (workshops) such as this should also help accelerate changes in the grant process to better accomplish

nanotechnology research priorities. Among the challenges that were discussed were obtaining instruments that can measure nanoparticles better, collection and dissemination of good work practices, use of EPA's particulate matter monitoring to evaluate nanoparticles, research that develops sampling equipment that replicates the deposition of engineered nanomaterials within the respiratory tract, and focused output of this workshop—hopefully to help prioritize NNI research objectives. The NNI should be positioned to communicate research priorities to all the participating agencies.

How can emission measurements be translated to personal exposures?

Converting emissions data into an estimate of worker exposure can certainly be attempted, but it will be with poor accuracy. Current models probably will not perform well for special nanoparticle behaviors. Static area sampler results would have the same issues when trying to convert or relate to personal exposure.

Are exposure registries feasible? What are the limitations?

One possibility of tracking nanomaterial workers is through their compensation records. If workers get paid, then they get registered. One participant described the experience in the semiconductor industry, which has used accounting codes and copies of pay records to correlate chemical exposures with job activities. This approach will depend on company size, since large companies have occupational health and safety programs that identify which jobs are involved with the handling of hazardous materials. A prime difficulty today is not having the ability to identify which companies are a part of the nanomaterial industry. This growing industry will include not just the primary manufacturers of nanomaterials, but also industries that incorporate nanomaterials into their products. Who would keep a national registry? Beryllium worker registries are kept by government or industry. Any proposed registry should be done on an Internet-based platform with a standardized way of inputting data. Individual companies could enter additional information as they desire. Sponsorship by NIOSH or some academic institution would help manage the issue of job and worker migration.

A starting point for an activity like this would be to characterize the type of engineered nanomaterial and identify all the different workers associated with its life cycle, e.g., anyone who works with 20 nm TiO_2 particles. R&D workers may be the best people to enter their own data. The feeling, though not validated, was that large companies might have the staff who could be responsible for entering data. Graduate school researchers could contribute to the registry to capture their engineered nanomaterial experience. This effort does not need to be complete; it just needs to start soon to collect the work and exposure experience of engineered nanomaterial workers before health effects or perceptions of risk cause a bias.

A national survey without names to gain information about the industry would serve as an inventory platform to spawn registry ideas. Registries could establish a benchmark of practices, e.g., if most workers use a hood, then other companies might want to follow suit. With a mobile workforce and privacy issues, a broad approach will be problematic, so it would be better to focus on a specific cohort that is proactively followed, versus trying to catch all workers across all industries. However, the nanomaterial production and use industry has so many new players and new products, a broad brush approach may be better. Perhaps models for surveys of this type are available from individual state departments of health. One participant stated that NIOSH had worked through the Internal Revenue Service for some survey data, but found this onerous.

Specific to the issue of dermal exposure, research is needed to evaluate the hazard of engineered nanomaterials and possible skin absorption. Dermal exposure data should be included in any survey.

Summary

A majority of the workshop participants stated that the state of the art for identifying workers who may be exposed to engineered nanomaterials and methods for characterizing those exposures varies a lot and in many cases is deficient. The research literature does not provide guidance specific to engineered nanomaterials. Participants noted the need for standard classifications of engineered nanomaterials and the creation of instrumentation to track exposure. Participants discussed adapting existing

practices such as premanufacture notices and product stewardship programs to address exposure. Adapting existing industrial hygiene exposure assessment methods was also discussed. While participants did not consider public health geographical information systems applicable to better identifying nanomaterial exposures among workers, they did suggest using techniques such as particle counting and size distribution, approaches being developed by NIOSH and OECD, to acquire information on personal exposure to engineered nanomaterials. Exposure registries would be another source of information, although questions about populating and maintaining the data were raised; if used, dermal exposure data should be included.

Recommendations

- Develop better, more effective methods of communicating current hazard information and risk management guidance.
- Develop a product stewardship program to track nanomaterials throughout their life cycles. Premanufacture notices are a logical starting point; the scheme should reflect the materials being used, the conditions of the task or process, the amount used, and the frequency of use.
- Develop clear categories of engineered nanomaterials, including reference materials.
- Apply the NIOSH and OECD approach to measuring emissions.
- Develop instrumentation for better measuring nanomaterials, including personal sampling that provides both sensitivity and specificity to the most biologically relevant metrics.
- Use EPA's particulate matter monitoring systems to evaluate nanoparticles.
- Develop sampling equipment that replicates the deposition of engineered nanomaterials within the respiratory tract.
- Start an effort to collect information for an exposure registry, including dermal exposure data.

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3. *Research Need 2:* Identify Population Groups & Environments Exposed to Engineered Nanomaterials

Guest Speaker/Co-Chair: **David MacIntosh (Environmental Health & Engineering, Inc.)**
Government Co-Chair: **Michele Conlon (EPA)**
Rapporteur: **Meghan Radtke (AAAS Fellow)**

Introduction

Key Points

There is a need to collect and analyze information about nanomaterial manufacture, processing, and direct use in consumer products to discern geographic areas where engineered nanomaterials may be emitted into the environment, consumed as ingredients of products, and/or disposed of in solid waste or wastewater. Population-based surveys should be conducted to obtain information on the use patterns for consumer products, which would help to refine the understanding of population subgroups more likely to be exposed to certain nanomaterials. Research should also focus on identifying potential subpopulations of organisms that are more susceptible to engineered nanomaterial exposure than others. In the long term, more quantitative assessments of those population groups most likely to be exposed to engineered nanomaterials will become available, once exposure assessment models to characterize human and environmental exposures are developed and validated.

Participants

In addition to the co-chairs, rapporteur, and NNCO representative, eight individuals participated in one or both of the Research Need 2 breakout sessions. Participants included four EPA representatives, one representative of private business (Everest National Insurance), one representative from academia (Woodrow Wilson International Center for Scholars), one representative from the U.S. Government Accountability Office (U.S. GAO), and one representative from DOE (Lawrence Berkeley National Laboratory). These participants came from the fields of environmental engineering, environmental health, physics, biology, risk management, research, and EHS management/oversight.

Invited Presentation

Progress in Human and Environmental Exposure Assessment

David MacIntosh, Environmental Health & Engineering, Inc.

Groups potentially exposed to nanomaterials include patients, consumers, and neighbors of production or utilization plants. Targeting surveillance on a potentially exposed group—and sensitive populations within groups, such as people with preexisting health problems—requires identification of group members. Demographic information also must be collected to allow for comparison of the cohort's injury and illness rates to expected rates for a group with similar demographics. Records of identifying information allow for longitudinal follow up of long-latency health outcomes and for notifying participants of indications that they should take actions to protect their own health.

Exposure assessment is a critical component in determining whether engineered nanomaterials pose safety or health risks for people in locations other than where the materials are produced, transported, and handled in occupational settings. Exposure assessment encompasses a source, a receptor, and the processes and transport mechanisms that comprise the pathway(s) between them. Knowledge about the sources of engineered nanomaterials and the pathways through which they have the potential to be transported is essential for identifying population groups and environments that may be exposed to them.

Sources of engineered nanomaterial emissions to the environment can be characterized in a number of ways, such as the following:

1. Type of release
    a. Point, area, or fugitive emission from a manufacturing facility, research facility, distribution channel, or disposal activity
    b. A component of a pharmaceutical or other medical use product
    c. A component of a consumer or other product
2. Receiving medium
    a. Air
    b. Water
    c. Land
    d. Internal organ or tissue of a human or ecological receptor
    e. External membrane or skin of a human or ecological receptor
3. Location of release and its proximity to human receptors or media (e.g., drinking water) used by populations
    a. Manufacturing or research facility
    b. Healthcare facility
    c. Home, automobile, or other personal environment
4. Manufacturing process
    a. Solid state engineering that produces engineered nanomaterials in a top-down manner through successive cycles of miniaturization
    b. Synthetic chemistry that produces engineered nanomaterials in a bottom-up manner by synthesizing compounds on the scale of a few atoms and macromolecules
5. Form of the engineered nanomaterial
    a. Nanofilms
    b. Nanowires
    c. Nanoparticles

6. Surface modification of the engineered nanomaterial
    a. Coatings that modify solubility, biological activity, charge, or other properties
    b. Stability of the coatings
7. Stage of the life cycle

The amount of information available on sources of nanomaterials is growing as a result of initiatives from entities within and without the Federal Government. The Nanoscale Materials Stewardship Program (NMSP) created by the U.S. Environmental Protection Agency (EPA) has attracted 29 participating organizations that have volunteered information on nanoscale materials used in their processes (*1*). Data collected through the NMSP indicate that metals, metal oxides, and carbon materials in the form of particles constitute the majority of engineered nanomaterials in commerce at present. Databases of publicly available information created by organizations such as Nanowerk (http://www.nanowerk.com/) and the Project on Emerging Nanotechnology (PEN) (http://www.nanotechproject.org/) also provide information on potential sources of engineered nanomaterials in the environment, including the types of materials in commerce, locations where engineered nanomaterials are used, and products that contain engineered nanomaterials. EPA has indicted that it will continue to consider other sources of information in addition to the NMSP to address potential gaps between the number of commercially relevant nanoscale materials and submissions to the NMSP (*1*).

A large number of different types of nanomaterials are being manufactured; therefore, the phrase "produced in significant volumes" may mean something different for nanomaterials than for other products. There are probably a few specific compounds (e.g., silver, carbon fullerenes) that are produced in large enough quantities that they warrant separate, specific attention. Many other nanomaterials are produced in small quantities, but their combined total could be defined as a significant volume. Therefore, the Research Need 2 group suggested creating two different strategies for focusing on nanomaterial risk research. The first is to look at individual materials that are being produced in large quantities. The second is to group materials that are similar (e.g., in terms of physical properties and/or uses) that are produced in lesser quantities, but whose total production is large. As the field of nanotechnology evolves and our understanding of the associated risks increases, it is likely that the definition of "significant volume" will also change. Conclusions, strategies, and protocols will have to be revisited on a regular basis.

Carbon fullerenes are one specific type of nanomaterial that may become very important to society in the future. Carbon fullerenes have a lot of uses, including some in the medical field and in industry (i.e., electronics). Their potential for a broad array of uses makes it likely that they will be produced in larger volumes than nanomaterials with more limited uses. Fullerene risk research would need to address how the materials move within the human body (i.e., as a result of medical uses) and how they move through the environment. Carbon nanotubes may be another such versatile material. Other common nanomaterials include calcium oxides, carbon products, iron, metal oxides, nanoperoxides, cerium oxide, silver, titanium dioxide, and zero-valent iron (ZVI).

The magnitude of engineered nanomaterials emissions to the environment from each source and stage in the life cycle has yet to be characterized from the public information that is available at present. Nonetheless, the use of free nanoparticles and nanotubes in consumer products such as clothing to give garments stain-resistant properties, in baby toys as an antibacterial agent, in dietary supplements, in makeup, and in aerosol products likely results in points of exposure. Such varied uses mean all human exposure pathways must be considered (inhalation, ingestion, absorption, etc.). Human and environmental exposure scenarios will vary depending on the product and how it is used and disposed of. Consumer exposure through use and misuse of products is not well understood. One study showed that nanosilver particles on socks came free after several cycles in the washing machine. Does this pose a risk for the consumer? What about nanoparticles that are contained in a polymer matrix? Does the matrix provide an inescapable structure for the nanoparticles? Some materials may present low risks to consumers, while others present high risks. Consumers may also inadvertently create nanoparticles, such as through the use of aerosol spray cans, from products that do not themselves contain nanomaterials.

Increased availability of information on sources of engineered nanomaterial use and emissions is important to identify populations at risk of exposure. Numerous existing emissions inventories and databases have proven to be useful for understanding potential exposures for other chemical substances. The environmental health community needs to explore whether emissions information for engineered nanomaterials can be added to information sources such as the Toxics Release Inventory, National Emissions Inventory, Clean Air Markets database, and permits granted under the National Pollutant Discharge and Elimination System.

Identification of populations that may be exposed to engineered nanomaterials also requires knowledge of the dominant processes that influence the transport and fate of these materials. Research is needed to understand how engineered nanomaterials differ from larger materials in properties that influence which population groups are at risk of exposure. For example:

- Will engineered nanomaterials in air coagulate and transform into accumulation model particles like other aerosols?
- Will engineered nanomaterials in water coagulate and deposit like many other suspended solids?

Preliminary research indicates that at least some engineered nanomaterials, such as multiwalled carbon nanotubes, may be suspended by natural organic matter in surface waters and therefore be available for transport over greater distances than larger materials suspended in water. Similarly, the extent to which the physico-chemical properties of engineered nanomaterials may have changed from their manufactured state has not been studied extensively at this time. However, changes in effective particle size as a result of coagulation or chemical properties as a result of instability in surface coatings could have a significant effect on potential exposure and dose.

Mathematical models can be used to simulate emissions and transport of engineered nanomaterials from sources and therefore estimate exposure to population groups. A number of modeling tools developed for single-media and multimedia chemicals may be applicable to assessing potential exposures to engineered nanomaterials. The validity of applying these tools to engineered nanomaterials depends upon the extent to which the key processes that influence their transport and fate are reflected in air models such as AERMOD, CMAQ, and CALPUFF; water models such as PRZM, EXAMS, and EPANET; and exposure models such as HEM and SHEDS. Like models that are currently used to assess pesticide exposure, modeling analyses of engineered nanomaterials may require the use of new or proprietary product information disclosed to regulatory agencies as confidential business information.

Measurements of engineered nanomaterials in environmental media such as air, water, soil, and food can also be used to infer useful knowledge about transport and fate as well as to identify population groups who may be exposed. Federal and state environmental agencies operate a large network of routine monitoring programs at present. A relevant question therefore is, "Can engineered nanomaterials be included in existing routine monitoring programs such as the State and Local Air Monitoring Sites (SLAMS), National Air Monitoring Stations (NAMS), Speciation Trends Network (STN), Interagency Monitoring of Protected Visual Environments (IMPROVE), and Clean Air Status and Trends Network (CASTNET) for air; National Aquatic Resource Surveys and municipal drinking water assays for water; and Total Diet Study and Pesticide Data Program for food and beverages?"

The specificity of existing measurement methods to engineered nanomaterials is a critical cross-cutting issue with regard to the utility of measurements for identifying population groups exposed to engineered nanoscale materials. For example, what techniques are appropriate or needed to:

- Distinguish engineered from nonengineered nanoscale materials in the environment?
- Distinguish among different types of engineered nanomaterials?
- Distinguish constituents of an engineered nanomaterial (e.g., a metal) from the sources of the same element or molecule?

The challenges to measurement-based approaches for identifying populations at risk of exposure are similar to those for understanding aggregate and cumulative exposure to pesticides as required by the Food Quality Protection Act. The complexity of these challenges is exacerbated by the potential for numerous types of metrics to be determined for engineered nanomaterials such as mass, size, shape, surface area, charge, and composition. Although the nano-monitoring field is in the early stages of development, numerous monitoring techniques are being explored:

- Identifying easily detectable surrogates for nanoparticles (possibly a physical effect of nanoparticle presence)
- Modifying existing ultrafine particle detection methods (air)
- Labeling nanomaterials to track how they move through the environment (lab only)
- Using carbon filters
- Using electron microscopy (qualitative data only)

The National Institute of Standards and Technology (NIST) is modifying some methods that are useful for detecting nanomaterials in solutions. The biggest challenge is that these methods, which work in a lab or in simple solutions, have not worked well in the field.

Direct measurement of substances in people and other organisms has proven to be useful for understanding status and trends in exposure on a population scale, the potential for differential exposure patterns among subpopulations, and linkages between exposure concentrations in the environmental media and internal dose. Biological markers of exposure to engineered nanomaterials are likely to be fundamentally different from the existing battery of analytical chemistry tools applied to elements and organic substances at present. For example, engineered nanomaterials may exhibit optical or electrical properties that produce a signature detectable by novel imaging techniques. Similarly, engineered nanomaterials may cause specific biomarkers of effect that can be associated with levels of exposure or dose. *Daphnia* have a detectable reaction in their gut when they have consumed nanotubes. Other useful biological reactions to nanomaterials almost certainly exist, but have yet to be identified. In identifying them, the focus should be on potential biomarkers that do well at reflecting a particular type of nanomaterial. Plants may be a good group to pursue. One specific idea is to identify an element that is found in a nanomaterial and also in low levels in an organism. Increases in the level in the organism may indicate an exposure event. Simple environmental tests could be designed from these results. Tools such as these may become available through research and used to determine if a population or ecosystem has been unintentionally exposed to engineered nanomaterials.

The information needed to strategically design research studies intended to advance knowledge about populations likely exposed to engineered nanomaterials is growing rapidly. Increased participation in voluntary reporting programs such as the NMSP and others will improve the ability to discern geographic areas where engineered nanomaterials may be emitted to the environment, consumed as ingredients of products, and disposed of in solid waste or wastewater. Detailed information may be available on engineered nanomaterial use within the Federal Government through records maintained by individual departments (e.g., Department of Energy) or agencies.

New information on use patterns of consumer products obtained through population-based surveys or other means would help to refine understanding of population subgroups more likely to be exposed to certain nanomaterials. Consumer tracking may be another way to discover adverse side effects of nanomaterials. The manufacture and sales of nanotechnology could be recorded for several years. Large retailers could be approached (e.g., Walmart) to see if they would share data about their products. In general, retailers keep very good track of product production and sales and where these are occurring. The challenge is to convince them to share the data with the scientific community. Another approach may be to use North American Industry Classification System (NAICS) codes to create a map (this may be more useful in the future if a code is designated specifically for nanotechnology). Simultaneously, additional data about patients could be collected,

such as the patient's place of work, geographical location (both home and work), etc. These data sets could be combined to look for patterns of health or environmental problems associated with nanotechnology.

References

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State of the Science

In discussing Research Need 2, "identifying population groups and environments exposed to engineered nanoscale materials," the following considerations should be taken into account, as noted in the 2006 NNI document, *Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials*:

> "Groups potentially exposed to nanomaterials include patients, consumers, and neighbors of production or utilization plants [and disposal sites]. Targeting surveillance on a potentially exposed group—and sensitive exposed populations within groups, such as people with preexisting health problems—requires identification of group members. Demographic information also is collected to allow for comparison of the cohort's injury and illness rates to expected rates for a group with similar demographics. Records of identifying information allow for longitudinal follow up of long-latency health outcomes and for notifying participants of indications that they should take actions to protect their own health." (*1*)

We must look beyond traditional nanomaterial occupational exposure and focus on consumers, patients, neighbors, etc. Once the [engineered] nanomaterial has left the factory, it is likely to morph into something different, especially if it is not used for its intended purpose. We must prioritize research and design a more systematic approach for identifying biomarkers. Research and data collection efforts should be directed towards nanomaterials of concern. We must identify and make effective use of existing data sources (patient admission forms, patents, consumer data, Internet queries, Small Business Administration information): in other words, mine data sources. Cross-disciplinary collaborations (government, nongovernmental organizations, industry, academia) are essential to developing safe nanotechnology practices. It is critical to promote better communication among these groups and foster collaborative relationshipss.

