National Nanotechnology Initiative

ENVIRONMENTAL, HEALTH, AND SAFETY RESEARCH STRATEGY

National Science and Technology Council
Committee on Technology

Subcommittee on Nanoscale Science, Engineering, and Technology

OCTOBER 2011

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The Nanoscale Science, Engineering, and Technology (NSET) Subcommittee is the interagency body responsible for coordinating, planning, implementing, and reviewing the National Nanotechnology Initiative (NNI). It is a subcommittee of the Committee on Technology of the National Science and Technology Council. 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 related to the NNI, including this strategy document. More information is available at http://www.nano.gov.

About this Document

This document is the NNI's Environmental, Health, and Safety (EHS) Research Strategy. The NNI EHS Research Strategy aims to ensure the responsible development of nanotechnology by providing guidance to the Federal agencies that produce the scientific information for risk management, regulatory decision making, product use, research planning, and public outreach. It describes the NNI's EHS vision and mission, the state of the science, and the research needed to achieve the vision. This 2011 plan updates and replaces the *2008 NNI Strategy for Nanotechnology-Related Environmental, Health, and Safety Research*.

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EXECUTIVE OFFICE OF THE PRESIDENT
NATIONAL SCIENCE AND TECHNOLOGY COUNCIL
WASHINGTON, D.C. 20502

September 16, 2011

Dear Colleague:

Nanotechnology has generated remarkable scientific and technological advances in a wide array of scientific disciplines, strengthening the U.S. economy through accelerated innovation, advanced manufacturing, and secure high-tech jobs for thousands of Americans. Much of this progress has been facilitated by the National Nanotechnology Initiative (NNI), which coordinates goals, priorities, and strategies among Federal agencies and promotes interdisciplinary research and infrastructure development critical to the advancement of nanotechnology.

In order to achieve nanotechnology's potential to address the Nation's greatest challenges, new nanomaterials and nanotechnology-enabled products must be safe for public use from their inception to their disposal. To this end, the NNI developed this Environmental, Health, and Safety (EHS) Research Strategy, which provides a framework to produce critical data for the science-based risk analysis and management that will both protect the public and the environment and support responsible product development and commercialization. This strategy will advance our Nation's international competitiveness, as called for in the President's *Strategy for American Innovation*, and bolster the U.S. economy.

Over a two-year period the NNI hosted four multi-disciplinary, multi-sector workshops to examine the current state of nanotechnology EHS science, gaps in research, and barriers to progress. The resulting 2011 NNI EHS Research Strategy incorporates a broad range of stakeholder perspectives and ideas. In addition, the Strategy incorporates recommendations from the President's Council of Advisors on Science and Technology and the National Academies.

By focusing on the principles of risk assessment and life-cycle analysis, this document illuminates a clear path forward to the responsible development of nanotechnology while promoting continued American leadership in this important area of technological innovation.

Sincerely,

John P. Holdren

John P. Holdren
Assistant to the President for Science & Technology
Director, Office of Science and Technology Policy

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Vision

In support of the National Nanotechnology Initiative (NNI), the vision for environmental, health, and safety research in nanotechnology is a future in which nanotechnology provides maximum benefit to the environment and to human social and economic well-being.

Mission

The NNI agencies serve the public good through the development and deployment of a coordinated nanotechnology environmental, health, and safety research strategy that:

- Protects public health and the environment
- Employs science-based risk analysis and risk management
- Fosters technological advancements that benefit society

Terminology Used in the NNI Environmental, Health, and Safety Research Strategy

Consistent with the 2006 NNI report *Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials*,[1] and for the purposes of this document, the term *engineered nanomaterials* (or ENMs)* refers to those materials that have been purposely synthesized or manufactured to have at least one external dimension of approximately 1–100 nanometers (nm)—at the nanoscale—and that exhibit unique properties determined by this size. In this document, when the term nanomaterials is used alone, it refers to engineered nanomaterials.

This definition also applies to *nanotechnology-enabled products (NEPs)*, that is, intermediate engineered nanoscale products, including ENMs embedded in a matrix material, that exist during manufacture and in final products. Additional definitions for terms such as *agglomerates* and *aggregates* that are used throughout this strategy document can be found in Appendix C.

NanoEHS is used in this strategtty document as a shorthand term to refer to nanotechnology-related environmental, health, and safety (research, etc.).