Challenges

Is it possible to identify which engineered nanomaterials are likely to be produced in significant volumes?

As Dr. MacIntosh wrote earlier in this chapter (p. 24),

> "A large number of different types of nanomaterials are being manufactured; therefore, the phrase 'produced in significant volumes' may mean something different for nanomaterials than for other products... The Research Need 2 group suggested creating two different strategies to focus on nanomaterials risk research. The first is to look at individual materials that are being produced in large quantities. The second is to group materials that are similar (e.g., in terms of physical properties and/or uses) that are produced in lesser quantities, but whose total production is large. As the field of nanotechnology evolves and our understanding of the associated risks increases, it is likely that the definition of 'significant volume' also will change. Conclusions, strategies, and protocols will have to be revisited on a regular basis."

For example, carbon fullerenes are a type of nanomaterial with a high potential for extensive uses in the future in a variety of applications in medicine, electronics, and construction. As such, fullerenes are more likely to be produced, shipped, and used in larger volumes than nanomaterials with more limited uses. Fullerene risk research would need to address how the materials move within the human body as a result of medical uses, their fate and transport through the environment, and their potential for putting humans and the environment at risk for exposure.

Similarly, carbon nanotubes and nanoscale silver are likely to be highly versatile materials, resulting in a large environmental and consumer presence. Other

nanomaterials expected to be widely manufactured are calcium oxides, metal oxides, nanoperoxides, cerium oxide, titanium dioxide, and zero-valent iron.

What are the points (physical and temporal) at which humans are likely to be exposed to engineered nanomaterials?

Nanomaterial risk must be characterized at every stage in the life cycle of a product. Risks may vary depending on the exposure scenario. For example, manufacturing a product presents different risks than using the product (intended and unintended uses) or disposing/recycling the product. Risk will be both a function of the physical characteristics of the nanomaterial and the exposure scenario.

Because of their wide-ranging useful properties, nanomaterials are incorporated in a wide array of products, including clothing, dietary supplements, makeup, baby toys, aerosol products, and many others. Such varied uses mean all human exposure pathways must be considered (inhalation, ingestion, absorption through the skin, etc.). Human and environmental exposure scenarios will vary depending on the product—how it is manufactured, transported, used, and disposed of.

Concern tends to focus on worker exposure during product production. Companies are not currently required to report their use or generation of nanomaterials, and these processes are often proprietary and not readily shared. The research community has many data needs; the workplace is the exposure scenario about which we have the most information.

More information is needed to be able to understand consumer exposure through use and misuse of products. Does the potential for silver nanoparticles on socks to come free after several cycles in the washing machine pose a risk for the consumer? When nanoparticles are contained in a polymer matrix (e.g., in optical communications, microelectronics and bio-engineering applications), can the nanoparticles escape the matrix? Consumers may inadvertently create nanoparticles, such as through the use of aerosol sprays, from products that do not contain nanomaterials. Ultimately, some materials may present low risks to consumers while others are high.

Little is known about the fate of nanomaterials in the environment. Decomposition, combustion, ultraviolet light exposure, and other processes may change nanomaterial characteristics or create unexpected environmental and human exposure pathways. For example, the disposal and environmental fate and transport of a sunscreen product containing engineered nanomaterials could lead to engineered nanomaterials in drinking water.

Assessing nanotechnology exposure is challenging; as with any exposure scenario, there are many variables. Distinguishing environmental contaminants from background is a further challenge, but the challenges of detecting and characterizing nanomaterials exponentially increases the complexity of evaluating exposure to, and risk from, engineered nanomaterials. One approach may be to begin research by assessing nanomaterials in controlled exposure scenarios, such as in hospitals, workplaces, or disposal sites.

At the points of exposure, will engineered nanomaterials have significantly changed from their manufactured states?

Through agglomeration, aggregation, chemical transformation, etc., engineered nanomaterials may have significantly changed from their manufactured states. As the scientific community researches whether nanoscale materials pose different risks than those in their macroscale form, we must discern the specific physical characteristics of nanomaterials that govern their unique behavior. Little is known about nanomaterial transformation over time and with exposure to different conditions, but we do know that the physical states of nanomaterials change under different conditions. For example, certain nanoparticles aggregate very quickly and transport like larger-scale constituents. But as we have found with airborne particulate matter, there is no direct relationship between particle size and environmental transport. Furthermore, manufacturers engineer nanomaterials to alter certain characteristics, often making nanoparticles less likely to agglomerate and more likely to travel farther in organisms and the environment. More research is needed to characterize nanomaterial transport before we can predict and model nanomaterial transport. In addition to physical transport, research is needed on environmental transport, including bioavailability. We need to learn how nanomaterials are taken up by biota and how they travel through the food chain. This biological

fate and transformation research will inform understanding of nanomaterial transport, in addition to helping research into biological effects.

How can unintentional exposure to nanomaterials be detected and measured?

Currently, it is not possible to determine if a population has been unintentionally exposed to engineered nanomaterials; the Research Need 2 group was not aware of any situation in which an engineered nanomaterial had been detected in the environment. Much research is being conducted on applying traditional detection and monitoring techniques to engineered nanomaterials. Several laboratory techniques exist, and NIST is working to develop methods. However, inexpensive, portable detection approaches for environmental detection and monitoring are not known at this time. One possible approach is to find surrogates for nanomaterials that can help in their detection, for instance, by a physical effect from the presence of a nanomaterial. Another possibility is labeling engineered nanomaterials, such as with radioactive tracers, to track how they move through the environment, and generalize that information to predict transport in the environment.

Clearly environmental and human exposure studies are needed. Existing data sets and data collection sources may provide valuable information. For example, useful nanoparticle air concentration data may already exist in information collected for particulate monitoring. Furthermore, there may be additional questions that could be added to yearly air monitoring surveys. Workplace studies could include personal worker monitors, workplace monitoring, and long-term health studies that track worker exposures and effects. Environmental studies could monitor nanomaterials that are not common in the natural environment, to track environmental fate and transport of nanomaterials. These could also be used for exposure screening in humans, the environment, and other organisms.

Is it possible to differentiate between exposures to engineered nanomaterials and naturally occurring nanomaterials?

Presently there is not a way to distinguish between exposure from engineered nanomaterials and those that are naturally occurring. Experiments to look for broad patterns could be designed that compare naturally occurring nanomaterials with engineered ones. Because nanotechnology is being actively developed in Europe as well as in the United States, comparative research between the two regions could be productive.

At a smaller scale, background levels of naturally occurring and engineered nanomaterials could be measured. Biological effects in specific organisms could be quantified (e.g., *Daphnia* gut reaction). Nanoparticle creation processes could be studied. For example, how many nanoparticles are created when using aerosol sprays that either contain or don't contain nanomaterials?

Opportunities

Is it possible to mine existing data to identify exposed populations?

What existing data (e.g., hospital admission statistics, industrial manufacturing records, consumer use data, etc.) can be mined to identify exposed populations and correlate exposure to potential effects?

Insurance companies are in the business of risk management, and some of them have begun collecting data about the use of nanotechnology at insured companies. The information ranges from the type of material produced and/or used to what the material is being used for (manufacture, sales, application—e.g., makeup demonstrations—etc.). Insurance company surveys could also document workplaces with no nanomaterial exposure, best practices for controlling exposure, and relative (or actual) levels of exposure, which could be useful for correlating exposure and potential health/environmental effects. Most information collected by insurance companies is privileged, but it may be possible to obtain access to aggregated data that does not identify specific companies or industries.

Consumer tracking may be another way to discover adverse side effects of nanomaterials. The manufacture and sales of nanomaterials could be recorded for several years. Simultaneously, additional data about patients could be collected (patient place of work, geographical locations—home and work, etc.). These data sets could be combined to look for patterns of health or environmental problems associated with nanotechnology.

Internet searches could also be a potential source of nanomaterial exposure information. For example, by keeping track of where people are doing searches about flu symptoms, the spread of the flu can be very accurately tracked. Something similar may be true for nanomaterial exposure, although the group was not exactly sure how it would work at this point in time. This idea would need to be more fully developed.

Can research studies be strategically designed to examine likely exposures to engineered nanomaterials and identify discernable geographic areas where given nanomaterials are manufactured, used, consumed, and/or disposed?

To target nanomaterial production, the sources mentioned in the breakout session (DOE, Resource Conservation and Recovery Act) can perhaps provide relevant information. Also, the Woodrow Wilson Research Center maintains a map that shows where nanomaterials are manufactured. The map is created by identifying products that contain nanomaterials, but it is not comprehensive because there are no Federal or state requirements to report the use of such materials. Another approach may be to use NAICS codes to create a map (this may be more useful in the future if a code is designated specifically for nanotechnology).

For consumer use of nanomaterials, retailers could be approached to share the geographic data they already collect regarding consumer and product purchase patterns. It may also be viable to analyze for consumer and social patterns that indicate product use, such as sunscreens at outdoor recreation areas, or industrial coatings in urban areas.

What biomarkers can indicate exposure?

Daphnia have a detectable reaction in their gut when they have consumed nanotubes. Other useful biological reactions to nanomaterials almost certainly exist but have yet to be identified. In identifying them, the focus should be on potential biomarkers that do well at reflecting a particular type of nanomaterial. Plants may be a good group to pursue. One specific idea is to identify an element that is found in a nanomaterial and also in low levels in an organism. Increases in the level in the organism may indicate an exposure event. Simple environmental tests could be designed from these results.

Are there population subgroups more likely to be exposed to certain nanomaterials?

It is almost certainly the case, as suggested in the previous paragraphs, that highly exposed groups could be identified using production and consumer information, as well as by conducting life-cycle analyses to determine the physical locations of the distribution, transport, disposal, use, and reuse of engineered nanomaterials. Examples of population subgroups more likely to be exposed to nanomaterials are workers at nanomaterial production plants, residents living along distribution routes, consumers using nanomaterial-containing products, workers and residents at disposal sites, consumers of treated municipal wastewater, and users of nanomaterial-containing recycled products.

Summary

To identify population groups and environments exposed, participants first considered likely engineered nanomaterial candidates and recommended looking both at individual engineered nanomaterials produced in large quantities and at engineering nanomaterials sharing similar properties produced in lesser quantities, but whose total production is large. Participants noted the need to identify exposure over an engineered nanomaterial's life cycle, and the need to develop the capacity to distinguish exposure to engineered nanomaterials versus background contaminants. Little is known about nanomaterial transformation over time, and establishing unintentional exposure is not currently possible. There is a need for environmental and human exposure studies. Useful information also may be drawn from existing data on, for example, particulate monitoring and by mining existing data sets.

Recommendations

- Prioritize research needs for nanomaterials by:
  - Looking at individual materials that are being produced in large quantities.
  - Grouping similar materials (in terms of their physical properties and/or uses) that are produced in lesser quantities, but whose total production is large.

- Begin immediately both short-term and long-term environmental and human exposure studies that can be based on existing data and collection methods (i.e., nanomaterial emissions).
- Focus biomarker development/discovery on markers that do well at reflecting a particular type of nanomaterial.
- Use existing databases (sales, insurance, DOE, patents) to answer exposure questions.
- Use consumer tracking to establish connections between engineered nanomaterial exposure and adverse human/environmental effects.
- Identify potential risk groups by using product databases to show subpopulations that are likely to be using products containing nanomaterials.
- Prepare a state-of-the-science paper in tandem with a national science survey (audience is everyone—broad audience, public, science, etc.); trade associations could be used as mechanisms to obtain information from industry.
- Increase "life cycle" grants (i.e., go beyond occupational exposure) to look at exposures throughout a nanomaterial's life cycle; use joint interagency solicitations to expand interdisciplinary collaborations.
- Broaden the number of agencies involved in interdisciplinary research and solicitations.
- Bring in industry by providing incentives (marketing or tax breaks or awards) and incorporating measures that respect confidentiality and liability considerations.
- Proceed with instrumentation development and standardization identification.
- Implement "lunch and learn" brown bag lunch series (with free food) to promote discussions among different sectors.

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4. *Research Need 3:* Characterize Exposure to the General Population from Industrial Processes and Industrial and Consumer Products Containing Nanomaterials

Guest Speaker/Co-Chair: **Paul Lioy (Rutgers University)**
Government Co-Chair: **Treye Thomas (CPSC)**
Rapporteurs: **Joe Cresko, Gina Schatteman (AAAS Fellows)**

Introduction

Key Points

In order to assess nanomaterial exposures to the general population from industrial processes and consumer products, further studies are necessary to characterize and detect nanomaterials in biological matrices and to understand transformations of nanomaterials during transport in the environment and in human bodies. More studies should be conducted looking at emissions and human contact during normal use and after wear-and-tear have degraded a product, and at human contact during repeated exposures. In the long term, engineered nanomaterial exposure assessment models should be developed. Existing models developed for traditional chemicals could be modified to serve this purpose. To facilitate this process, critical exposure descriptors need to be identified.

Participants

In addition to the co-chairs, rapporteurs, and NNCO representative, 25 individuals participated in one or both of the Research Need 3 breakout sessions. Participants included eight representatives from EPA; four representatives from CPSC; two representatives from NIST; two representatives of foreign government organizations (European Commission, Danish EPA); two representatives of private business (Maya Tech Corp., Bio Nano Systems); one representative each from DOE, FDA, the National Library of Medicine (NIH), the U.S. Army, and USDA's National Institute of Food and Agriculture (NIFA); one representative of academia; and one private individual. These participants came from the fields of chemistry, environmental engineering, microbiology, law, economics, health science, toxicology, and EHS management, among others.

Invited Presentation

Comments on Nanotechnology in Exposure Science

Paul J. Lioy, Rutgers University

The issue of the general population's exposure to engineered nanoparticles has not been the subject of much research to date. This is in contrast to the studies that are being done on the exposure of workers during the production of engineered nanoparticles, and the work that is being done on the toxicology and the fate of nanoparticles in the ecosystem. Worker exposure and toxicology and fate studies are important; however, they leave out the point of contact and the intensity of contact (*1*, *2*) of the public with consumer products that can release nanoparticles that are embedded in the product (e.g., a tennis ball) or are an integral part of the product (e.g., facial cosmetics) during use. Thus, to continue with these two examples, the types of exposure studies that are necessary include emissions and human contact during normal use, after wear and tear has degraded the product, and during repeated use. The results must then be coupled with relevant product studies on similar exposure patterns and intensities in animal systems.

In a review published in 2006, Davies indicated that, at that time, "[m]any of the current commercial applications of NT [nanotechnology] were high-exposure uses such as cosmetics, clothing and drugs" (*3*). Since there are now over 800 consumer products (http://nanotechproject.org), the issue of consumer exposure should be revisited for additions and modifications. Davies also indicated, "The only way to deal with potential adverse effects of NT in most cases will be to design the product or tailor the use of the material so that the NT material does not get into the environment or the human body in the first place" (*3*) This is true, but as we know, these materials are in products that are in close contact with the human body, therefore, the issue is to achieve *de minimis*[1] exposure and, when coupled with any identified hazard, to achieve *de minimis* risk to the consumers. Also, as noted by Thomson *et al*. (*4*), "the population exposed to nanoscale materials in consumer products would be representative of the entire population…, because many of these products appeal to a diverse range of individuals." It would be expected that the consumer base will increase.

The National Nanotechnology Initiative has indicated in its 2008 NNI EHS strategy (*5*) that understanding the health and safety impacts of nanotechnology for researchers, workers, consumers, and the public is a priority: "Responsible development of nanotechnology includes supporting fundamental discovery-based research as well as targeted research and other activities to understand potential risks associated with the manufacture and use of engineered nanoscale materials. Since the inception of the NNI, the participating agencies have supported research to safely develop and apply nanotechnology for societal benefit and economic growth, as well as research to better protect public health and the environment" (p. 3).

As stated previously, examining our contact with nanoparticles directly, or indirectly through carrier materials such as food or clothing, is necessary, and was mentioned by Nel *et al*., in 2006 (*6*). A report by the Nanomaterial Toxicity Screening Working Group of the Risk Science Institute also stressed the need to assess exposure to nanoparticles via various exposure routes, including via airborne (inhalation) route (*7*).

In most of the studies on health effects of nanoparticles, the particles in question are produced and delivered along the exposure route under study and are not a part of the complex environmental matrix where such particles would be encountered in the real world and during actual usage. Thus, it is important to obtain accurate exposure characterization and to examine the release of nanoparticles and associated exposures in a way that simulates the actual handling and use of nanomaterials and their products. Such studies would be able to determine and quantify human exposure to engineered nanoparticles at home and in the "personal cloud" that surrounds people over the course of the day. Once the information on exposure is obtained, the results can be used for critical risk assessments or appropriate health studies designed to assess health risks due to

1 According to the 2007 IUPAC Glossary of Terms Used in Toxicology [*10*], risk *de minimis* is "risk that is negligible and too small to be of societal concern (usually assumed to be a probability below 10-5 or 10-6); [it] can also mean 'virtually safe'."

nanotechnology-based products in general commerce and manufacturing. Risk assessments up to now only have good quantitative information on toxicity and not, for the second half of the risk analysis, human exposure.

An investigation of nanoparticle release during manufacturing found that when agitation is present, unrefined material can release such particles into the air (*8*). However, up to this point, very little attention has been paid to the investigation of nanoparticle release from consumer materials. The Woodrow Wilson International Center of Scholars estimates that there are more than 800 nanotechnology-based consumer products (http://www.nanotechproject.com/) in a variety of categories (*9*). As the use of such products increases, so does the potential for consumer exposure to nanoparticles, especially as the products age and disintegrate over time. For some products, such as many cosmetics, their typical application route is dermal. For others, such as sprays, the airborne route is most likely, due to their specific application mode, but the frequency and intensities of such contacts are unknown. The potential for exposure will be determined and quantified by measuring the concentration as well as size, surface area, and volume distributions of the nanoparticles released from various products, with surface area playing the most significant role for the toxicity of the manufactured product.

As we are aware from aerosol science, however, nanoparticles have a high affinity for each other and will quickly coagulate; therefore, compared to the contact that occurs during production, the particle size distribution produced by emissions from consumer products will be different. The particle size distribution presented at the time of contact and exposure will probably be in the 0.1–2.0 nm size range, which will have different impacts if inhaled, ingested, etc., and the particle variable of concern may be mass-deposited along a route of exposure. Of course the sizes will be much larger for dermally applied materials and will be associated with strong forces necessary to have a cream. A point that has not been thoroughly addressed in the literature is whether or not, or what percentage of, the carrier nanoparticles will be able to be transported below the epidermis and distributed throughout the body, and whether or not this is of any consequence to health. Since dermally applied materials—as well as sprays and brush-applied cosmetics—are repeated applications, the issue may be bioaccumulation over a long period of frequent use at low concentrations, and not the impact of a bolus of material.

The nature of these coagulated materials will also need investigation to determine whether or not they can be re-released as smaller agglomerates/aggregates after entering the body because of weak binding forces. This would facilitate entering the circulatory system at some point after ingestion or inhalation, etc. Included is the issue of bioavailability for each route of exposure.

Implementation Steps

At the current time, any exposure studies will require a series of carefully designed implementation steps. The first step is to complete a taxonomy of nanoparticle products. This should be separated first by product type and use, then by the most likely intended and unintended routes of exposure, by the population that will use the products, and finally, by the anticipated frequency and duration of use.

The second step in this process should be the design and completion of studies that simulate exposure for realistic use patterns of classes and type of consumer products. The key here is the word "realistic." It is not sufficient to use passive or unconventional approaches, since such approaches will increase uncertainties in any estimates of exposure. Thus, accurate product use information is essential for designing any experiments with clothing, cosmetics, tennis balls, etc., with high-end users being the individuals whose product-use activities need to be mimicked. In addition, unintended uses that could lead to high exposure should be documented.

Part of the third step of the process will be the characterization of emissions, but the experiments must be specifically designed to determine the emission rates during product use. Thus, these experiments can be used to look at a variety of emission characteristics during normal product use, for example, emissions when the product is first used, and then the emissions after the product has been in use over time or after multiple applications. The exposure characterizations could also be influenced by emissions after multiple applications

during a short period of time. Thus, intended product use information and/or surveys of actual usage are essential before such experiments are conducted to obtain information that can be generalized to the public at large. Pilot studies on emission rates can be conducted before survey information is available. In fact, in some cases such pilot studies can give information on whether or not detailed studies are necessary or can be ignored because of lack of potential exposure.

The fourth step is measuring the duration of the activities and release of the nanoparticles or agglomerates/aggregates from the products. In some circumstances these will be short-duration contacts and exposures, but the frequency of these contacts could also be high, for example, in the case of facial cosmetics. Other contacts will be less frequent and related to the so-called "pigpen effect," named after Charles Schultz's Peanuts' character Pigpen, who always had a cloud of dust surrounding his body. In the 1970s Lance Wallace coined the phrase "personal cloud" to suggest that there is a cloud of particles and gases that can be quantified around a person. The term is an adequate representation of the pigpen effect and, if properly examined, it can describe many types of processes and distributions that can lead to contacts with particles and gases. In the case of nanoparticles or their agglomerates, one would attempt to measure the concentration of these materials around the head or the rest of the body, and then to use this information to estimate the potential full dose.

The fifth step that should be considered is determining the bioaccessibility of nanoparticles in both the lung and the digestive system. Such studies use simulated biofluids to examine the ability to release nanomaterials from a matrix or from coagulated particles that are deposited intact as agglomerates/aggregates in the lung or in the digestive system. These data can assist in designing studies that can look at the transport of the releasable materials into the circulatory system and then into individual organs.

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State of the Science

Most of the workshop participants agreed that assessing human exposure to manufactured nanomaterials may pose a challenge for exposure scientists, including the need to develop unique methods that can characterize and quantify nanomaterials in a variety of media such as air, water, sweat, etc. In addressing nanomaterial exposures, there are many physico-chemical factors to consider in addition to size, including shape and surface area. Techniques do exist to measure these factors, but how do characteristics of particles change during use (e.g., release from textiles)? Analytical methods necessary for conducting exposure measures in the general population do exist, but they are not always commercial methods that are widely available. There are still many questions regarding what analytical methods are fully validated for these types of studies. How are methods fine-tuned to simulate use (e.g., simulated urine or saliva)? Particle size can be measured very accurately, but determining the composition of a nanomaterial is often difficult and requires sophisticated instrumentation to measure composition and morphology. Adequate testing is necessary not only on a product as finished or presented by the manufacturer, but also throughout the product life cycle to assess changes from product use. For example, for clothing treated with nanoparticles, the durability of these particles during laundering is a key question.

Challenges

In general, concerns of characterization and detection seem to focus on air, but we are looking at air, dermal, and ingestion means of exposure. If nanoparticles can cross membranes (blood/brain, placenta, etc.) do technologies exist to measure these after they have entered the body, which is past the exposure stage? So, do we know where exposure is? In biology, tests for small particles (viruses, etc.) exist. Can these and other experiences guide us in the prioritization of research?

The Research Need 3 breakout group participants agreed that there is a dearth of data quantifying exposures of the *general population* to engineered

nanomaterials. Very little research can be found in the peer-reviewed literature. There are considerably more studies on worker exposure during the production of engineered nanomaterials and on the fate of nanomaterials in the ecosystem. Addressing issues of occupational and environmental exposures are important; however, they ignore the large number of individuals who may be exposed to nanomaterials through the use of consumer products. Thus, the types of studies that are necessary include emissions and human contact during normal use, emissions and human contact after wear and tear has degraded the product, and human contact during repeated applications. The results must then be coupled with relevant product studies on similar exposure patterns and intensities in animal systems.

There are a number of issues that must be assessed related not only to toxicology and exposure, but in many cases, also to the chemistry and physics of nanomaterials. More specifically, when there is an exposure event, is the exposure to individual products or to agglomerates/aggregates? How do the physics of agglomeration and deagglomeration impact exposure? Further, what are the pathways in the body? What happens when things get wet or are on the skin? If nanomaterials agglomerate in the air, what happens? When they enter the soil/atmosphere, how do fate and transport occur?

Opportunities

This workshop should start the process to develop a roadmap—a method to evaluate engineered nanomaterials from source to human exposure. EPA has supported research that focuses on fate and transport, and toxicity. The Research Need 3 group suggested that there should be a major overall call from multiple agencies to obtain resources and support exposure studies for the general population. EPA has requested additional money for these issues; people are already being exposed. When an adequate roadmap is developed, the agencies participating in the NNI should coordinate to prioritize the issues.

While developing the roadmap, several questions should be addressed. What amount of Federal funding is directed to nanotechnology-EHS research? How much of this total amount should be allocated to human exposure assessment? What information is currently reported to the government and to which agencies, and could this information be used in addressing data gaps in exposure? Is it feasible to require that recipients of Federal research money report any exposure data to EHS? The group suggested that there should be requirements on reporting back EHS information if a company gets Federal research money. Moreover, the group recommended that where it makes sense to do so, requests for applications (RFA) and requests for proposals (RFP) should require exposure measurement and reporting as part of the proposals.

Specific aspects of this roadmap plan include the following:

- **Data warehouse**. Could NIH or the NNI or another NNI agency act as a central repository? This has been done at NIH with respect to the human genome, so a model exists that the NNI agencies could emulate. Also, EPA's volatile organic compound (VOC) work (and work on other particles) could act as a template for nanomaterials.
- **Models**. Will models used for bulk-scale compounds or incidental nanoparticles (or ultrafines) need to be validated? How should they be used? What are the test methods: should existing methods be applied or new methods developed? It is likely that some combination of life cycle assessment (LCA), toxicity, and screening-level modeling will help determine the greatest potential effects.
- **Decision tree**. Can a simple test be developed for industry to determine go/no-go for a specific nanomaterial? For example, when a company has three products under development, a simple test might be able to screen them for potential toxicity and thus give direction on which to develop. ASTM International tests are a start, but specific tests need to be developed with priorities based upon use.

Summary

Assessing human exposure to engineered nanomaterials may pose challenges for exposure scientists, including in the development of unique

methods that can characterize and quantify nanomaterials in a variety of media such as air, water, sweat, etc. In contrast to bulk-scale materials, there are many physico-chemical factors to consider in addition to size, including shape and surface area, when conducting an assessment of nanomaterial exposure to the general population. Currently, very little data exists that quantifies exposures of the general population to engineered nanomaterials or the methods for conducting these types of studies. There are considerably more studies being conducted on the exposures to workers during the production of engineered nanomaterials and the fate of nanomaterials in the ecosystem.

A clear strategic plan for human health that identifies a path forward for identifying and addressing exposures to engineered nanomaterials is not available; thus, the NNI agencies should start the process to develop a roadmap as a method to evaluate nanomaterials from source to human exposure. As exposure data are developed, existing databases should be modified, when necessary, for nanomaterial studies. The Federal Government has a critical role to play, including funding exposure assessment work and producing research solicitations that promote collaboration between toxicologists, exposure scientists, and scientists from other disciplines. Manufacturers, industry associations, professional societies, physicians/nurses, and other organizations and individuals also play a role in providing information and supporting exposure studies.

Exposure assessment plays a key role in adequately addressing EHS issues associated with the use of nanomaterials and the responsible development of this technology.

Recommendations

- Develop a roadmap for exposure from source to dose.
- Decide what characteristics need to be included in an exposure database.
- Determine which, if any, existing databases can be used for exposure data.
- Develop strategies that will result in grant awardees collecting and depositing exposure data in a Federal database.
- Identify a topic and develop a test case for public outreach.
- Work with companies to decrease confidential business information (CBI) claims with respect to exposure data.
- Identify which new tools are needed.
- Develop a protocol to prioritize particles for testing.
- Identify and train people to test for exposure to engineered nanomaterials.

5. *Research Need 4:* Characterize the Health of Exposed Populations and Environments

Guest Speaker/Co-Chair: **William Halperin (University of Medicine & Dentistry of New Jersey)**
Government Co-Chair: **Paul Wambach (DOE)**
Rapporteur: **Jessica Eisner (AAAS Fellow)**

Introduction

Key Points

Employer provision of occupational medical services to nanotechnology workers creates opportunities to establish workplace health surveillance programs. Health information captured through the operation of occupational medicine programs could be analyzed to identify unexpected events or patterns of events that can be investigated to determine if they are associated with exposure to engineered nanoscale materials. The opportunities to establish health surveillance programs among the general population are more limited due to difficulties in identifying members of exposed groups and accessing their health information. The benefits and feasibility of such programs should be reassessed as more health effects information is generated. The feasibility of establishing surveillance programs for biota in nanomaterial-impacted habitats was not addressed during the Research Need 4 group's meetings. A mechanism to support and conduct both human health and environmental surveillance programs should be established for programs that are determined to have merit

Participants

In addition to the co-chairs, rapporteur, and NNCO representative, 11 individuals participated in one or both of the Research Need 4 breakout sessions. Participants included three representatives of U.S. military departments (U.S. Navy National Medical Center, and U.S. Army Environmental Command); two representatives of private industry (BASF and Occupational Health Link, Inc.); two representatives of NGOs (AFL-CIO and CropLife America); two representatives from DOE; and one representative each from CPSC and USGS. These participants came from the fields of occupational medicine, industrial hygiene, public health, toxicology, and EHS management.

Note: The focus of the Research Need 4 discussions were confined to human health and surveillance issues; the participants felt unqualified to properly address issues pertaining to health of the environment and biota or pertaining more broadly to exposure.

Invited Presentation

The Role of Epidemiology in the Prevention of Adverse Human Health Effects of Nanotechnology

Jun Tashiro, University of Medicine and Dentistry of New Jersey (UMDNJ)
William Halperin, UMDNJ, New Jersey Medical School, School of Public Health

Background

In recent years, the use of nanometer-sized particles has been increasing in a wide range of fields of science. Applications are being researched in areas such as lightweight, yet durable, materials, enhanced drug delivery, and even among cosmetic products (*1*). In particular, the healthcare industry has taken great interest in exploring nanoparticles for therapeutic applications, since these particles have been shown to behave differently from their larger counterparts, even if they share the same chemical structure. This simple principle has led many researchers to explore the vast, new field of nanomedicine (*2*, *3*). While many branches of industry, academia, and Federal grant agencies have focused their research on the potential benefits of using nanomaterials, the possibility of adverse health outcomes caused by exposure during the manufacturing, use, and disposal processes has yet to be adequately investigated (*4*, *5*). Even with the establishment of new legislation concerning increased efforts for investigating adverse outcomes, the number of and amounts of funds available for projects in hazard research are easily dwarfed in comparison to industrial research and development of new products (*1*, *6–7*). In addition, due to the wide range of heterogeneity in size, shape, chemical composition, and purpose, the task of tracking exposures to nanomaterials, particularly among workers, presents a more difficult challenge as compared to other more typical, workplace hazards (*1*, *5*). At this time, there are no definite ways of confirming the safety of individuals coming into contact with nanomaterials, primarily due to the difficulties faced in quantifying exposures and the lack of known adverse outcomes (*5*, *8*).

Under the presumption that exposure to nanomaterials may cause serious adverse human health effects, appropriate measures should be taken before manufacturing, use, and disposal become widespread. To address the growing concern over nanomaterials, an adaptive system of prevention, including research contributions from industry and academia, as well as strict enforcement of registering known exposures by regulatory agencies, must occur in concurrence with an active exchange of information through effective channels for surveillance. With the implementation of an active feedback system, a potentially disastrous outcome may be avoided (*9*, *10*). This scheme becomes especially critical at a point when the potential hazards associated with nanomaterials have yet to be uncovered (*11–13*). This section is intended to summarize the findings of the authors regarding the role of epidemiology in the prevention of adverse human health outcomes due to the manufacturing, use, and disposal of products utilizing nanotechnology.

The Cascade of Prevention and the Role of Surveillance

Occupational health prevention, as applied to the issue of nanotechnology, can be summarized using a "cascade of prevention," as shown in Figure 4.1 below (*10*, *14*).

Figure 4.1 shows that beginning with the stage of initial research and development, a potentially hazardous outcome to individuals exposed can be avoided at various levels. For example, at the "toxicologic testing" stage, the hazard–outcome relationship is confirmed, using primarily animal models (*14–16*). In further testing, the dose-response relationship is examined, with the intention of defining the minimal levels at which the adverse health outcomes may occur.

The addition of surveillance feedback loops adds an element of dynamism to the cascade of prevention. The role of surveillance in occupational health prevention is to facilitate the exchange of information backward from later steps in the cascade, with the goal of refining the process toward preventing potentially hazardous outcomes (*10*, *14*). For example, clinicians may discover a suspicious dermatitis among workers at an industrial site where individuals are frequently exposed to nanomaterials. A properly designed surveillance system would

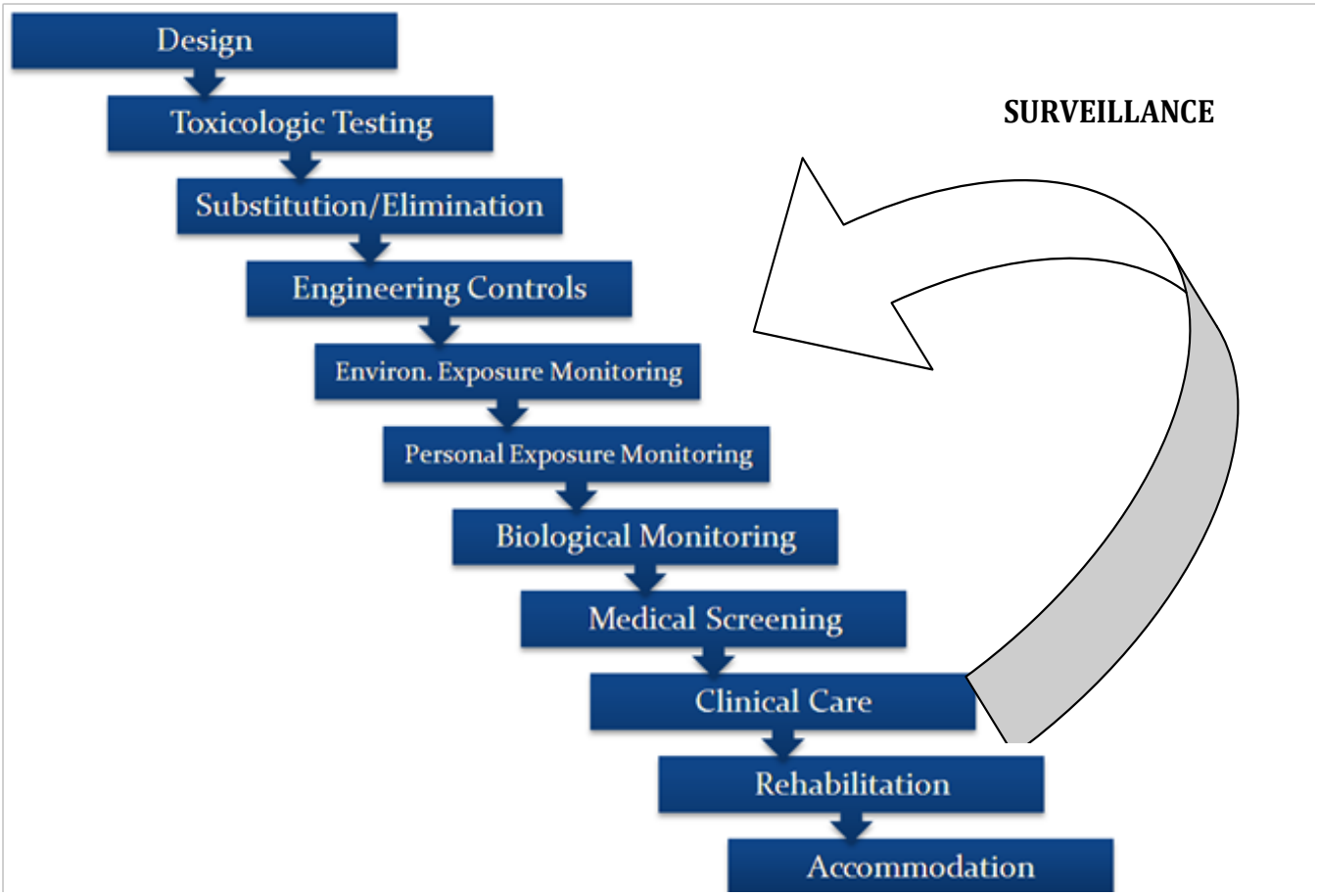

Figure 5.1. Nanotechnology-related occupational health prevention: Cascade of prevention. Adapted from W. E. Halperin, et al., Medical screening in the workplace: Proposed principles. *Journal of Occupational Medicine* 28 (8), 547-552 (1986)

channel this information back toward improving engineering controls, which may provide better protection against exposure for workers during the manufacturing process, or perhaps push for the development of personal exposure monitoring devices to accurately measure individual exposure.

Innovation in industry can take place at remarkable speed. It is the role of the occupational health community (that is, the full range of voluntary and regulatory, industrial hygiene and occupational medicine, human health effects research, and toxicological research in other species, etc.) to keep pace with industrial development, ensuring that no time or opportunity is wasted in safeguarding the health of those who manufacture and use nanotechnology. Information collected on relevant publications, grants in progress, and available grants can help gauge whether the field of occupational health is keeping pace with or lagging behind industrial innovation related to nanotechnology.