* The term *engineered nanomaterial* is applicable to the NNI 2011 EHS Research Strategy and overall nanotechnology-related EHS research. This term does not necessarily apply to Federal regulatory statutes or policies relevant to nanotechnology.

1. NSET/NSTC, Washington, DC; http://www.nano.gov/NNI_EHS_research_needs.pdf.

Executive Summary

Nanotechnology allows scientists to work at the nanoscale to produce technological advances in such diverse areas as electronics, energy, environmental remediation, medicine, security, and space. To promote nanotechnology innovation and economic benefit, the National Nanotechnology Initiative (NNI) was established in 2000 as the Federal Government's multiagency, multidisciplinary research and development (R&D) program. The goals of the NNI are fourfold: (1) to advance a world-class nanotechnology R&D 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.

Environmental, health, and safety (EHS) research is essential to successful achievement of all four NNI goals; however, it is most closely linked to the goal of responsible development. The NNI agencies collaboratively developed a nanotechnology EHS research strategy that focuses on the use of science-based risk analysis and risk management to protect public health and the environment while also fostering the technological advancements that benefit society. The strategy serves as guidance to the Federal agencies that produce and use scientific information to develop nanotechnology risk assessments that inform risk management and regulatory decisions. Given the dynamic nature of research in this area, the NNI incorporated adaptive management into its first NNI EHS Research Strategy, the 2008 NNI *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research*. This document, the 2011 NNI *Environmental, Health, and Safety Research Strategy*, is a result of that process and revises and replaces the 2008 strategy.

Formulating a Science-Based Risk Management Research Framework

The 2011 NNI EHS Research Strategy is grounded in the principles of risk assessment and of product life cycle analyses. Risk assessment includes understanding the magnitude of the potential exposure to humans and the environment and the magnitude of the potential hazard or effects presented by the nanomaterials. Through the risk assessment process, risks and benefits may be compared between a nanomaterial and other substances, between different nanomaterials, or for a single nanomaterial.

Risk assessment may be conducted at selected points along the life cycle stages of product development, manufacture, commercialization and disposal or end of life. Integration of risk assessment with the study of life stages of nanotechnology-enabled products (NEPs) permits identification of critical risk assessment data needs. These data needs have been translated into nanoEHS research needs and organized into core nanoEHS research categories: (1) Nanomaterial Measurement Infrastructure, (2) Human Exposure Assessment, (3) Human Health, (4) Environment, and (5) Risk Assessment and Risk Management Methods. The adaptive management process also identified (6) Informatics and Modeling and ethical, legal, and societal implications (ELSI) of nanotechnology as important additions to the strategy.

In addition to this matrix of research needs, the 2011 NNI EHS Research Strategy was informed by multiple stakeholder consultations: reviews by the President's Council of Advisors on Science and

Technology and the National Academies as well as four multidisciplinary, multi-sector NNI workshops that examined the 2008 NNI EHS Research Strategy, the current status of the science, and gaps and barriers to nanotechnology EHS research.

Structuring the 2011 NNI EHS Research Strategy

The nanoEHS research needs are organized into six chapters (Chapters 2–7), covering each of the core nanoEHS research categories, followed by a chapter on the means to effectively move nanoEHS research forward (Chapter 8). Each of the first five research category chapters contains a set of goals, research needs to achieve those goals, and an analysis of ongoing research in the category. New in the 2011 NNI EHS Research Strategy are the chapter describing the critical role of informatics and modeling in organizing the expanding nanoEHS knowledge base and the chapter promoting timely and effective achievement of strategic NNI nanoEHS goals. ELSI considerations are woven throughout the research chapters of this document to inform research planning and data and product management at all levels. (Appendix D provides a comprehensive chart of all the nanoEHS research needs.)

Targeting and Accelerating Research

To move expeditiously toward realization of the vision and goals of the 2011 NNI EHS Research Strategy and to address several challenges that span all of the research categories, it will be necessary for NNI agencies and programs to be highly focused and to take advantage of the benefits of collaboration and information-sharing among representatives from NNI agencies, academia, industry, nongovernmental organizations (NGOs), the general public, and international governance bodies. The Nanoscale Science, Engineering, and Technology (NSET) Subcommittee and its Nanotechnology Environmental and Health Implications (NEHI) Working Group will serve as a nexus for communication about and facilitation of this focused interagency collaboration. The NEHI Working Group has identified the following key principles to assist agencies in making strategic decisions about research programs that will efficiently advance the NNI EHS research agenda while meeting their respective missions:

- ***Prioritize Nanomaterials for Research.*** The NEHI Working Group has developed research-focused criteria to identify and prioritize engineered nanomaterials (ENMs) and nanotechnology-enabled products (NEPs) that may pose a plausible risk to human health and the environment. These criteria include the risk assessment concepts of the potential for hazard and the likelihood of exposure and ENM-related properties such as high surface reactivity and biological novelty.
- ***Establish Standard Measurements, Terminology, and Nomenclature.*** Standardized measurements ensure the accuracy, precision, and reproducibility of research results and, thus, provide a trustworthy knowledge base for evaluating and understanding exposure and hazards to humans and the environment. Standard terminology and nomenclature are vital to fully characterize and categorize ENMs.
- ***Maximize Data Quality.*** The NEHI agencies recognize the complexity of experimental design and execution of nanoEHS research. Criteria for physico-chemical characterization of ENMs and

establishment of reliable and reproducible assays, methods, and alternative test methods are critical for the production of the highest quality data.

- ***Stratify Knowledge for Risk Assessment.*** Depending upon the decision-making context, a qualitative or quantitative risk assessment may be performed. These two types of risk assessment require different data sets to achieve their respective knowledge thresholds and support the development of tiered risk management tools.
- ***Partner to Achieve NNI EHS Research Goals.*** The NNI agencies recognize the importance of public–private partnerships with industries, NGOs, and universities to develop the data for nanoEHS knowledge thresholds. The NNI Nanotechnology Signature Initiatives (http://www.nano.gov/initiatives/government/signature) are examples of such scientific and investment collaborations.
- ***Engage Internationally.*** The societal challenges for which nanotechnology may provide solutions are global, and as such, provide opportunities for transparent, inclusive, and international collaboration. International engagement is a priority of the NNI and a critical component of 2011 NNI EHS Research Strategy.

Implementing and Coordinating the 2011 NNI EHS Research Strategy

This interagency strategy document will guide programs and investment decisions by the individual agencies as well as in coordinated interagency activities in the coming years. It should be noted that the agencies have varied missions, and their individual priorities may differ in scope and focus from those outlined in this report. For these reasons, continuous coordination is essential, and agencies will work through the NSET Subcommittee, its NEHI Working Group, and the NNCO Coordinator for EHS to ensure the integration of agency implementation plans.

The NNI, as a program, does not fund research; rather, its funding is the sum of nanotechnology-related funding allocated by each of the participating agencies. Through its member agencies, the NNI informs and influences the Federal budget and planning processes.

The 2011 NNI EHS Research Strategy is predicated on both concurrent and sequential progress in all core nanoEHS research categories. Continuous coordination is essential to ensure the integration of agency implementation plans. The NSET Subcommittee and its NEHI Working Group's implementation and coordination framework includes:

- ***Increasing agency participation in NNI EHS research.*** As guidance to the NNI agencies, the 2011 NNI EHS Research Strategy identifies research areas that agencies may recognize as aligning with their missions.
- ***Utilizing the NNI EHS Coordinator.*** The NNI EHS Coordinator facilitates efforts of the NNCO, NSET Subcommittee, and NEHI Working Group in identifying and leveraging nanoEHS research collaborations domestically and internationally; serves as the NNI point-of-contact for stakeholders; and spearheads the 2011 NNI EHS Research Strategy's implementation, coordination, and evaluation.

- ***Refocusing the NEHI Working Group.*** Through consultation with agency representatives, NEHI leadership adapted its monthly meeting format to ensure better coordination and assessment of research to achieve the goals of the 2011 EHS Research Strategy.
- ***Implementing media and networking opportunities.*** The NSET Subcommittee and NEHI Working Group are exploring new social media opportunities to improve interagency communication and stakeholder interactions.
- ***Enabling a broad base of nanoEHS research to support regulatory decision making.*** The NNI 2011 EHS Research Strategy fundamentally depends on sustaining a broad spectrum of basic and applied research. Support from agencies that investigate the fundamental properties of nanomaterials and directly apply research for responsible development is critical to achieve the NNI EHS goals.
- ***Coordinating existing and fostering expanded agency efforts to address priority EHS research needs and identified gaps.*** Through monthly meetings and workshops, the NEHI Working Group will continue to clarify priorities and identify synergistic opportunities to pursue the goals of the strategy through collaboration and joint programs.
- ***Facilitating partnerships with industry.*** The NEHI Working Group will continue to utilize existing small business programs and explore and develop new mechanisms for NNI agencies to partner with industry.
- ***Coordinating standards efforts internationally.*** Several NNI agencies participate in national and international efforts to develop standards, nomenclature, and terminology for nanoEHS research.
- ***Adaptively managing the NNI EHS Research Strategy.*** The NEHI Working Group will periodically review the status of nanoEHS science, progress towards the goals of the 2011 NNI EHS Research Strategy, and stakeholder concerns. These reviews will inform update of the research needs and priorities to maintain a dynamic and timely strategy.

Conclusion

Nanotechnology is a multidisciplinary field requiring the engagement of scientists in disciplines as diverse as materials science, physics, biology, chemistry, engineering, toxicology, clinical practice, social science, and risk assessment, as well as leaders in industry, public health advocacy, healthcare, and participation of the general public. The multicomponent risk management research framework that forms the foundation of this strategy will require focused and sustained coordination by the NEHI Working Group and regular review by the NNI agencies and stakeholders.

1. Introduction to the 2011 NNI Environmental, Health, and Safety Research Strategy

Introduction

Nanotechnology allows scientists to work at the nanoscale to create, explore, and manipulate the biological and material worlds. This capability is leading to technological advances across the landscape of American society in such diverse application areas as electronics, energy, environmental remediation, medicine, security, and space. To capitalize on the novel material properties that emerge at the nanoscale to solve critical issues for U.S. citizens, the National Nanotechnology Initiative (NNI) was established in 2000 as the Federal Government's multiagency, multidisciplinary nanotechnology research and development (R&D) program. Since its establishment, the NNI has served as a locus for communication, cooperation, and collaboration among participating Federal agencies and has provided a framework of shared goals, priorities, and strategies.

The goals of the NNI[2] are fourfold: (1) to advance a world-class nanotechnology R&D 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. Environmental, health, and safety research is essential to successful achievement of all four NNI goals; however, it is most closely linked to the goal of responsible development. Responsible development of nanotechnology encompasses research to understand the environmental, health, and safety (EHS) impacts, as well as the ethical, legal, and societal implications (ELSI) of nanotechnology. Responsible development includes such diverse activities as promoting public outreach and engagement, and the use of nanomaterials to solve environmental challenges such as ensuring a clean water supply and remediating soil contamination.

To integrate responsible development across the broad spectrum of nanotechnology R&D, manufacturing, and material use activities, the NNI agencies have collaboratively developed a research strategy specifically focused on environmental, health, and safety aspects of nanotechnology. As a Federal strategic guidance, this document contains a vision and mission statement for the NNI Environmental, Health, and Safety Research Strategy, goals and research needs for five of the core nanotechnology-related EHS research categories, and evaluations of the status of the science in 2011 and of the Federal portfolio for nanotechnology-related EHS (nanoEHS) research in Fiscal Year (FY) 2009, the last year for which Federal agencies have complete data. Integrated into the strategy are concepts for accelerating the pace of nanoEHS research, for incorporating product life cycle approaches, and for addressing ethical, legal, and societal issues.

2. NSET/NSTC, *NNI Strategic Plan*. Washington DC, 2011; http://www.nano.gov

The NNI EHS Research Strategy provides guidance to the Federal agencies as they develop their agency-specific nanotechnology EHS research priorities, implementation plans, and timelines. Given the dynamic nature of research in this area, the NNI incorporated adaptive management into its first NNI EHS Research Strategy, the 2008 NNI *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research*[3] to allow for modification of the strategy based on research progress, new findings, and product development. This document, the 2011 NNI *EHS Research Strategy*, is a result of that adaptive management process and revises and replaces the 2008 strategy. Agencies whose missions support nanomaterials research are encouraged to use this 2011 document to better understand where their missions and responsibilities are consistent with those of the NNI EHS Research Strategy, identify opportunities for collaboration and cooperation, and assist the NNI in achieving U.S. Federal goals for nanotechnology-related environmental, health, and safety research activities. Overall priority is given to the EHS research that decreases the uncertainty in assessing and managing risk and that addresses the EHS objectives in the NNI 2011 Strategic Plan. (Table 8-1 in this document sets forth the linkages between the NNI's Strategic Plan and its EHS Research Strategy.)