Methods

Review of Literature

Searches of published literature in the *PubMed*, *Medline*, and Cochrane Library databases were performed, using the following keyword combinations: "nanotechnology AND surveillance," "nanotechnology AND occupational," "nanoparticles AND surveillance," and "nanoparticles AND occupational." The articles considered were limited to publications in English. Duplicate references were eliminated, and unique articles were combined into a single database. To analyze these articles based on the subject of research, the following categories were used.

Systematic or literature reviews on the implications of nanotechnology

- Basic science studies for adverse health outcomes (or nanotoxicology studies)
- Basic science studies for beneficial applications
- Controlled clinical trials for adverse health outcomes
- Controlled clinical trials for beneficial applications
- Methods for occupational exposure assessment
- Methods for community exposure assessment
- Methods for environmental exposure assessment
- Development of exposure registries
- Epidemiologic studies on morbidity
- Epidemiologic studies on mortality
- Nonrelevant articles

Review of NIH Grant Awards

To gain a broader perspective of ongoing research on the subject of nanotechnology, an analysis of grants awarded by the National Institutes of Health (NIH) was performed. The organization of grant awards by category found on the NIH database was used to find studies funded for research in nanotechnology only. Yearly totals for NIH grant awards between fiscal years 2005 and 2008 were plotted. The authors also performed a cross-sectional analysis of fiscal year 2008, which detailed grant award titles and amounts within the nanotechnology category. To analyze these grant awards based on the subject of research, the following categories were used:

- Field development awards
- Basic science studies for adverse health outcomes (or nanotoxicology studies)
- Basic science studies for beneficial applications
- Controlled clinical trials for adverse health outcomes
- Controlled clinical trials for beneficial applications
- Methods for occupational exposure assessment
- Methods for community exposure assessment
- Methods for environmental exposure assessment
- Engineering research in nanotechnology
- Development of exposure registries
- Epidemiologic studies on morbidity
- Epidemiologic studies on mortality
- Nonrelevant articles
- Unknown (unable to be determined from available information)

Review of Open Federal Grant Opportunities

For further analysis of future research, open Federal grant opportunities were analyzed using publicly available databases. Searches of http://www.grants.gov, NIH, and National Science Foundation (NSF) databases were performed, using the keywords "nanotechnology" and "nanoparticles." These databases detailed grant award titles and abstract summaries. Duplicate references for grant opportunities were eliminated, and unique grant

opportunities were combined into a single database. The same categories as used for organizing NIH grant awards were used for the open grant opportunities.

Results

Review of Literature

The searches, performed on January 25, 2009, resulted in a total of 292 total references, of which 154 were found to be unique publications. The 154 publications were examined for primary subject matter using the publication's title and abstract summary, of which 27 were found to be unrelated to the subject of nanotechnology. The remaining 127 relevant articles were organized into the predetermined categories listed above. The largest category consisted of 56 articles (44.1%); these were systematic or literature reviews of current research on nanotechnology. The second largest category consisted of 36 articles (28.3%); these described basic science studies on adverse health outcomes (i.e., nanotoxicology) studies. The remaining articles fell into three categories: basic science studies on beneficial applications, 18 (14.2%); controlled clinical trials on beneficial applications, 11 (8.7%); and methods of occupational exposure assessment, 6 (4.7%). No references were placed into the remaining six subject categories. The results of the analysis are shown in Table 4.1 below.

Table 4.1. Articles Found in Literature Review Pertaining to Nanotechnology and Public Health

Type / Year	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	TOTAL
Review	0	0	0	0	1	1	2	8	14	15	14	1	56
Basic Science: Benefits	1	0	1	0	1	0	1	2	2	4	6	0	18
Clinical Trial: Benefits	0	0	0	0	0	0	0	1	4	4	2	0	11
Basic Science: Adverse Outcomes	0	0	0	0	0	0	1	2	5	11	17	0	36
Clinical Trial: Adverse Outcomes	0	0	0	0	0	0	0	0	0	0	0	0	0
Occupational Exposure Assessment	0	0	1	0	0	0	0	0	1	1	2	1	6
Community Exposure Assessment	0	0	0	0	0	0	0	0	0	0	0	0	0
Environmental Exposure Assessment	0	0	0	0	0	0	0	0	0	0	0	0	0
Exposure Registries	0	0	0	0	0	0	0	0	0	0	0	0	0
Epi: Morbidity	0	0	0	0	0	0	0	0	0	0	0	0	0
Epi: Mortality	0	0	0	0	0	0	0	0	0	0	0	0	0
Non-relevant	0	0	0	0	1	2	3	3	4	11	3	0	27
TOTAL	1	0	2	0	3	3	7	16	30	46	44	2	154

Review of NIH Grant Awards

Total grant awards for fiscal years (FY) 2005 through 2008, as found on the NIH grant awards website, are shown in Table 4.2.

Table 4.2. NIH Nanotechnology-Related Grants (USD, in millions and rounded)

Research / Disease Area	FY 2005 Actual	FY 2006 Actual	FY 2007 Actual (NIH Historical Method)	FY 2007 Actual (NIH Revised Method)	FY 2009 Actual
Nanotechnology	$165	$192	$215	$257	$304

A detailed analysis of FY 2008, for which grant title and award amount information were available, showed that NIH and its subsidiary organizations funded 962 projects categorized under "nanotechnology" in FY 2008. Of the total projects, a random sample of 198 projects (20.0%) was used to estimate the number of grant awards in each category. SPSS for Windows Version 14.0 statistical software was used for random selection of the 20 percent sample. Of the 198 grant awards analyzed, 8 were classified as non-relevant. Of the remaining grant awards, 133 (70.0%) were categorized as basic science studies for beneficial applications. This figure was used to estimate that 665 articles within the total could be placed in the same category. The same estimation calculations were performed for all categories of grants, as well as the funds, awarded by NIH in FY 2008. Table 4.3 shows the principle findings of the analysis.

Table 4.3. Sample NIH Grant Awards

FY 2008 NIH Grant Awards, by Primary Category	Sample Grants (n = 198, 20%)	Estimated Total Grants	Sample Grant Awards (USD) (n = 198, 20%)	Estimated Total Grant Awards (USD)
Field Development	5	25	$731,795	$3,658,975
Basic Science: Benefits	133	665	$39,819,190	$199,095,950
Basic Science: Adverse Outcomes	4	20	$1,486,892	$7,434,460
Occupational Exposure Assessment	1	5	$323,280	$1,616,400
Engineering	2	10	$449,722	$2,248,610
Exposure Registries	1	5	$127,015	$635,075
Non-relevant	8	40	$4,510,031	$22,550,155
Unknown	44	220	$9,651,061	$48,255,305
TOTAL	198	962	$57,098,986	$285,494,930

Review of Open Grant Opportunities

The searches for open Federal grant opportunities, performed on February 1, 2009, resulted in a total of 103 references to open grant opportunities, of which 56 were determined to be unique grant opportunities. Of the 56 opportunities, 24 were determined to be non-relevant. Following categorization of the opportunities, the largest group was composed of 27 (79.4%) opportunities in basic science research for beneficial applications. Two opportunities were categorized under "field development," and three were classified under "methods of exposure assessment." No references were placed into the remaining subject categories. Table 4.4 presents a graphical summary of the findings, organized by primary category.

Table 4.4. Open Federal Grant Opportunities, by Category

Category	Funded Projects	Percentage (%)
Field Development	2	3.57
Basic Science: Benefits	27	48.20
Clinical Trials: Benefits	0	0
Clinical Trials: Adverse Outcomes	0	0
Methods for Exposure Assessment	3	5.36
Epidemiology: Morbidity	0	0
Epidemiology: Mortality	0	0
Registries	0	0
Toxicology	0	0
Non-relevant	24	42.90
TOTAL	56	100

Analysis

Current Research on Nanotechnology

The analysis of published literature shows that a large majority of articles are reviews of literature, giving advice on approaches for addressing potentially hazardous exposures to manufacturing processes associated with nanomaterials. Meanwhile, there were no studies found among the categories involving methods for community and environmental exposure assessment, the development of exposure registries, or epidemiologic studies on morbidity and mortality. Further analyses confirm that beginning in 1998, the overall number of articles published on nanotechnology has increased steadily over time. Even in the early months of 2009, there have been two articles published on the health effects of nanotechnology. An analysis of references by category by year show increases in basic science studies on beneficial applications, as well as those focusing on adverse health effects, of nanotechnology.

An analysis of NIH grants awarded in fiscal year 2008 shows that a large number of grants are estimated to be focused on basic science regarding beneficial applications. Very few grants were awarded for research projects on validating hazard–outcome or dose–response relationships. Using data derived from the analysis of open Federal grant opportunities, similar conclusions can be drawn regarding research grants that are yet to be awarded.

Assuming that the grant opportunities analyzed will soon become grant awards, and grant-funded research will be published and entered into PubMed, Medline, and Cochrane Library databases, it is possible to foresee an exponential increase in funding and research regarding basic science studies on beneficial applications. Under the assumption that private industry research is taking similar approaches to nanotechnology, one can see that research to uncover potential hazards due to worker exposure to nanomaterials will lag significantly in upcoming years.

Future Directions

Future directions for research will be composed of two arms of prevention: proactive and reactive. From the proactive perspective, stakeholders will be required to share knowledge and resolve impediments to progress (e.g., protection of proprietary knowledge), improve toxicology and exposure assessment knowledge bases, and also control worker exposure in a prudent manner. These points should be realized with the ultimate goal of achieving a consensus on the hazard-outcome relationship, and of identifying minimum levels of exposure that will insure protection from toxicity. The reactive arm would exist to handle any unanticipated findings, such as

sentinel health events detected by occupational health clinicians, or clusters of illnesses identified by workers or their employers. This arm would exist to process "incidental" findings, which may not have been anticipated using the proactive approach or that are occurring due to failure to minimize exposure to a healthful level. Both the proactive and reactive epidemiological approaches would be facilitated by the establishment of registries of workers that would document information on occupational exposure and other personal health information that would be useful in deciphering any potential relationship between exposure and adverse health effects. Registries are also useful in facilitating dissemination of useful information to registrants or their health care providers.

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State of the Science

This breakout group addressed the state of the science in Research Need 4 (characterize the health of exposed populations and environments) by developing answers to the question, "Are there ongoing health or environmental surveillance programs that include an identifiable subset of individuals or habitats exposed or impacted by engineered nanomaterials or surrogates for engineered nanomaterials (such as ultrafine particulates like ultrafine particulate air pollution)?"

Since "surveillance" is a dictionary word with many meanings, the group agreed that its use of the word would conform to the CDC definition (Center for Disease Control and Prevention, Division of Integrated Surveillance Systems and Services; http://cdc.gov/ncphi/disss/nndss/phs/overview.htm):

> *Public health surveillance* has been defined as the ongoing, systematic collection, analysis, and interpretation of data (e.g., regarding agent/hazard, risk factor, exposure, health event) essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those responsible for prevention and control.

Challenges

Are there fundamental barriers to the operation of surveillance programs that characterize the health of exposed populations and environments that require new methods development or other research?

Surveillance is most effective when it can be targeted at groups with well-defined exposure characteristics or on health outcomes known to be associated with exposure. Poorly targeted surveillance will fail to identify adverse effects that are small or subtle. For example, an increased rate of health outcomes would be masked if unexposed workers are misclassified as exposed, and vice versa, if exposed workers are misclassified as unexposed. While granularity increases with increased ability to target, even poorly targeted surveillance is able to detect large health effects sooner than they would otherwise be detected.

A single case of an unusual illness can be significant enough to trigger more extensive investigations, including epidemiological studies. This is called a "sentinel health event." Similarly, a single large exposure excursion can be a "sentinel exposure event." Defined sentinel events are an aid to targeting. As knowledge of the health effects associated with exposure to engineered nanomaterials increase, a consensus process for establishing an agreed-upon list of sentinel health events would enhance surveillance programs. The Research Need 4 group suggested that toxicology findings of cell-mediated inflammatory responses to engineered nanomaterials indicate that a diagnosis of granulomatous lung disease would be a leading candidate for inclusion on a list of sentinel health events associated with exposures to nanomaterials. An agreed-upon list of exposure limits would also aid in targeting by identifying individuals with significant exposure.

Medical screening tests for specific health outcomes increase the value of health surveillance by identifying opportunities for improving working conditions before exposure causes clinical disease and opportunities for early medical treatment that minimize morbidity or mortality. Ultrafine air pollutants have cardiopulmonary health effects, and it is thought that unbound engineered nanoparticles will have analogous effects. Screening tests for these effects are quite limited. Tests for heart and lung disease generally detect lost function or macroscopic changes visible in X-ray studies. Tests that would detect effects earlier are desirable. Because toxicology studies are identifying specific cellular and molecular mechanisms for the heart and lung damage caused by nanoparticles, the opportunity exists to develop tests that detect cellular or molecular biomarkers of a response before damage has occurred.

Public health, environmental and occupational health protection, and healthcare delivery are the shared responsibilities of industry, state and local governments, and the Federal Government. Existing health surveillance programs have been developed to meet the needs of the groups operating the programs. As a result, there is little standardization of the data collected, the data format, or the terminology used to describe the data, which limits the ability to combine data from separate programs.

The paucity of publications or ongoing projects indicates that the community capable of conducting health and environmental surveillance is engaged

in studying other risks. Initially, requests for applications may not yield the quality of proposals desired. Attracting the health and environmental surveillance community of researchers to nanotechnology may require significant outreach. Evidence of an ongoing commitment to fund projects would help recruit researchers and students to the field. Opportunities for training that would expand the community capable of conducting this work is another important tool for recruitment.

Opportunities

Assuming agreement that significant gaps exist, are there ongoing surveillance programs that could be expanded to include individuals and habitats exposed to engineered nanomaterials?

Are there specific health effects associated with exposure to engineered nanomaterials that could be targeted for active surveillance (i.e., inflammatory responses triggered by oxidative stress)?

The Research Need 4 group identified ongoing programs that would be leading candidates for expansion to include engineered nanomaterials used in consumer products. The National Health and Nutrition Examination Survey (http://www.cdc.gov/nchs/nhanes.htm) (NHANES) and the National Health Interview Survey (http://www.cdc.gov/nchs/nhis.htm) (NHIS) have the potential to begin associating self-reported use of engineered nanomaterials in consumer products to health information. The mission and function of the National Institute for Occupational Safety and Health (NIOSH) Division of Surveillance, Hazard Evaluations, and Field Studies includes the conduct of industry-wide studies (e.g., see http://www.cdc.gov/niosh/contact/im-dshe.html). This group's existing statutory authority to access records and worksites and protect privacy and trade secrets makes it the logical choice for conducting or managing industry-wide health surveillance and exposure registry projects. Similarly, the Agency for Toxic Substances and Disease Registry (http://www.atsdr.cdc.gov/) (ATSDR) has the statutory mission and authority to conduct health surveillance in communities impacted by nanotechnology.

Are there specific health effects associated with exposure to engineered nanomaterials that could be targeted for active surveillance (i.e., inflammatory responses triggered by oxidative stress)?

There also is a wide range of programs for investigating accidents, injuries, and illness outbreaks that are being conducted by industry, state and local governments, and the Federal Government. Poison control centers (e.g., see American Association of Poison Control Centers, http://www.aapcc.org/DNN/) and the CPSC National Electronic Injury Surveillance System (http://www.cpsc.gov/cpscpub/pubs/3002.html) are two types of program that collect information on adverse outcomes associated with consumer products. Existing labeling and other health risk communication requirements for industrial and consumer products have yet to include provisions for identifying engineered nanomaterials for users. As a result, users would not likely know that the products they were using contained engineered nanomaterials. Better labeling would increase the chances that suspected associations between products and adverse outcomes would be recognized and investigated. Pre-incident planning for field investigation by public health agencies would increase the likelihood that suspected associations are investigated and that the resources needed are made available.

Summary

Health and environmental surveillance have significant potential to contribute to nanotechnology risk management and to the promotion of research on those risks. Fundamental research, applied research, and surveillance are complementary. New knowledge of the health effects associated with exposure to engineered nanomaterials and new tools for characterizing exposure will increase the efficiency and effectiveness of surveillance. In turn, surveillance aids fundamental research by identifying associations that create hypotheses for research, identifies problems that help set priorities for research, and identifies populations and habitats that can be research subjects.

A barrier to meeting this research need is the lack of a community of researchers focused on nanotechnology

risk. This barrier can be overcome if public health agencies can provide the leadership and resources needed to recruit researchers into the field and train students who can operate surveillance components of ongoing nanotechnology risk management programs for government and industry.

Recommendations

- Get past discussion and begin funding and designing research tools.
- Encourage awareness about potential nanomaterial exposure issues among medical, governmental, industrial, and academic leaderships.
- Translate this awareness into a vision for protecting the environment and public health as well as mechanisms of multidisciplinary activity (grants) to investigate nanotechnology issues.
- Identify what will be considered a "nanotechnology" substance and modify this as the field grows and develops new nanomaterials.
- Establish exposure registries in a manner that facilitates epidemiological research.
- Characterize what a nanotechnology worker does to facilitate creation of exposure registries.
- Convene medical, occupational health, epidemiological, industrial hygiene, toxicology, and nanotechnology experts to develop hypotheses to attempt to define what could be included in a preliminary list of sentinel health events; add and delete events as the field of knowledge grows.
- Develop large-scale and inclusive study designs and data regarding potential nanomaterial exposures (including consumers, the general public, etc.).
- Provide guidance to companies that identify themselves as having nanotechnology workers on how they might develop registries and track listed sentinel events on those workers as they arise.
- Coordinate nanomaterial exposure and nanotechnology occupation data and studies across government agencies, academia, and industry.
- Develop systematic standards for capturing nanomaterial exposures and nanotechnology occupations.
- Integrate nanomaterial exposures and nanotechnology occupations as an essential part of the (electronic) medical record in accordance with national standards currently being developed.
- Reinforce the need for all (primary care) physicians to collect exposure and occupation data consistently (perhaps as part of national healthcare reform) with a category for using or working with engineered nanomaterial included among possible exposures.
- Be aware of barriers to nanomaterials exposure and surveillance studies that are not technical, but may be political or social.
- Develop informatics that could be used for more efficient data exchange (in addition to electronic medical records).
- Promote the public and personal vision of protecting people and the environment with regard to nanotechnology (with assurances such as confidentiality and protection of trade secrets).
- Identify a clear (single) agency to collect, analyze, and disseminate all voluntary nanomaterial exposure and incident reports/data; do not create a new agency for this.
- Consider developing "hazard communication" for nanotechnology substances (i.e., putting a label on "nano" products—like trans-fats, organic, etc.).
- Put 10 percent of all Federal nanotechnology dollars aside for applied EHS R&D and surveillance and training activities.
- Encourage and promote new, innovative research for funding as well as coordination of previously assessed research needs.

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6. *Research Need 5*: Understand Workplace Processes and Factors that Determine Exposure to Nanomaterials

Guest Speaker/Co-Chair: **Susan Woskie (University of Massachusetts, Lowell)**
Government Co-Chair: **Aleksandr Stefaniak (NIOSH)**
Rapporteur: **José Zambrana, Jr. (AAAS Fellow)**

Introduction

Key Points

Additional studies should be conducted to understand processes and factors that determine exposure to nanomaterials in the workplace. In the near term, exposure classifications of nanomaterials and of processes should be developed. In addition, near-term research opportunities include developing of internationally harmonized and validated protocols for exposure surveys, sample collection and analysis, and reporting through existing international frameworks such as the International Organization for Standardization (ISO), Organisation for Economic Co-operation and Development (OECD) and United Nations (UN). In the long term, comprehensive predictive models should be developed for workplace exposure covering a broad range of nanomaterials and processes.

Participants

In addition to the co-chairs, rapporteur, and NNCO representative, 18 individuals participated in one or both of the Research Need 5 breakout sessions. Participants included three representatives of U.S. military departments (Army Research Lab, U.S. Army Center for Health Promotion and Preventive Medicine, and U.S. Air Force Surgeon General's Office); three representatives of the EPA; three representatives from DOE (including one from Argonne National Laboratory); 2 representatives of private industry (TNO Quality of Life, Evonik Degussa); two representatives of NGOs (International Joint Commission [of Canada and the United States], American Society of Safety Engineers); two representatives of foreign government organizations (Health Canada and Germany's Federal Institute for Occupational Safety & Health); and one representative each from NIOSH, NIST, and OSHA. These participants came from diverse fields, including chemistry/chemical engineering, ecology, epidemiology, industrial hygiene, occupational health, public health, toxicology, and EHS management. Among these professions, participants ranged from laboratory researchers to senior managers, which provided a range of unique perspectives on the research need. The Research Need 5 and Research Need 1 groups combined on Day 2 of the workshop to discuss cross-cutting exposure issues pertinent to workers specifically.

Invited Presentation

Understand Workplace Processes and Factors that Determine Exposure to Nanomaterials

Susan Woskie and Dhimiter Bello, Department of Work Environment, University of Massachusetts, Lowell

Background

The National Nanotechnology Initiative document on environmental, health, and safety research identified five key research gaps. One of these was Research Need 5, "Understand workplace processes and factors that determine exposure to nanomaterials."(1)

Subcategories of needed research included developing an exposure classification of nanomaterials, developing an exposure classification of process, and developing predictive models of workplace exposure. Unfortunately, to respond to all of these needs would require a substantial amount of research, and to date only about 2 percent of the Federal funds spent on nano-related EHS activities as of 2006 were spent on human and environmental exposure assessment. Thus the data sources from which we can draw to answer these research needs is inadequate.

To begin to classify workplace processes and materials and determine what factors are important determinants of exposure to([engineered) nanomaterials, we first have to agree on the sectors in which exposures could potentially occur. Figure 6.1 shows the workplace sectors as including the manufacturing of raw or base nanomaterials, the functionalization of those base nanomaterials, and then finally the formulation or manufacturing of nanomaterial-based intermediates and products. All of these sectors occur first in an R&D setting, then in a pilot plant setting, and finally in a manufacturing/commercial setting (Figure 6.1). Other sectors where exposure to engineered nanomaterials may occur include the consumer use of nanotechnology-based products and the disposal of those products. However since these are nonoccupational exposures, they fall outside the charge of this research area.

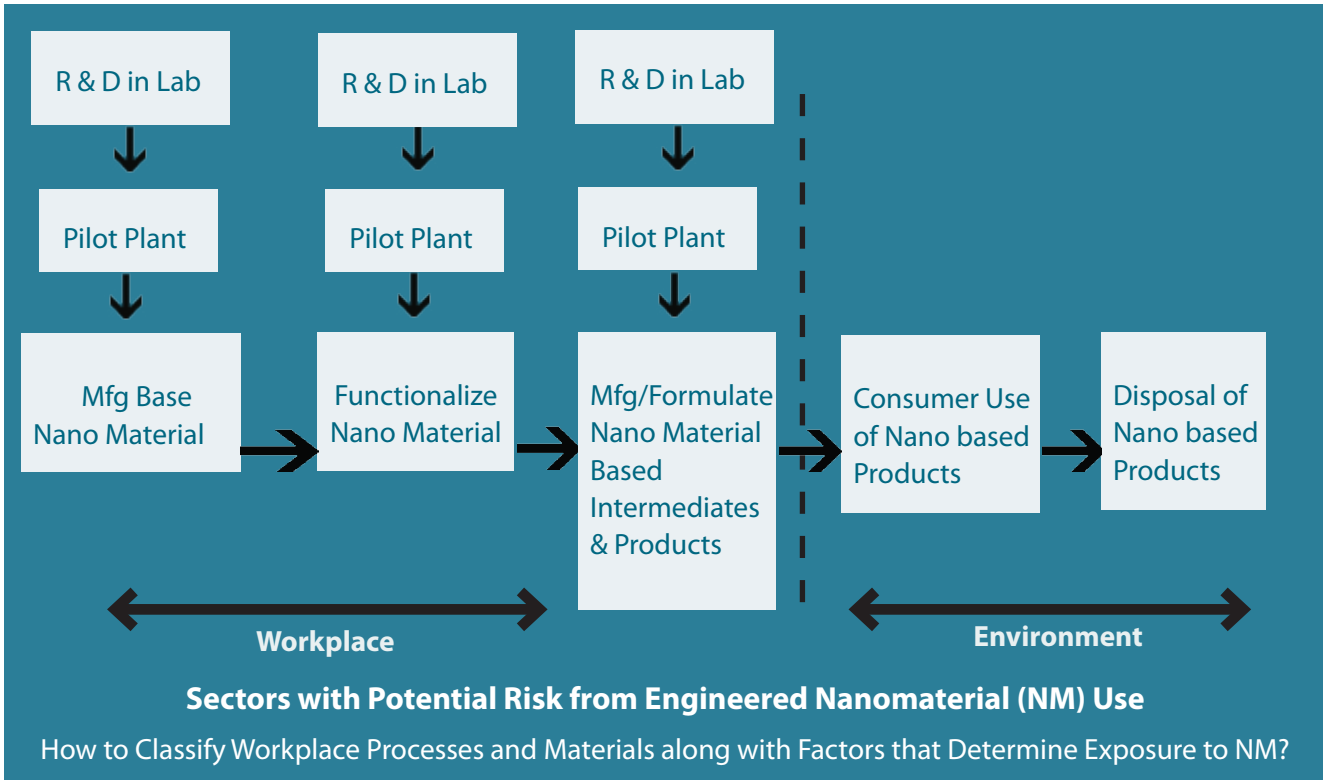

Figure 6.1. Nanomaterials (NM) sectors.

Exposure Determinants

The potential exposure determinants for nanomaterials occur at three levels. The first is the macroscale level, where we look at differences in exposure across all engineered nanomaterials industry sectors or product types; the second is the mid-level, where we look at exposure differences between organizations by nanomaterial industry sector or by nanomaterial used; the third is the microscale level where we look at exposure differences between operations or tasks using nanomaterials.

Macro-Level Exposure Determinants

Information on macro-level nanomaterial potential exposure determinants is very limited. The International Council on Nanotechnology (ICON) review of current practices in the nanotechnology workplace surveyed a variety of organizations using nanomaterials (*2*). It reports that the most common activity of these organizations is R&D, followed by manufacturing of nanomaterials, and then by manufacturing of products containing nanomaterials. In general, these organizations are small, having fewer than 50 employees. They tend to be new to the industry, with 56 percent being less than 10 years old and 86 percent having used nanomaterials for under 10 years. ICON has developed six basic categories of nanomaterials. In its survey of users, it found that 45 percent of users reported use of metal oxides or pure metals, 45 percent reported using carbon nanotubes, another 19 percent reported using fullerenes, 14 percent use quantum dots, and 20 percent use nanopolymers or dendrimers.

To summarize what we know about the macro-level determinants of potential nanomaterial exposures, there currently is no data linking these macro-level determinants to actual exposure measurements.

If we wanted to use the frequency of reporting from the ICON survey to prioritize our targets for exposure evaluation, the focus would be on R&D and base nanomaterial manufacturers, small and young organizations, and organizations that use carbon-based nanomaterial or metal oxides or pure metals.

The problem with this approach is that it still is not very specific for targeting nanomaterials, since it does not in any way include the relative toxicity of nanomaterials within a category as a priority, nor does it consider the other nanomaterial groups identified by ICON that could be more hazardous even though less commonly used at this time.

Mid-Level Exposure Determinants

Mid-level potential determinants of nanomaterial exposure would compare organizations within a nanomaterial sector such as the manufacturing of raw nanomaterials or formulation of nanomaterial intermediate products. Alternatively, we could compare exposures between organizations that produce a nanomaterial product type, for example, within composites or textiles or coatings or a manufacturer of quantum dots or carbon nanotubes. Potential determinants to examine this data might include the type of product, rate or volume of production, company demographics, descriptors of the physical worksite, rating of worksite health and safety programs, geographic location, or target sales audience. To date there is only one study looking at the mid-level determinants.

Kuhlbusch and colleagues (*3*, *4*) looked at three carbon black plants. They looked at two operations in these plants: the reactors where the carbon black was manufactured, producing particles of a 10 to 100 nm size, and the pelletizing and packaging of the carbon black. A unique feature of this work was the repeat sampling of the same process at each plant so that the authors present not only a mean level but also a measure of the variance (the 25th to 75th percentile) for the particle counts for each of the operations at each of the plants. In addition, they took ambient measurements outside the plant. The results of this study show that for Plant 1 there was no difference between inside and outside or between the reactors or pelletizers in number concentration of particles in the 10–100 nm size range. In Plant 2 there was also no inside to outside difference, but overall particle counts were higher, which the researchers attributed to the plant being nearer to traffic. Plant 3, on

the other hand, had significantly higher inside than outside differences for both the reactor and the pelletizer operations. The authors analyzed filters for organic and elemental carbon and found high levels of organic carbon, so they surmised that some of the exposure could have been from process leaks (oil and flue gases).

Micro-Level Exposure Determinants

When we look at the micro-level potential exposure determinants, we need to start looking at the job or operation level (Figure 6.2), since a worker's daily exposure is proportional to the sum of his exposures in each task across the day. Each day's task exposure is a combination of the task exposure intensity and the task duration. This highlights the importance of looking at tasks within a job or operation. The determinants of task exposure can be a result of process factors, environmental factors, or personal factors.

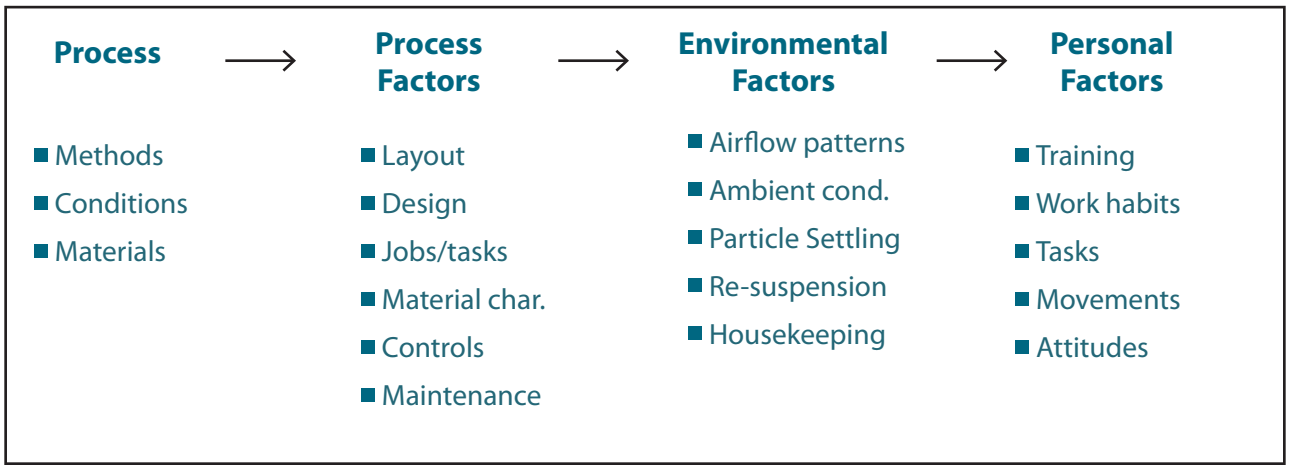

Figure 6.2. Micro-level (job/operation/task) exposure determinants.

Task-Level Determinants within the Manufacture of Base Nanomaterials

The first sector in Figure 6.1 represents the manufacturing of base nanomaterials that are produced in two ways. Top-down manufacturing takes larger bulk materials and breaks them down into nanoscale size using mechanical, chemical, or other energy. The bottom-up approach uses synthesis from atomic or molecular subcomponents through complex chemical reactions. The instruments in which these types of processes occur are numerous, but they all are rather enclosed processes that lead most people to believe that reactors are not likely sources of exposure while operating. Where exposures may more likely occur is in other tasks associated with the manufacture of these base materials. Examples of some of the tasks involved in manufacturing of base nanomaterials include setting up and running reactors; unloading reactors; finish processing such as drying, maintenance, or cleaning; packaging and shipping; and accidental spills or waste product handling. There are only a few studies that look at task exposures in the base nanomaterial manufacturing industry.

A study of a fullerene manufacturer looked at the reactor area of the facility and found that the technician's tasks included starting off by vacuuming out residual nanomaterials in the reactor, followed by placing graphite rods inside the reactor, sealing it, and running the arc to produce the nanoparticles (*5*). When that process was complete, the technician removed the materials via sweeping them out of the reactor into a jar. The monitoring of these tasks suggest that it was the vacuuming process that produced the highest concentration of nanoparticles, and that these nanoparticles, which were <100 nm, could be measured both at the reactor and two meters away. The authors also noted that on some days there were high particle counts during sweeping of the fullerenes into jars as well. Unfortunately, although the authors monitored 12 production runs, they did not use a statistical presentation of the exposures during these tasks, so we do not have a real sense of the mean and variance in particle counts per task.

Fujitani and colleagues (*6*) also looked a fullerene production and found that the particle count of small (10–50 nm) particles increased during bagging/weighing and vacuum cleaner use. They also found that although

the number of large (>2000 nm) particles did not increase in terms of volume, they did increase during the bagging and vacuuming operations, suggesting that agglomeration of the fullerenes was occurring.

- There does not appear to be significant leakage from the reactors themselves.
- One study suggested that unloading the reactors could produce exposures.
- There was anecdotal information from one study about potential exposures from drying operations adjacent to a pelletizing operation.
- One study found maintenance and cleaning of reactors to be a source of exposure.
- Two studies have indicated that packaging of final products can be a potential source of nanomaterial exposure.
- All the nanomaterials studied to date have been carbon-based, and none of the other five categories of nanomaterials have yet been studied in this fashion.

Task-Level Determinants for Functionalized Nanomaterials

Once base nanomaterials have been made, they are often functionalized to make them more useful for product development (Figure 6.1). Much of the work for functionalizing nanomaterials is done in R&D laboratory settings. In these lab settings there can be a significant potential for personal contact, including during tasks such as mixing and pouring of nanomaterials, cleaning apparatus, weighing nanomaterials, and preparation for quality assurance/quality control (QA/QC) testing. ICON reports (2) that only 47 percent of those handling dry powder reported using a fume hood.

How successful are laboratory fume hoods at containing nanomaterials? Tsai and colleagues (7) looked at two types of tasks: the transfer and pouring of nano alumina in a conventional laboratory ventilation hood and in a bypass lab ventilation hood. They reported their results after subtracting out the background particle counts. When the hoods are running at their recommended face velocity of 100–150 ft./min., the bypass hood does much better at containing particle release. Nevertheless, even in a conventional hood, the number of particles released above the background was only about 5,000 at the peak size of about 10–20 nm. Clearly, the use of fume hoods can be a very effective control for the use of nanomaterials.

Nevertheless, this same study of lab hoods documented that nanomaterials could be measured one meter outside of the laboratory hood for up to eight minutes after completion of the nanomaterial task of pouring or transferring nano alumina. Particle counts outside the hood were very high during clean up inside of the laboratory hood, although they dropped relatively quickly.

To summarize what we know about exposure determinants for functionalized nanomaterials, we know virtually nothing about exposures during these tasks. The ICON report says 23 percent of organizations used nanomaterials as a dry powder only; 37 percent use nanomaterials as a dry powder and nanomaterials in a suspension, and as reported previously, it is the minority that use these materials inside a laboratory hood (2). This is particularly troublesome because the types of functionalized nanomaterials are so vast that we will need to coordinate with toxicologists to target those functionalized nanomaterials of greatest concern. In addition, more work needs to be done to evaluate other types of hood designs, as well as to examine other tasks inside the hood, including those that add thermal load to the ventilation demands.

Task-Level Determinants for Manufacturing and Formulation of Nano-Based Products

The final sector to look at for workplace exposure determinants is the manufacturing and formulation of nano-based products (Figure 6.1). Much of this work is also done in R&D laboratory settings, where there is significant potential for personal contact. Many of the tasks of particular concern are similar to those in the functionalization sector. However, they also include sonification of dispersions, mixing and pouring of composite materials, running extrusion processes, and machining of nanomaterial-containing products.

Methner and colleagues (*8*) looked simply at total carbon mass concentrations in carbon nanocomposite lab tasks at a university. Although these are simple mass concentrations, several processes had significantly higher exposure levels compared to background levels.

One example of nano-based products is nanocomposites. One type of a nanocomposite is a hybrid that incorporates a nanomaterial, in this case, carbon nanotubes, in between substrates such as graphite or alumina cloth. This sandwich of materials is held together with epoxy resins. Another type of nanocomposite uses a compounding process. A heated extruder is used to mix plastic polymers with nano alumina.

Tsai and colleagues (*9*) looked at what difference it made to add the nano alumina via different methods in the extrusion process. In one case, the alumina was premixed with the polymer, and in the other cases, it was added downstream through separate ports in the extruder. The premix process produced higher particle counts; however, the engineers wanted to continue to use this process because it produced a more even distribution of the alumina throughout the polymer product. An interesting outcome of this project was the significant impact in background particle counts when the lab floors and equipment were washed and hygiene was maintained over time.