The adaptive management process remains part of the 2011 NNI EHS Research Strategy to ensure proactive, science-based management of engineered nanomaterials (ENMs) into the future. Ongoing evaluation of research progress is conducted by members of the Nanotechnology Environmental and Health Implications (NEHI) Working Group of the multiagency Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the National Science and Technology Council's Committee on Technology. They will review and evaluate progress on an annual basis to ensure that the NNI EHS Research Strategy and activities keep pace with the rapid development of nanotechnology and evolving information on the effects of human and environmental exposure to nanomaterials. Research and development remain essential to the fundamental understanding and development of tools and materials for nanotechnology. Fundamental research, development of infrastructure, and education will continue to contribute to the knowledge needed for Federal nanoEHS research.

Framing the 2011 NNI EHS Research Strategy

The 2011 NNI EHS Research Strategy aims to ensure the responsible development of nanotechnology by providing guidance to the Federal agencies that produce and use scientific information to develop risk assessments that inform decision making. These assessments may compare risks and benefits between a nanomaterial and other substances, between different nanomaterials, or they may evaluate a single nanomaterial. The process of risk assessment (Figure 1-1) is comprised of hazard identification, exposure assessment, dose-response assessment, and risk characterization. Risk characterization, or the systematic and rigorous analysis of available hazard and exposure data, directly informs risk management practices.

3. NSET/NSTC, *NNI Strategy for Nanotechnology-Related EHS Research*. Washington, DC, 2008; http://www.nano.gov/NNI_EHS_Research_Strategy.pdf.

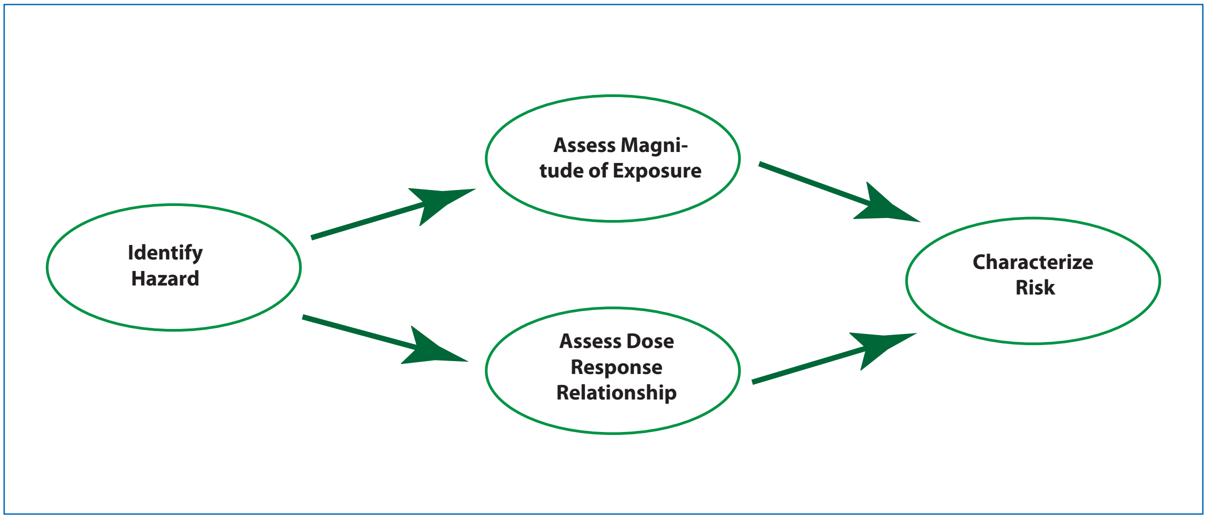

Figure 1-1. Risk assessment process. The risk assessment process is often defined as a mathematical equation Risk equals Hazard times Exposure, or R = H x E, and indicates that the magnitude of the risk is equal to the magnitude of the hazard measurement (dose-response) made for a material multiplied by the magnitude of the exposure.

Source: U.S. EPA.

Figure 1-2 incorporates these key risk assessment components—exposure assessment, hazard identification, and dose–response (left-hand column)—with nanomaterial life cycle stages—from raw materials through commercialization and end of product life (across the top) and the exposure–effects pathways. The concentration of nanomaterials in the environment will depend on factors such as the nature and amount of the nanomaterial released, its physical and chemical properties, and time.

As depicted in blue and red in this continuum, nanomaterials released into the environment may undergo transformation by environmental conditions such as temperature and salinity, biological conditions such as habitat, and the presence of co-contaminants. In turn, the transformed nanomaterials may modify atmospheric, soil, or water chemistry. These transformations may alter the form of the nanomaterials that are transported through the environment, and hence, the ENMs to which humans and ecosystems are exposed. The clustering of nanomaterials into aggregates or agglomerates is an example of transformations that may alter transport and exposure potential. Biological or environmental systems may be exposed to these ENMs and respond through systems and pathways designed to buffer exposures to substances that could perturb human health or adversely impact the environment.