When it comes to nanocomposite machining, Bello and colleagues (*10*) found some very interesting results with the hybrid composite materials. First, they found very little difference in total counts between the composite materials with and without the carbon nanotubes, although all composites when cut produced higher particle counts than background. They also found that the composites without any carbon nanotubes had higher counts of the small (<10 nm) particle sizes. And finally, they looked at dry-cutting versus wet-cutting and, as expected, found that dry-cutting produced much higher particle counts than wet-cutting.

However, in the process of examining the composition of the aerosolized material during the cutting process, they found that respirable-sized fibers were produced. Using the NIOSH counting rules, the concentrations were 1.6–3.8 fibers/cc. The carbon nanotube-alumina composite produced fewer fibers than the carbon nanotube-carbon composite. Han and colleagues (*11*) have also reported finding multiwalled carbon nanotube fibers in workplace air samples from a research lab setting.

To summarize what we know about exposure determinants for manufacturing and formulating of products based on nanomaterials and composites, we know very little about most of these tasks. To date, most of the work has focused on carbon nanotube-containing products and nano alumina, rather than any of the other types of nanomaterials. To narrow our focus in the future, we will need to coordinate with toxicologists to target those nanomaterials of greatest concern. Of particular current concern is the possible production of respirable-sized fibers of dimensions similar to asbestos.

Conclusions

In conclusion, we are missing exposure information on many tasks within each sector. We're missing basic information on many of the six basic nanomaterials identified by ICON, not to mention the many subgroups within each of those basic categories. We're missing information on many potential exposure determinants. However, we do know that maintenance reduces background exposure but increases cleaners' exposures; that some lab hoods are better than others; that when mechanical processes like sawing are applied, some composites produce more fibers than others; that dry sawing produces more exposures than wet sawing; that pelletizing and bagging base nanomaterials can produce exposures; and that drying operations may also be a source of exposure.

Where do we want to go from here? It is important that we determine what the relevant exposure metrics for sampling should be. We also need to do repeat sampling of the same tasks within and between organizations. We need consistent sampling approaches, especially due to the variety of real-time particle count size fraction samplers that are in current use. We need background measurements of near field and far field and outdoors before and after each task, including size distribution and concentration data, and in some cases, compositional analysis. We need to agree on common size fractions within which to sum our concentration data. We need to

agree on common sampling times over which to average concentration data. We need a targeted list of potential exposure determinants to use routinely in the collection of all samples. And finally, we need to consider using video exposure monitoring, in combination with direct-reading measurements, to allow detailed examination of potential exposure determinants.

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State of the Science

Understanding workplace processes and factors that determine exposure implies that the discussions center on human, rather than environmental exposure; however, in the vicinity of the workplace, human exposure often has implications for environmental exposure. Indeed, the converse may be important as well, for it may be critical to consider outside "background" exposure when evaluating workplace exposure. This research need focuses on workplaces where engineered nanomaterials are intentionally being fabricated and/or are a component in a fabrication process. It is rational to initially focus research on workplaces where engineered nanomaterials are produced or are part of a production process, because then the lessons learned in these environments will be generally applicable to workplaces where non-engineered particles exist in the nanoscale (1 to 100 nm). This "mid-level" issue is a reminder that determinants of exposure, as they relate to workplace processes and

and factors, must be considered from the macro-level, to the mid-level, to the micro-level. To date, only limited micro-level determinants of exposure have been evaluated and reported in the literature, and they are the primary focus of this state-of-the-science review.

The main question facing exposure assessors is whether the process of producing, handling, and manipulating engineered nanomaterials leads to worker exposure. Investigation of this question involves three overarching research challenges:

a. On what basis is it determined, to some acceptable degree of certainty, that what is measured directly corresponds to an engineered nanomaterial in the workplace?

b. What determines whether/how what is measured as the concentration of a produced nanomaterial in the workplace translates into an exposure?

c. What determines whether exposure leads to a (deleterious) health effect?

While there is overlap and interplay between these challenges, each lends itself to certain technical issues and potential solutions. The first challenge (a) encompasses technical hurdles of measurement, survey protocols, detection, characterization, and background consideration. The second challenge (b) also involves characterization, but moreover focuses on processes and factors in the workplace. The third challenge (c) also includes workplace processes and factors, but refers mostly to toxicological considerations. While occupational exposure assessment focuses more closely on the first two challenges, it is important to note that the third challenge (c) articulates an important assumption: exposure assessment necessarily involves determining the extent to which exposure leads to dose, which leads to response, which leads to a health effect. In fact, an important point is that exposure studies need to inform toxicological studies, and vice versa.

Challenges

Progress toward Research Needs

To address the need for understanding workplace processes and factors that determine exposure to engineered nanomaterials, the NNI emphasized three research topics in its 2008 *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research*:

1. Develop exposure classification of nanomaterials
2. Develop exposure classification of processes
3. Develop predictive models of workplace exposure

These NNI research topics align closely with the three state-of-the-science challenges for exposure assessment. For example, NNI research topic (1), develop exposure classification of nanomaterials, maps closely with challenge (a) to determine with acceptable certainty that what is measured in the workplace directly corresponds to an engineered nanomaterial. Similarly, NNI topic (2), develop exposure classification of processes, tracks with challenge (b). The final research topic, (3) develop predictive models of workplace exposure, requires knowledge gained from full investigation of topics (1) and (2) and includes elements of challenge (c), such as making the connection between exposure and health effect.

Exposure Classifications

New engineered nanomaterials are being developed at a rate faster than our ability to fully understand their potential environmental, safety, and health implications. As such, scientifically defensible strategies are needed for the development, if feasible, of models for exposure classification of engineered nanomaterials. Few published reports on the feasibility of exposure classification schemes exist. In broad terms, views on the feasibility of nanomaterial classification schemes for exposure can be divided into three categories:

1. Schemes based on engineered nanomaterial physico-chemical properties: These permit simplified approaches for exposure assessment using current tools and technologies and could feasibly be implemented in the near future; however, such schemes do not account for the dynamic behavior of engineered nanomaterials in biological systems (e.g., formation of biofilms, or surface binding of proteins).
2. Schemes based on the nature and severity of potential engineered nanomaterials-induced health effects: These are end-point driven but

also do not account for the dynamic behavior of engineered nanomaterials in biological systems.

3. Schemes based on behavior in biological systems: These propose to account for dynamic changes of nanomaterials during their "life cycles" in biological systems rather than material properties.

Additional efforts are needed to understand and articulate the advantages and disadvantages of each of these approaches to classification schemes for engineered nanomaterials.

Process Classifications

Process conditions directly influence the physical, chemical, and physico-chemical properties of engineered nanomaterials. As such, efforts are underway to categorize synthesis processes for engineered nanomaterials. Current initiatives include the NIOSH Nanoparticle Information Library (NIL) and InterNano. The NIL is a web-based searchable database (http://nanoparticlelibrary.net/) that contains information on particle characteristics and synthesis processes for engineered nanomaterials. InterNano (http://www.internano.org/) is a project of the National Nanomanufacturing Network and is a web-based "open network for collaboration and information exchange among the nanomanufacturing research, development and education community" hosted by the University of Massachusetts-Amherst and funded by NSF.

Predictive Models of Exposure

Development of predictive models of exposure to engineered nanomaterials will require information on both exposure and process conditions, as well as knowledge of material toxicity. Currently, schemes for classifying exposures and nanomanufacturing processes are incomplete, precluding development of predictive models of exposure. Thus, future efforts should also consider defining the goals of needed classification schemes and developing a vision for how a family of robust classification schemes could be developed and how they would work together to cover both hazard potential and exposure potential.

In summary, within Research Need 5, "understand workplace processes and factors that determine exposure to nanomaterials," progress is being made toward developing exposure classifications of nanomaterials, developing exposure classifications for processes, and developing predictive models of workplace exposure. Consistent with the proposed NNI timeline of near-term research (within three to five years) in its 2008 NNI EHS strategy, efforts to date are weighted more heavily towards classification of exposures and processes; however, it may be necessary to articulate more clearly the need to link exposure to health effects in order to better inform overall exposure assessment. Such efforts will support development of predictive models for exposure, which are identified in the 2008 NNI EHS strategy as a mid-term (within five to 10 years) research need. Additionally, as progress is being made toward these current research topics, new technical concerns are beginning to emerge and are discussed in more detail below under "Opportunities."

Technical Concerns

Several technical concerns were raised during the workshop regarding the need to further understand workplace processes and factors that determine exposure to engineered nanomaterials. Participants agreed that the major obstacles facing exposure assessors trying to evaluate whether the process of producing engineered nanomaterials leads to worker exposure are technical limitations to identifying, measuring, and characterizing an engineered nanomaterial in the workplace. Many of these technical concerns apply to all aspects of nanoEHS research. Specific technical concerns were:

- What properties of engineered nanomaterials should be measured, e.g., composition, impurities, and size distribution below 100 nm and/or above 100 nm?
- How can an engineered nanomaterial of interest be discriminated from other agents such as ultrafine particles, other nanoscale particles that are by-products of the manufacturing process itself, and/or from nanomaterials in the ambient environment?
- How is "background" best defined—at the near field or the far field relative to a process within a facility or outside ambient environment?
- What are the important macro-, mid-, and micro-level determinants of exposure?

- What is the proper way to analyze concentration measurement data in order to translate into exposure-information–appropriate time scales; task, job, or process monitoring; averaging, variances, and other statistical parameters; and material characteristics?
- Is it possible to build a single real-time instrument capable of specifically and simultaneously measuring engineered nanomaterial composition, impurities, and size distribution?
- Can such a sampler be built as a personal sampler to measure exposure rather than the current approach of using area-sampling instruments to measure concentrations in the work environment as surrogate metrics for exposure?

Concomitant with these cutting-edge technical concerns, several emerging research opportunities were identified, as described in the section below.

Opportunities

Emerging Research Trends

A key opportunity identified for Research Need 5 was the development of internationally harmonized and validated protocols for inhalation and dermal exposure assessment. Specifically, clear opportunities exist to harmonize protocols for:

- Walk-through surveys, including information on the nanomanufacturing process, different kinds of nanomaterials that may cause different exposures, and identification of potential work tasks of interest.
- Measurement strategies, including use of complementary instruments, real-time and/or integrated, to obtain needed information.
- Sample collection, including properties of engineered nanomaterials that should be measured, with special emphasis on characterizing background exposure to non-engineered nanoscale particles.
- Documentation of determinants of exposure at the macro-level, mid-level, and/or micro-level.
- Sample analysis, including handling, care, and data quality requirements.
- Minimum data reporting to facilitate comparison of study results, including what data to report, the form of summary statistics (geometric mean, geometric standard deviation, range, variability, etc.; accounting for and reporting background concentrations; and time course and averaging real-time measurements over a task or full day), process descriptions, and factors that determine exposure.

Additionally, there is an opportunity to develop linkages between toxicological outcomes observed in the laboratory and real-world exposures. Specifically, there is an opportunity to clarify whether metrics of engineered nanomaterial characteristics used in toxicology studies correlate with metrics that can be measured in the field. There also is an opportunity for toxicology to inform exposure assessment with regards to which nanomaterials are hazardous and vice versa (exposure assessors to inform toxicology of real-world nanomaterial characteristics).

Where Do We Want to Be in Five Years?

Based upon efforts to date, it is reasonable that within the next five years our understanding of classes of nanomaterials and nanomanufacturing will be clearer, but incomplete. Progress toward these initial research topics will enable progressively more emphasis to be placed on emerging research opportunities such as the development of internationally harmonized protocols for walk-through surveys, measurement strategies, sample collection, documentation of determinants of exposure, sample analysis, and data reporting. Several avenues were identified for expediting the development of these harmonized protocols including building upon existing protocols from large industrial producers with experience in handling engineered nanomaterials and government organizations in the United States and Europe.

Do Current Research Needs Correctly Reflect the State of the Science?

The current NNI strategy for environmental, health, and safety research acknowledges the need to understand workplace processes and factors that determine exposure to nanomaterials. To accomplish this need, the NNI emphasizes three research topics (2008 EHS Research Strategy): (1) develop exposure

classification of nanomaterials, (2) develop exposure classification of processes, and (3) develop predictive models of workplace exposure. As described in the previous sections, progress is being made toward understanding these research topics, and new research topics are emerging. Thus, the need to understand workplace processes and priorities should remain a high priority of the NNI research strategy; however, over time, increasingly more emphasis should be placed on international harmonization of exposure assessment protocols and establishing linkages with the nanotoxicology community.

Summary

A need exists to understand processes and factors that determine exposure to nanomaterials in the workplace. As progress continues to be made in the near term (within three to five years) on the three existing research topics, a concomitant shift toward addressing emerging state-of-the-science research topics is necessary and should be initiated in the near future. Key near-term research opportunities include development of internationally harmonized and validated protocols for:

- Walk-through surveys
- Measurement strategies
- Sample collection
- Documentation of macro-level, mid-level, and/or micro-level determinants of exposure
- Sample analysis
- Minimum data reporting to facilitate comparison of study results

Importantly, there is also an opportunity to clarify whether metrics of engineered nanomaterial characteristics used in toxicology studies correlate with metrics that can be measured in the field and for toxicity testing to inform exposure assessment with regards to which nanomaterials are hazardous and which exposure assessments inform toxicology of real-world nanomaterial characteristics.

Current and emerging research topics face many cross-cutting issues, especially with regard to information exchange. Informatics is a seemingly viable and advantageous mechanism for enabling the efficient exchange of information; several databases currently exist, and coordination of these resources under a centralized clearinghouse may be beneficial to stakeholders. Existing international bodies such as ISO and OECD may serve as mechanisms for development and validation of needed internationally harmonized protocols for exposure assessment, and industry has a role to play via product stewardship.

Additional key barriers include a general lack of research funding for evaluating the environmental, health, and safety implications of accidental exposure to engineered nanomaterials and the lack of a clear model of the relationships among government (Federal, state, and local), nongovernmental organizations (NGOs), academia, industry, trade organizations, professional societies, and unions in developing collaborative cross-cutting research. Opportunities exist for government (Federal and state) and industry to fund and perform research, academia will perform and help to determine research needs, and NGOs and unions may be important research collaborators. Finally, clear mechanisms to foster communication and collaboration among U.S. researchers and international researchers are needed to enhance research quality and leverage scarce funding dollars.

Recommendations

- Develop a harmonized protocol for walk-through surveys; this includes gathering information on nanomanufacturing processes, the specific nanomaterials in question, different possible exposures (including dermal and accidental ingestion), and work tasks of interest.
- Develop a harmonized protocol for measurement strategies; this includes how to measure different exposures (inhalation, dermal, accidental ingestion) as well as the use of complementary instruments.
- Develop a harmonized protocol for sample collection; this includes measuring the various necessary properties of engineered nanomaterials and characterizing background exposure.
- Develop a harmonized protocol for documenting the determinants of exposure.
- Develop a harmonized protocol for sample analysis and data collection for the purposes of facilitating meaningful comparison of study results.

- Develop a harmonized approach to review, evaluate, and disseminate best practices and protocols; a relevant federation of databases should be vetted and coordinated with European and other international partners.
- Tackle the challenges associated with registries.
- Bring together toxicologists and exposure assessors in the short term to facilitate better coordination of studies.
- Clarify agency roles, mechanisms for referring to agencies, and the role of the NNI.
- Develop a clear model of the relationships among various sectors, including governments, NGOs, industry, trade organizations, professional societies, and unions, that enables collaborative, cross-cutting research.

7. Emerging and Cross-Cutting Research Needs

Chair: **Paul Schulte (National Institute for Occupational Safety & Health)**
Rapporteur: **Katya Delak (AAAS Fellow)**

Introduction

Key Points

There is an urgent need to define a standard desirable data set to identify relevant health concerns, which in the long term would assist with predicting and testing for hazards during new material development and, therefore, with reducing product risk at the nanomaterial/product design stage. A global nanomaterial exposure and hazard database should be developed and should include such a standard data set. Support should be given to the development and maintenance of a global "information clearinghouse" for communicating good practices and protocols.

Opportunities exist to address the cross-cutting need for development and validation of harmonized protocols for exposure assessment, measurement methods, and data interpretation and reporting through established and recognized international bodies. Support also should be considered for an information clearinghouse containing nanomaterial exposure information and modification of existing databases to accommodate distinct features of nanomaterials

Participants

In addition to the chair, rapporteur, and NNCO representative, 15 individuals participated in one or both of the Emerging Research Needs breakout sessions. Participants included 6 representatives of private businesses (Crowell & Moring LLP, Evonik, NanoReg, R.J. Lee Group, SAIC, Washington CORE); 2 representatives of DOE; and 1 representative each from academia (Michigan State University), an NGO (the American Chemistry Council), EPA, FDA, NIOSH, NIST, NSF, and the U.S. Navy (Bureau of Medicine and Surgery). These participants came from the fields of law, industrial hygiene, toxicology, and management, among others. This topic covers emerging and cross-cutting research needs that are not covered by the five research needs and addresses whether there is a need for recommendations for additional research areas. This chapter also incorporates discussions of cross-cutting issues that took place at the other five topical breakout sessions.

Emerging and Cross-Cutting Issues in Nanotechnology Exposure R&D

Health and Safety Research

Investment in nanoEHS research is slowly, but steadily, increasing. Research on the health implications of nanotechnology has been conducted, but the results of these studies have not been synthesized in a manner that would be useful to manufacturers, researchers, and consumers. Rather, a systematic and driven approach towards understanding the effects of nanotechnology on health is necessary. This importance of this need is underscored by the significant challenges facing nanotechnology researchers.

The diversity of nanomaterials represents a significant challenge to nanotechnology health and safety research. To test every material and every permutation of a material is currently an insurmountable task. Similarly, it would be difficult to develop recommended exposure limits for each material. An approach that would diminish this task in scope would be to identify hazard categories into which nanomaterials could be grouped. The categorization may initially be driven by the physico-chemical traits of the material, but ultimately, the concern is the health effects that materials may have. Certain combinations of physico-chemical traits may be more hazardous than others. Based on mechanistic understanding, recommended exposure limits could be developed for categories of nanomaterials. Another approach to tackle this challenge is to develop a prioritization scheme for hazard testing.

There has been little investigation of agglomeration and deagglomeration on health effects. The physico-chemical aspects of these phenomena are not novel, but what is a concern is how agglomerated materials are moved through the body. How does the body respond to materials that are ingested or inhaled, and are agglomerated materials cleared through the kidneys in the same way that non-agglomerated materials are? Related to these unknowns are the health and safety implications of second-generation nanotechnology materials. To date, these have not been addressed.