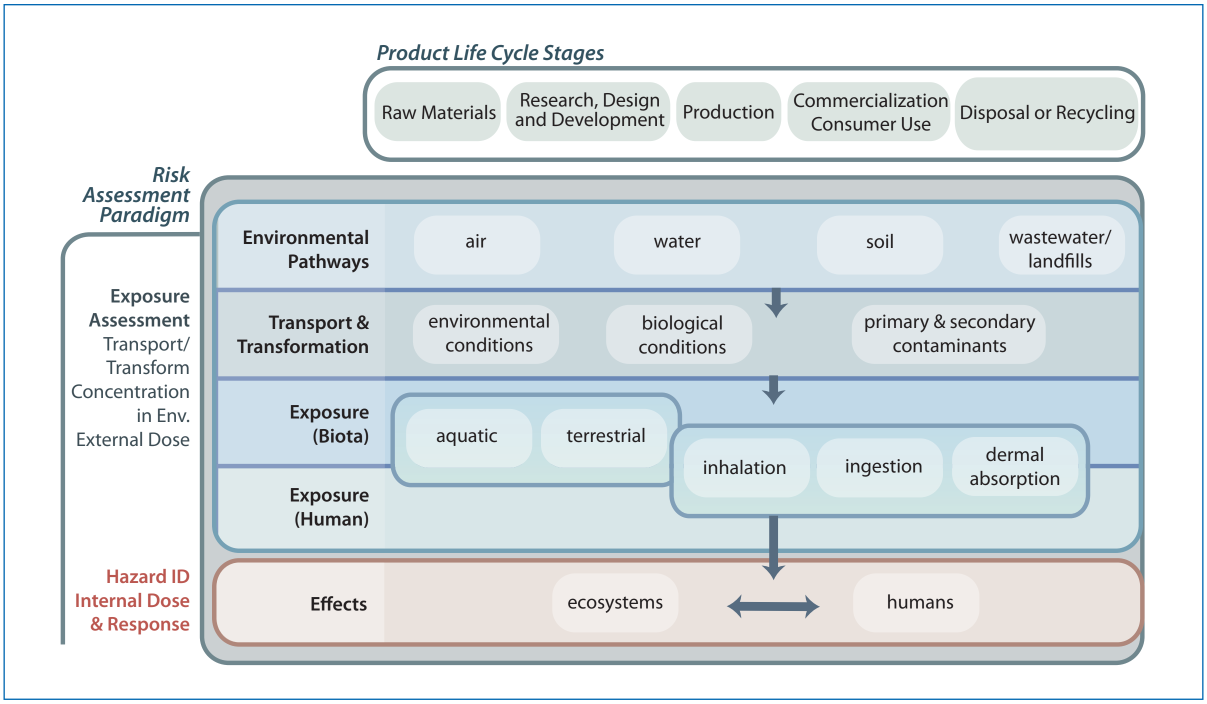

Figure 1-2. The risk assessment paradigm applied across all nanomaterial life cycle stages.

Source: NEHI and N.R. Fuller, Sayo-Art.

These important risk concepts have guided the development of the risk management research framework underpinning the NNI EHS Research Strategy (Figure 1-3). This research framework identifies core research areas to understand and manage risk that provide critical scientific information on (1) nanomaterial measurement infrastructure, (2) human exposure assessment, (3) human health, and (4) the environment. Data from these categories are integrated and employed in the core research area, (5) risk assessment and risk management methods, and are applied to product life cycle, regulatory decision making, public outreach, and research planning. Also serving in an integrative capacity is (6) informatics and modeling, an increasingly essential tool for managing and sharing data and for developing and refining theories, models, and simulations. Ethical, legal, and societal implications of nanotechnology encircle these research components to highlight the need to include ELSI considerations in the design of all of the core categories of EHS research. The dynamic and iterative nature of the NNI EHS Research Strategy is captured in Figure 1-3 by feed-forward and feedback loops that indicate how newly developing data inform and modify the research process and risk management decisions.

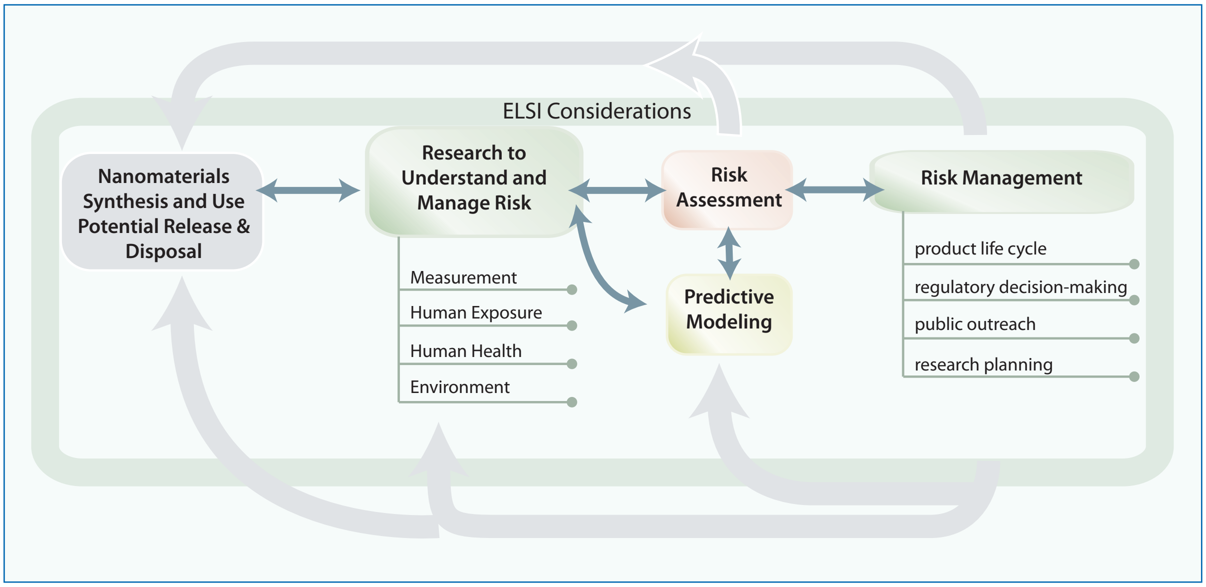

Figure 1-3. Risk management research framework for nanotechnology-related risk management, regulatory decision making, product use, research planning, and public outreach. This research framework identifies core research areas that provide critical scientific information to understand and manage risk. In addition, informatics and predictive modeling are increasingly essential tools for managing and sharing data. Finally, ELSI circles all components of the framework to highlight the need to include ELSI considerations throughout the framework.

Source: NEHI and N.R. Fuller, Sayo-Art.

Process for Developing the 2011 NNI EHS Research Strategy

This strategy is the product of detailed and collaborative planning efforts. As indicated below, the NNI agencies established a comprehensive framework to reassess the 2008 NNI EHS Research Strategy. This included the solicitation, collection, and analysis of relevant information from Federal agencies with responsibility for the oversight of research, development, manufacture, import, sale, or use of engineered nanomaterials and nanotechnology-enabled products. It also included the solicitation, collection, and analysis of input from other stakeholders, including academia, industry, public health advocates, and the general public. The NEHI Working Group reviewed information obtained from multisector meetings and individual comments to identify priority research needs, and gaps and barriers to accomplishing the needed research.

Assessment of Federal EHS Research: Strengths and Weaknesses

Stakeholder consultations included four public workshops, reviews by the National Academies (NA) and the President's Council of Advisors on Science and Technology (PCAST),[4] and other interactions between government scientists and the public.

Between February 2009 and March 2010, the NEHI Working Group, under the auspices of the NSET Subcommittee, convened four nanoEHS workshops open to the public to evaluate the 2008 NNI EHS Research Strategy:

4. PCAST is designated as the National Nanotechnology Advisory Panel and is tasked with biennial reviews of the NNI.

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

At these workshops, representatives from NNI agencies and stakeholder groups reviewed the state of the science and identified critical gaps and barriers to needed research. This information was significant to the Federal dialogue to revise the 2008 NNI EHS Research Strategy; the complete workshop reports are publicly available at http://www.nano.gov.

In 2009, the National Academies conducted a scientific and technical review of the Federal EHS Research Strategy.[5] The NA review committee established a list of elements it considered to be part of an effective nanotechnology risk-research strategy, evaluated whether the Federal strategy had these elements, and assessed how the research identified in the strategy would support risk-assessment and risk-management needs. Specific NA technical recommendations were considered in the development of this 2011 strategy.