Standardization

Health and safety research in nanotechnology could further be enhanced if standardized approaches for assessing exposure could be used consistently. Standardization is a cross-cutting research area with significant challenges, especially with the need for international standardization of validated protocols for exposure (dermal and inhalation) assessment, measurement methods, and data interpretation and reporting. Opportunities exist to address the cross-cutting need for the development and validation of harmonized protocols through established and recognized international bodies such as the International Organization for Standardization (ISO) and the Organisation for Economic Co-operation and Development (OECD). Established member-represented international bodies such as ISO and OECD could provide structured mechanisms for reaching consensus on standardized protocols or for delegating responsibility for developing standardized protocols; however, these development and approval processes can take years. As such, a need exists for more rapid approaches to international standardization of protocols.

Standardization of data collecting and reporting would also facilitate further analysis and application of informatics tools.

Informatics

Without a doubt, there is a need for disseminating best practices related to processes and factors that affect exposure. An extraordinary amount of information on nanotechnology is becoming available at an almost overwhelming rate. Compounding the problem of "information overload" is that much of the information is coming from diverse fields such as physics, biochemistry, chemistry, toxicology, and exposure sciences. Thus, a major barrier for information dissemination is the absence of a credible centralized source of information for interested stakeholders. In this regard, informatics is a viable mechanism for enabling the efficient exchange of information and could prove advantageous for communicating good practices and protocols, especially to small- and medium-size enterprises that generally lack on-site health and safety resources.

Currently, several databases exist such as the ICON Virtual Journal (http://icon.rice.edu/centersandinst/icon/virtualjournal.cfm), a web-based centralized resource for nanotoxicology studies; ICON GoodNanoGuide (http://icon.rice.edu/centersandinst/icon/projects.cfm?doc_id=12207), a web-based forum designed to facilitate the ability of experts to exchange current ideas on best practices for handling nanomaterials in the workplace; the National Nanomanufacturing Network's InterNano online database (http://www.internano.org/content/view/390/284/) of nanomanufacturing processes; and the NIOSH Nanoparticle Information Library (http://www.cdc.gov/niosh/topics/nanotech/NIL.html) (NIL), a database of nanomaterial characteristic information. A viable option for centralizing available information resources might be a "federation of databases" to serve as an information clearinghouse. In principle, such an approach is feasible; however,

several practical challenges were raised and will need to be addressed to enable this federated clearinghouse of information:

- Confidence in the quality of information contained in federated databases, including some level of review and evaluation of best practices and protocols
- Coordination with European and other international partners' knowledge bases
- Ownership of databases and associated maintenance

The role of informatics is critical for using the National Center for Computational Toxicology (NCCT) ToxCast™ system and a parallel new system, ExpoCast, as models.[1] They need to be made publicly accessible. Although participants viewed having a database as critical, developing a special database for nanomaterials was not viewed as necessary. However, those who responded concurred that nanomaterial data should be included with data for conventional chemicals, because there will be cross-cutting issues. For example, nanomaterial-specific fields (e.g., composition, characterization of the molecule, characterization of exposure) could be added to cross-cutting chemicals and existing systems such the ToxNet database maintained by the National Library of Medicine. It was further agreed that work needs to be done with NCCT to make sure the database specifically addresses nanomaterial-relevant parameters, e.g., surface activity, composition, size, and so forth.

A number of organizations such as ISO Technical Committee 229, OECD Working Party for Manufactured Nanomaterials, and a multi-stakeholder grassroots community initiative called Minimum Information for Nanomaterial Characterization Initiative (MINChar) (http://characterizationmatters.org/) drew up minimum sets of characterization parameters; these parameters should be used as "administered info" and not "manufactured info." A requirement for a minimum set of characterization parameters should be put into Federal grant applications to gather information. It was also agreed that NCCT should include these parameters in its final data set and that the OECD should be asked to examine existing databases to determine which, if any, are most suitable [for holding data on engineered nanomaterials] and might contain the essential minimum characterization parameters.

Even if such a database is created, private data must also be included, which could be problematic. Confidentiality may become an important issue, specifically, what is considered confidential business information (CBI) and what is not. Exposure data may be CBI. One solution could involve the EPA aggregating and summarizing data, although there are questions about access to data and about data quality (inventory update rule [IUR] data is poor; not readily obtainable [NRO] data is not available). The government may have the most data, but it is protected as CBI. EPA participants felt that they could probably provide some aggregate data, but at the moment, they have use-and-release data only, with probably not much on exposure. It was suggested the same would be true of FDA. An EPA representative noted that there is a push at the organization to get industry to make fewer claims under CBI so that more data can be released. Participants in the breakout group determined there were no clear solutions to the problem of collecting data from private sources.

Medical Surveillance

Medical surveillance involves the collection and analysis of health effects data and communication of the results. For workers involved with nanomaterials there is a need for collecting information in similar formats and with standard elements. The inclusion of occupational variables in electronic medical records would enhance medical surveillance of nanotechnology workers.

Exposure Databases

Is there value in establishing a database of exposure measurements? A key criterion is defining who the users of such a database would be, as well as who other stakeholders are. A cursory examination suggests that researchers, businesses, students, governments, workers, and perhaps most

1 ToxCast (http://www.epa.gov/comptox/toxcast/) is "an EPA program to develop a cost-effective approach to toxicity testing of many chemicals in a short time." ExpoCast (http://www.epa.gov/NCCT/expocast/) is a program started by EPA "to create exposure science and computational tools for rapid characterization of exposure potential. The goal is to develop novel tools focused on the 'potential for biologically relevant' human exposure to inform priorities and exposure testing." ExpoCast was just getting started at the time of the NNI workshop.

importantly, regulators all have interests in such a database. Private corporations and universities have little incentive to create or use such a database, given the costs of implementation and maintenance and the jeopardy of releasing proprietary information. Overall, the demand for a database of measured nanomaterial exposures has not been demonstrated; that is not to say that the need is lacking. Clearly, in order to benchmark exposures, employers and health authorities may find such a database valuable. Authorities also could use such a database to help frame exposure recommendations. The question is the extent to which a database would be of any value beyond merely collecting exposure data from published literature.

A further concern relative to the establishment of databases is the kind of information that should be included. Previous databases have included synthesis and characterization protocols, but where health concerns are an issue, additional information must be included (e.g., particle type and particle size). Likewise, in the manufacture of products that contain nanomaterials, information such as the supplier may also be relevant. What is therefore necessary is a clear identification of a minimum data set that must be included in a database where correlations to health or environmental effects may be made in the future.

Exposure Registries

Exposure registries consist of lists of specific workers who may have had exposure to nanomaterials. The lists may also contain related information on exposure circumstances, levels, and extent. Again, as with much that is related to nanotechnology health and safety efforts, the costs of generating these registries are a significant barrier to their implementation. Also, legal concerns come into play. To many people, exposure registries appear to be the largest waste of money where nanotechnology is concerned. Registries are enumerations of people who have been exposed, and by initiating data collection, workers may come to expect that something is wrong. In this respect, collection of exposure data appears to many to be a "lawsuit waiting to happen." Consequently, the incentives to collect exposure data are not apparent to operators of nanomanufacturing facilities.

The most practical scenario for initiating an exposure registry may be to start on a pilot scale. Collection at a few large manufacturers rather than many small manufacturers may be easier to coordinate and implement.

Exposure registries may serve as a prerequisite for epidemiological studies. There are many issues in developing epidemiological studies for workers exposed to engineered nanomaterials. These include particle heterogeneity, temporal factors, and finding the appropriate study population.

Assessing Exposure to Nanomaterials

Exposure assessment in facilities that produce engineered nanomaterials or use them in the manufacture of consumer products is necessary to enable the nanotechnology community to understand health and safety concerns. There is already a wealth of information on particle monitoring for clean room management, as well as for aerosols monitoring, from which inline nanomaterial exposure monitoring can follow. However, the case with many nanomaterials in commerce is much more difficult to address because the nature of workplace tasks and, ultimately, exposures is not well-characterized. Likewise, differentiating the relevant material from background signal is also a much more difficult task and more necessary than for standard clean room methodology.

In order to make rapid inline monitoring a reality in nanomaterial manufacturing, novel technological capabilities are necessary. It is not currently practical to use tools that are commonplace in nanotechnology research for routine inline monitoring. Techniques such as high-resolution transmission electron microscopy (HRTEM) and scanning electron microscopy (SEM), which allow for the identification of particle shape, size, and counts, are slow in throughput, and require a keen eye for detail in interpreting the images. To be able to implement such data acquisition on a routine basis would require improvements in optical recognition algorithms as well as significant cost decreases. In order for this to happen, a critical mass of customers for the technology needs to exist, so that it becomes affordable. There is no clear way to initiate this, in part because many manufacturers of nanomaterials are small operations without the capital necessary to invest in such equipment. Workshop participants

agreed that an exposure assessment "toolkit" needs to be developed, but no specific tools were mentioned. Some suggested that most of the necessary tools are extant and just need to be adapted. There was concern, however, that even if appropriate tools were developed or do exist, there may not be enough trained people to do the testing and interpret the data. This was considered a significant potential problem.

In addition to basic physical characterization in monitoring processes, a supplemental approach could be biological monitoring. Examination of nanomaterial interactions with DNA or present in tissues or fluids may be another means to assess exposure or early biological effects. Development of biological monitoring protocols would subvert the need for identifying specific material types; instead, hazardous biological responses could be identified more rapidly. Although challenges still exist with identifying proper control conditions, the reward is that the cost would likely be significantly lower, and the methods would likely be significantly cheaper than high-throughput screening via electron microscopy.

Product Life Cycle

Investigation of the health effects of nanomaterials must take into account the entire life cycles of products. The research that was described during the workshop addresses materials primarily in their native form. However, the fate of materials once they are embedded in products and are then subject to everyday use has not been heavily investigated. One useful approach would be to establish a testing laboratory for crude handling tests, such as drilling and sanding. This would not require much in the way of resources. With the proper tests and analysis identified, a relevant data set from which handling and disposal recommendations would emerge could be produced in one to two years. Furthermore, although such testing may result in a larger number of questions, the data may indicate what controls or concerns should be addressed.

Examples of successful product stewardship models already exist in the United States and Europe (particularly Germany).

Recommendations

- Identify hazard categories for nanomaterials that are based on adverse health effects (rather than nanomaterial physico-chemical characteristics).
- Define and develop experiments to examine the health effects of agglomeration and deagglomeration of nanomaterials.
- Develop and validate harmonized protocols for assessing nanomaterial exposure through established and recognized international bodies such as ISO and OECD.
- Establish crude testing protocols to examine the effects of product wear and tear on exposure.
- Identify a minimum data set that must be included in a database where correlations to health or environmental effects may be made in the future.
- Establish a database for deposition of data generated by Federally funded research.
- Standardize data formats to facilitate surveillance studies.
- Identify facilities that would be willing to participate in a pilot registry for nanomaterial exposures.

8. Implementation Issues

Introduction

Key Points

A roadmap should be developed for a comprehensive source-to-dose exposure assessment throughout the life of nanotechnology-enabled products and materials; it should be executed in coordination with major international standards-setting organizations to provide a framework for effective national and global collaborative research efforts. In the long term, such a roadmap will support prioritization of nanomaterials, populations, and techniques for exposure assessment studies and, therefore, will facilitate proactive risk assessment and risk management.

Participants

General discussions on implementation issues took place during the breakout sessions on the second day of the workshop.

Implementation

Barriers and Mechanisms

Fund Research

Resource limitations are viewed by many as a barrier to increasing research on nanotechnology health effects. For the most part, health and safety funding has been only that provided by individual agencies. Funding flowing through the NNI has mostly been used for development of applications, not health and safety. A larger proportion of NNI funds should be made available to the agencies for health and safety research.[1]

Properly designed and executed research studies of the environmental, health, and safety (EHS) implications of engineered nanomaterials require multidisciplinary approaches and are time- and labor-intensive. To date, funding priority for emerging nanotechnologies has been given to the creation and development of nanomaterials and nanomanufacturing processes. Relative to development and manufacture, research funding for environmental, health, and safety implications of engineered nanomaterials is highly disproportionate (see the NNI's Supplement to the President's FY 2010 Budget) (*1*). On the other hand, an industry-based participant pointed out that Federally funded research often has little connection to what can be commercialized. New nanomaterials are often developed without regard to safety; a lot of money can be spent to develop a material without doing safety testing. It is unlikely that industry will be willing to take on the entire testing burden.

Nanotechnology health effects are a worldwide concern because the consumer products of which engineered nanomaterials are components are not subject to trade regulations. International efforts in nanotechnology health and safety research should therefore be coordinated. This would prevent a potentially costly duplication of efforts. To some degree, the Organisation for Economic Co-operation and Development (OECD) has already made progress in this vein, but progress has been slow due to the political nature of the OECD. Furthermore, the OECD partners consist of a limited set of countries. A goal would, therefore, be to facilitate a more inclusive global collaboration in nanotechnology health and safety research in which the process of consolidating information is less cumbersome than it is currently.

1 NNI funding represents the sum of the nanotechnology-related funding allocated by each of the participating agencies.

Establish Collaborations

Research specialization, the broad range of audiences affected by exposure, and the intellectual property and competitive concerns of industry all may interfere with the ability to productively engage in nanotechnology EHS research. Cross-disciplinary communication is essential in collaborative, integrated research. Specifically, participants suggested that organizations such as Society of Toxicology (SOT) and International Society of Exposure Science (ISES) develop joint meetings. Funding entities could require both toxicology and exposure data in any request for proposals (RFPs). Cross-agency RFPs could be developed to encourage these types of collaborations, and centers could be established. In addition, funding agencies could have RFPs in each area and then bring all grant recipients to an annual meeting.

Workshops allow people from many disciplines to come together for discussions and potential collaborations. Advertising for workshops should make it clear that academia, government, nongovernmental organizations (NGOs), and industry are all welcome and encouraged to come to the table. To achieve a balance, a minimum number of participant slots could be designated to each group. Alternatively, certain groups could be targeted with a focused advertising campaign.

Another idea is to bring stakeholders together in a series of brown bag lunches that are open to a wide variety of people. Lunches could be structured around a short presentation (30 minutes) and allow attendees another 30 minutes to talk. These types of programs have worked well to foster interdisciplinary collaborations in the academic world. Providing a free lunch or other incentive would help draw participants to the event.

Industry may be the most difficult sector to engage in interdisciplinary collaborations. Businesses are often worried about losing their competitive edge by compromising trade secrets. One incentive might be an award or tax incentive for interdisciplinary collaborations and public–private partnerships. Another way to motivate industry to consider broad human health and environmental effects is to create nanotechnology equivalents of programs like Energy Star and Water Wise. The public's positive perceptions of these programs translate to tangible benefits to the participating companies, such as better public relations and higher sales.

Industry could be invited to government discussions addressing nanotechnology and environmental/human health risks. The opportunity to participate in the design of governmental nanotechnology programs and/or regulations is a huge incentive for industry. This could work well for large companies, but it still may be challenging to identify smaller companies to invite to participate. Assuming small companies can be identified, their incentives may be somewhat different, for example, acquiring new information of interest or raising their corporate profiles.

The discussion group identified several negative forms of pressure that could be applied to industry to encourage interdisciplinary collaborations. For example, currently there are no penalties or regulations for nanomaterial use and/or production because risks have not yet been identified. A big advertising campaign (sponsored by the government or another group) could highlight the uncertainties associated with nanotechnology. Essentially, this creates a penalty for industry and motivates companies to participate in a government nanotechnology program. Alternatively, the labeling of nanomaterials (probably several years away) may motivate industry to consider EHS implications as a way to assure consumers that its products are safe.

Existing mechanisms can be leveraged to help address research needs for environmental, health, and safety implications of accidental exposure to engineered nanomaterials. The NNI acts to foster collaboration and integration of nanotechnology research initiatives across Federal agencies. Better clarification of the roles of government agencies in funding research may also be beneficial, especially with regard to jointly developing research portfolios and grant solicitations to ensure funding opportunities for multidisciplinary cross-cutting research.

Learn from Others

Finally, knowledge can be gained from European Union (EU) Framework research initiatives on mechanisms to better foster communication and collaboration among U.S. and international researchers. Suggestions included the use of a

strategy similar to the EU Framework Programmes in Europe, wherein several universities have been brought together in projects, although the strategy is not nanotechnology-specific. The EU has three areas of focus: (1) schools/colleges/museums, (2) web focus groups/stakeholder meetings between the public and government, and (3) test cases with the public, with scientists, and with industry. In Germany producers along the supply chain were brought together using the REACH[2] format. The room was packed. Now these meetings must include exposure scenarios. The United States and European Union held a joint meeting on nanotechnology and life cycle assessment several years ago that raised points similar to those mentioned during the two days of the exposure assessment workshop (2). One point largely left out of workshop discussions was economics: What is the economic benefit of including an EHS focus in nanotechnology activities?

Fund Data Collection and Sharing

Contract administration procedures can help by assuring that funds go to data collection and data sharing and by making sure that grantees follow through on collecting and reporting the data. It was noted that although NSET Subcommittee members and NNI department and agency representatives have expertise that no one else does, they are not necessarily leads (for issuing grants or contracts).

The question of whether or not there is a suitable exposure metric in existence was addressed by the participants. Although toxicologists and exposure scientists do communicate, do exposure scientists know what toxicologists need, and vice versa? In defining "minimum characterization," toxicologists and exposure scientists need to collaborate.

At this point it was reiterated that any data collected needs to go "somewhere" and that development of an appropriate database is key. It was also pointed out that as the process moves forward, combination exposures need to be considered. Thus, the nanotechnology data must fit into existing frameworks where possible.

In addition to the need to develop the appropriate tools, there need to be qualified scientists who can perform the analysis, interpret the data, and perform related tasks.

Develop a Roadmap Test Case

A roadmap for a comprehensive source-to-dose[3] exposure assessment throughout the life of nanotechnology-enabled products and materials is needed to provide a framework for effective national and global collaborative stakeholder research efforts. This roadmap will further prioritization of nanomaterials, populations, and techniques for exposure assessment studies and, therefore, will facilitate proactive risk assessment and risk management. This roadmap must also include standardization of methods and, therefore, its development and execution should be conducted in coordination with major international standards-setting organizations.

The roadmap may also pull in groups thus far missing from the discussion (i.e., industries of interest, catalyst chemists). The first step is to identify the key goals in the roadmap, then determine where efforts need to be placed. Three sources of exposure must be included: manufacturing, processing, and use; a fourth source, disposal, occurs from all three sources. Several Federal agencies have rough proposal maps to work from, which need to be integrated. Besides this central issue, the following two points concerning barriers for cross-cutting research issues and the respective roles of government, academia, industry, and NGOs all fall under the roadmap.[4]

Given that one key problem identified is the lack of dialogue between toxicologists and exposure scientists (although, it was also noted that there is so little exposure data that they would have nothing to talk about), it was suggested that the roadmap should include an additional objective of expanding networking between these communities.

2 REACH stands for registration, evaluation, authorization, and restriction of chemical substances and is the EU regulation on chemicals and their safe use (EC 1907/2006; http://ec.europa.eu/enterprise/sectors/chemicals/reach/index_en.htm).

3 The EPA website http://epa.gov/nerl/goals/health/models.html defines source-to-dose models as understanding the risk from exposure to chemicals from "the accurate estimation of the route/pathway and concentration of the chemical [by which an individual is exposed], ... how much of the chemical is absorbed into the body (absorbed dose), and the amount of the chemical that is delivered to the targeted body organ (targeted tissue dose)."

4 Since the workshop, the National Research Council has been charged with developing a comprehensive research roadmap to establish short- and long-term priorities, mechanisms for achieving priorities, objectives under different funding scenarios, and criteria for measuring research progress.

It was suggested that in parallel to the development of the roadmap, one test case should be applied to the roadmap: run the test case through the entire roadmap with the involvement of the public (for example using a test case such as fibers or cosmetics containing nanomaterials in a venue such as PBS KIDS™ Roadshow). The test case should bring all parties together, including, for example, chemists, product formulators, and toxicologists.

Parties to include in designing the roadmap are the pigment industry, trade organizations, Society for Risk Analysis (SRA), Society of Toxicology (SOT), International Society of Exposure Science (ISES), medical organizations, industrial hygiene nurses, patent offices, American Chemical Society (ACS), and educators. The parties can assist in developing the source-to-dose relationships, filling in the data gaps, standardizing methods to measure exposure, fate, transport, etc. It will be important to:

- Fill the "gap" of exposure; exposure scientists must be at the table when RFAs are solicited.
- Develop the exposure metrics (number count, shape, etc.) and minimum characterization.
- Develop tools: Are there funds to adequately address this? Can tests be done (on surrogates, etc.), chambers studies, emission studies?
  - Example tool: Risk Information Exchange (RiskIE)[5].

The roadmap was once again identified as a critical factor in developing these tools, but how does the roadmap fit within a bigger picture with respect to the goal of safe products and synergistic events of multiple exposures?

Engage the Public Appropriately

It is important to effectively promote public participation. Ultimately, the public has to be engaged and helped to become reasonably confident, comfortable, and accepting of nanotechnology.

How is the public to be represented and effectively engaged? Some possibilities include the following:

- Consider a case study approach to developing the roadmap. NNI agencies would be charged with putting the roadmap "to work" in a public forum as a hands-on way to involve the public.
- Webcast a road show case study (e.g., on engineered nanomaterials in cosmetics).
- Create an unaffiliated consumer ombudsman position.
- Determine what amount of risk communication has to happen.

The ultimate endpoints of assessment work are communication with the public, public acceptance, and risk communication (e.g., the current DuPont and Environmental Defense Fund nano risk framework with three case studies [3]).

Sector Roles

In the United States there is some confusion regarding the missions of the Federal agencies which perform and/or fund research. Exacerbating this confusion is the general lack of a clear model for the relationships among government entities (Federal, state, and local), NGOs, academia, industry, trade organizations, professional societies, and unions in the development of collaborative cross-cutting research programs.

All sectors (academia, government, NGOs, and industry) must play a role in training the next generation of scientists. For example, fellowships could be offered that bring in people from different sectors.

Government

Because the responsibilities and roles for health and environmental surveillance are distributed across industry, government, academia, and NGOs, there is a built-in vulnerability to parochial interests that creates barriers to an integrated approach. Federal public health agencies can play an important role in collecting and providing access to information created through taxpayer-funded work. Policies promoting this are in place, but require a sustained effort to implement. The availability of this information provides opportunities to solicit proposals from academia for innovative analyses or epidemiologic research that would not otherwise be practicable. The Federal public health agencies will need to take

5 RiskIE is an Internet database that "contains notification about human health risk assessment projects in progress or just completed with the intention of communicating among government, industry, academic, and environmental stakeholders" (http://www.allianceforrisk.org/RiskIE/RiskIE_FAQ.htm).

a leadership role in creating a vision and translating it into a multidisciplinary approach, which would be needed to succeed. Government agencies engaged in materials research and engineered nanomaterial utilization, such as the Departments of Energy and Defense, could establish exposure registries that would help them manage nanotechnology risks and potentially support collaborative research with academia.

The government plays a role in both R&D and regulation. Nanomaterials may often be very different than other materials; thus, there is no clear model on which to base regulatory decisions. The main role for the government at this early stage is conducting research. This research should be "visionary," "goal-oriented," and focused on the newest and latest technologies. The government is a large source of funding both for internal and external (i.e., academic) research. Consequently, it is possible for government laboratories to explore lines of research other than those of academia or industry. The lack of emphasis on publications and tenure also allows government scientists to more easily engage in group and cross-disciplinary work. Participants also suggested funding studies during the premanufacturing phases to determine occupational exposures, commercialization pathways of these nanomaterials, where these materials are commercialized, the products they may be incorporated into, and the likely consumer exposure scenarios. As part of this effort, developing standardized tools is needed (e.g., saliva test/bioavailability studies, chamber studies) as well as providing training and support for skilled scientists to conduct experiments and adequately interpret data. Existing methods must be adapted to nanomaterials.

Joint RFAs on nanotechnology safety should be created by agencies (e.g., NIEHS and EPA) so that both toxicology and exposure are included. For example, NIEHS has supported joint solicitations on other topics with both NIOSH and EPA. It was suggested that "centers" should not be used; rather, there should be subgroups for exposure, toxicology, and epidemiology, and the entire group should meet annually, as a requirement in the RFA, so groups can see how they fit into the roadmap, since the RFA is a cooperative agreement. There will be a need for a strong contract administrator—one with dose–source background—who can see the big picture. The NSET Subcommittee is best equipped to see the big picture at this time and should bring all Federal agencies together as part of the NNI to address issues specific to nanomaterial exposure assessment.

Given its resources, the U.S. Federal Government may be best poised to perform large complicated studies such as cohort epidemiology studies, but it also needs to be a major source of research funding on environmental, health, and safety implications of engineered nanomaterials. Federal agencies such as NIOSH, OSHA, NIST, and the Department of Commerce have roles to play pertaining to how their missions intersect with needs for assessing exposure to nanomaterials in the workplace and constitute research drivers through programmatic needs, oversight, and/or regulation. Some state and local governments may drive cross-cutting research through regulation. NGOs and unions may not have the capacity to fund research, although they should be considered as important collaborators for planned research because of their knowledge of production processes, job practices, etc.

Nongovernmental EHS Organizations

NGOs include standards-setting organizations that have already played a role in establishing the industry consensus standards needed to make nanotechnology possible, and they will continue to play a large role in providing the nomenclature and metrics that will make surveillance possible. Industry associations, labor unions, and professional societies can serve as the focal point for surveillance projects of mutual interest to their members. The Synthetic Vitreous Fiber Occupational Exposure Database is an example of a project organized by an industry group (*4*).

NGOs often focus on consumer or environmental advocacy issues. They offer a grassroots perspective about public opinion—what people accept, fear, and reject with regards to nanotechnology. NGOs generally do not perform research (although they may develop some basic statistics and figures from databases), but they can recommend future research directions that meet their constituents' needs.

A number of groups and professional societies were identified as needing to play a key role, including ISES, SOT, SRA, trade organizations, industry associations, Chemical Abstracts, occupational/environmental medicine, nursing/medical

practitioners, pharmacologists, and educators. It is important for these groups to help determine what networks among groups should be developed, and what specific deliverables should result.

Academia

Academia has the role of performing research, and given its expertise, is well positioned to help determine research needs.

Academia should be encouraged to form multidisciplinary approaches. Surveillance can promote health research by identifying health outcomes that would benefit from research to understand biological mechanisms. Health research and toxicology can generate hypotheses on outcomes that can be targeted in surveillance programs and epidemiology studies. Surveillance can identify cohorts at risk for a disease and should invite their participation in the voluntary human subjects research needed to validate the effectiveness of screening tests and therapy. Collaboration between field and bench scientists makes each more productive.

Academia is often asked to confirm or deny scientific premises. Via independent research, journal articles, and conferences, academia's role is to act as a neutral party and to provide factual information. A requirement that all Federally funded research yield a research paper written in layman's terms could be beneficial in broadening access to nanotechnology research results.

Industry

Industry's role with regard to environmental, health, and safety [matters] is to comply with government regulations and to perform its own due diligence when handling nanomaterials. Generally, industry is expected to be a leader in innovative research, since there are market-driven incentives for new and beneficial technologies. Manufacturers and marketers also have the responsibility to their workers and the consumers to research adverse and unintended consequences of their products. When regulating authorities have sound information on which to base regulations, government oversight can simplify risk–benefit decisions and provide useful guidelines to companies that help mitigate their liabilities and risks. A national risk assessment questionnaire might also be a safe way for industry to share information. The survey could be kept confidential and information only distributed in a cumulative form.

It would be valuable to have a mechanism whereby industry could share its current nanomaterial practices with outsiders. Industry is often reluctant to invite the government in the door because of the risk of liability and loss of secret or competitive information. It may be possible to create a "safe place" for industry-government conversations by using trade associations as mediators. Professional organizations (i.e., the Association of Industrial Hygienists) can translate governmental concerns into worker and health exposure concerns—topics that industry understands and that are much less threatening than "show me your data."

In December 2008, the Woodrow Wilson Center held a successful forum where industry members came together to talk about nanomaterial safety in food packaging. Science was the focus, and questions and concerns about nanomaterials (all aspects, including regulation and research) were openly discussed.

Industry may also sponsor research to meet regulatory requirements such as toxicological studies for producing useful Material Safety Data Sheets (MSDS) and premanufacture notices (PMN) and product bulletins, and for overall product stewardship. Industry trade associations may serve as clearinghouses for research funding of common interest to member companies and may also play a central role in gathering data, developing knowledge (e.g., determining and publishing guidelines), and disseminating information, including to downstream users.

Adaptive Management of EHS Strategy

The NSET Subcommittee and its NEHI Working Group should consider the following outcomes or discussion points in its adaptive management process for EHS research:

- The need for valid and harmonized protocols for exposure assessment was a recurring theme throughout the workshop.
- The need for better coordination among toxicology and exposure assessors was also emphasized, particularly with regard to what

each party can bring to the table for collaborative research.

- Funding for EHS research on nanomaterials remains a high-profile concern.
- Related to funding, there was considerable discussion on who does what, who funds research, and who does not. There appears to be a need to better clarify what the NNI is and how government agencies and the NNI relate to one another.
- Organization of information, quality of information, and ability to locate information were also important, related issues.

There are no fundamental barriers to beginning useful nanoEHS R&D programs, with the recognition that these will need to adapt as the industry changes and as knowledge of health and environmental effects increases.

Recommendations

- Foster collaborations among all stakeholders.
- Establish mechanisms to better foster communication and collaboration among U.S. and international researchers.
- Fund studies during the premanufacturing phases to determine occupational exposures, where these materials are commercialized, the products they may be incorporated into, and the likely consumer exposure scenarios.
- Develop a roadmap for nanomaterial exposure assessment.
- Establish collaborative programs to train the next generation of scientists.

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Appendix A. Workshop Agenda

Day 1, Tuesday February 24, 2009, CPSC, Bethesda, MD

8:00 a.m.	Welcome
	Nancy Nord, Acting Chair, Consumer Product Safety Commission
	About the National Nanotechnology Initiative, Dr. Clayton Teague, Director, National Nanotechnology Coordination Office
8:10	*About the Nanotechnology Environmental and Health Implications Working Group (NEHI)*, Conference Overview and Charge to Participants, Dr. Vladimir Murashov, NIOSH
8:30-11:00	Presentations on the state of the science or technological development globally with respect to supporting risk management needs identified in the NNI document *Strategy for Nanotechnology-Related Environmental, Health, and Safety (EHS) Research* (NSET 2008)
	Research Need 1: Characterize exposure among workers Dr. Robert Herrick, Harvard University.
	Research Need 2: Identify population groups and environments exposed to engineered nanoscale materials Dr. David MacIntosh, Environmental Health & Engineering, Inc.
	Research Need 3: Characterize exposure to the general population from industrial processes and industrial and consumer products containing nanomaterials Dr. Paul Lioy, Rutgers University
	Research Need 4: Characterize health of exposed populations and environments Dr. William Halperin, University of Medicine & Dentistry of New Jersey
	Research Need 5: Understand workplace processes and factors that determine exposure to nanomaterials Dr. Susan Woskie, University of Massachusetts, Lowell
	Emerging Needs in Human and Environmental Exposure Assessment Dr. Paul Schulte, NIOSH
11:10	Group discussions: State of the science
12:00 p.m.	Lunch
1:00	**BREAKOUT DISCUSSIONS**
	Main objective: develop "adaptive management" statements based on discussions of the following:
	■ Where we are in addressing research needs?
	■ Where we need to be in addressing research needs in 5 years?
	■ Are the current research needs framed correctly in consideration of evolving understanding of the state of the science? What are the emerging trends?
	Specific technical questions for each research need
	Research Need 1, Session Co-Chairs: Dr. Robert Herrick and Dr. Charles Geraci (NIOSH) Rapporteur: AAAS Fellow Jane Dennison, NNCO: Marlowe Epstein, Liesl Heeter
	Research Need 2, Session Co-Chairs: Dr. David MacIntosh and Ms. Michele Conlon (EPA) Rapporteur: AAAS Fellow Meghan Radtke; NNCO: Ken Vest

Research Need 3, Session Co-Chairs: Dr. Paul Lioy and Dr. Treye Thomas (CPSC)
Rapporteurs: AAAS Fellows Joe Cresko, Gina Schatteman; NNCO: Heather Evans

Research Need 4, Session Co-Chairs: Dr. William Halperin and Dr. Paul Wambach (DOE)
Rapporteur: AAAS Fellow Jessica Eisner; NNCO: Pat Johnson

Research Need 5, Session Co-Chairs: Dr. Susan Woskie and Dr. Aleks Stefaniak (NIOSH)
Rapporteur: AAAS Fellow Jose Zambrana; NNCO: Phil Lippel

Emerging Research Needs, Session Chair: Dr. Paul Schulte (NIOSH)
Rapporteur: AAAS Fellow Katya Delak; NNCO: Geoff Holdridge

16:00 p.m. Break (Breakout leaders prepare a single summary of findings)

16:30 p.m. Breakout discussion reports in plenary session

16:40 p.m. Open discussion: Building dialogue

17:30 p.m. Closing remarks

Day 2, February 25, 2009

8:00 Recap of Day 1 and charge for Day 2, Vladimir Murashov

8:15-10:45 **BREAKOUT DISCUSSIONS**

Six concurrent breakout sessions on general/cross-cutting issues for the five research needs and for the emerging needs:

- What is the role of informatics; how exchange of information could be made more efficient?
- How can cross-cutting research issues be addressed?
- What are the barriers for addressing cross-cutting research issues?
- What is the role of government/academia/industry/NGOs?
- What mechanisms exist or should be established to address research needs?

Research Need 1, Session Co-Chairs: Dr. Robert Herrick and Dr. Charles Geraci (NIOSH)
Rapporteur: AAAS Fellow Jane Dennison; NNCO: Marlowe Epstein/Liesl Heeter

Research Need 2, Session Co-Chairs: Dr. David MacIntosh and Ms. Michele Conlon (EPA)
Rapporteur: AAAS Fellow Meghan Radtke; NNCO: Vivian Ota Wang

Research Need 3, Session Co-Chairs: Dr. Paul Lioy and Dr. Treye Thomas (CPSC)
Rapporteurs: AAAS Fellows Joe Cresko, Gina Schatteman; NNCO: Heather Evans

Research Need 4, Session Co-Chairs: Dr. William Halperin and Dr. Paul Wambach (DOE)
Rapporteur: AAAS Fellow Jessica Eisner; NNCO: Pat Johnson

Research Need 5, Session Co-Chairs: Dr. Susan Woskie and Dr. Aleks Stefaniak (NIOSH)
Rapporteur: AAAS Fellow Jose Zambrana; NNCO: Phil Lippel

Emerging Research Needs, Session Chair: Dr. Paul Schulte (NIOSH)
Rapporteur: AAAS Fellow Katya Delak; NNCO: Geoff Holdridge

10:45 Break (Breakout leaders prepare a single summary of findings)

11:15 Breakout discussion reports in plenary session

11:25 Open discussion: Building dialogue, next steps, and how you can participate

12:30 p.m. Closing remarks

Appendix B. Workshop Participants[1]

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Appendix C. List of Acronyms

AAAS	American Association for the Advancement of Science
CBI	Confidential business information
CDC	Centers for Disease Control and Prevention
CPSC	Consumer Product Safety Commission
DOC	Department of Commerce
DOD	Department of Defense
DOE	Department of Energy
EHS	Environment(al), health, and safety
ENM	engineered nanomaterial(s)
EPA	U.S. Environmental Protection Agency
EU	European Union
FDA	Food and Drug Administration
GIS	geographic information system
HHS	U.S. Department of Health and Human Services
ICON	International Council on Nanotechnology (Rice University)
ISES	International Society of Exposure Science
ISO	International Organization for Standardization
MSDS	Material Safety Data Sheet
NAICS	North American Industry Classification System
NEHI	Nanotechnology Environmental and Health Implications Working Group of NSET
NGO	Nongovernmental organization
NIEHS	National Institute of Environmental Health Sciences (NIH)
NIH	National Institutes of Health
NIL	Nanoparticle Information Library (NIOSH)
NIOSH	National Institute for Occupational Safety and Health (CDC)
NIST	National Institute of Standards and Technology
NMSP	Nanoscale Materials Stewardship Program (EPA)
NNCO	National Nanotechnology Coordination Office
NNI	National Nanotechnology Initiative
NOES	National Occupational Exposure Survey
NSET	Nanoscale Science, Engineering, and Technology Subcommittee of the National Science and Technology Council's Committee on Technology
NSF	National Science Foundation
NSTC	National Science and Technology Council
OECD	Organisation for Economic Co-operation and Development
ORNL	Oak Ridge National Laboratory (DOE)
OSHA	Occupational Safety and Health Administration (DOL)
R&D	Research and development
REACH	Registration, Evaluation, Authorization, and Restriction of Chemical substances (EU regulation)
RFA	Request for application
RFP	Request for proposal
SOT	Society of Toxicology
SRA	Society for Risk Analysis
SBIR	Small Business Innovation Research program (across several U.S. Government agencies)
TEM	Transmission electron microscopy
TLV	Threshold limit value
TSCA	Toxic Substances Control Act (1976)
UMDNJ	University of Medicine and Dentistry of New Jersey
UN	United Nations
USDA	U.S. Department of Agriculture
USGS	U.S. Geological Survey
WTEC	World Technology Evaluation Center

National Science and Technology Council; Committee on Technology
Subcommittee on Nanoscale Science, Engineering, and Technology

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