The most recent PCAST review of the NNI was completed in March 2010. This review included "an assessment of NNI's performance in helping to orchestrate the identification and management of potential risks associated with nanotechnology, with particular attention paid to reviewing progress the NNI has made in following through on recommendations made in the 2008 National Nanotechnology Advisory Panel review of the NNI."[6] Specifically, the report recommended that the NSET Subcommittee's NEHI Working Group:

- ***Develop clear principles to support the identification of plausible risks associated with the products of nanotechnology.*** (While principles provide a conceptual framework for consideration of plausible risk, NEHI, in keeping with the more practical guidance provided by the NNI EHS Research Strategy, has chosen to develop research-focused criteria to identify and prioritize ENMs and NEPs that might pose a plausible risk to human health or the environment [EHS Research Strategy Chapter 8].)
- ***Further develop and implement a cross-agency strategic plan that links EHS research activities with knowledge gaps and decision-making needs within government and industry to make commercial and regulatory decisions that ensure safe use of nanotechnology products.*** (This NNI EHS Research Strategy is directly responsive to the PCAST request to further develop a cross-agency strategic plan.)

5. *Review of the Federal Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* (National Academies Press, Washington, DC, 2009; http://www.nap.edu/catalog.php?record_id=12559).

6. *Report to the President and Congress on the Third Assessment of the National Nanotechnology Initiative* (PCAST, Washington, DC, 2010; http://whitehouse.gov/sites/default/files/microsites/ostp/pcast-nni-report.pdf), p. 7.

- ***Develop information resources on crosscutting research and nanotechnology EHS issues that are relevant to businesses, health and safety professionals, researchers, and consumers.*** (This recommendation remains a high priority for the NNI agencies. Specifically, Chapter 7 in this document addresses the use of informatics tools to aid in the development, analysis, organization, archiving, sharing, and use of data acquired through nanoEHS research projects.)

Additional input to the NNI EHS Research Strategy has come from detailed public responses to a Request for Information published in the Federal Register and an online dialogue at the NNI Strategy Portal (http://strategy.nano.gov/), which are further described in Appendix A of the 2011 *National Nanotechnology Initiative Strategic Plan*.[7]

In addition to stakeholder consultation and public comment, the Office of Management and Budget (OMB) requested that NNI agencies provide the NSET Subcommittee with detailed information on EHS research projects funded in FY 2009 and that the agencies identify the 2008 EHS research category and need that each project informs. These data were used to identify areas of strength or need when formulating the 2011 NNI EHS Research Strategy. Summaries of the data on these EHS projects are presented by core EHS research category in Chapters 2–6 of this document, and six examples of research progress are highlighted in this report. A complete listing of the FY 2009 EHS research projects is available online at http://www.nano.gov/publications-resources.

The reader should note the difference between the scopes of the research included in the OMB-requested project data reported here for FY 2009 and that reported for environmental, health, safety, and risk mitigation as a part of Program Component Area 7 in the annual NNI Supplement to the President's Budget. The annual budget supplement reports funding for research that is "primarily aimed at understanding risks posed by nanomaterials." Data presented online and elsewhere in this report also include research that supports five of the core EHS research categories but that may not be primarily aimed at understanding potential risks of engineered nanomaterials; this research is predominantly in instrumentation and metrology that enables characterization and measurements of ENMs, and in medical applications research that assesses the safety of nanomaterials being considered for use in the human body. Projects focused on risk mitigation and other topics that the NNI EHS Research Strategy writing teams deemed "not EHS research" are not included in this analysis.

Writing Process

NEHI formed writing teams (over 70 members from 12 NNI agencies; see Acknowledgements) that analyzed the Federal portfolio of projects to determine the balance of efforts focused on the priority research needs and to identify areas of significant investment and under-investment. In addition to tabulating the number of projects and total funding in each core EHS research category, the teams compared the FY 2009 project analysis to the FY 2006 analysis published in the 2008 NNI EHS Research Strategy in order to gauge progress. In developing the projection of future research needs, the teams also considered the relationship of the research needs within and across the core research areas, that is, the sequencing of various kinds of research that depend on results from, or progress in, other research areas, or the need to develop the capacity for specific types of research. A draft version was posted at

7. NSET/NSTC, *NNI Strategic Plan*. Washington, DC, 2011; http://www.nano.gov/.

strategy.nano.gov for public comment (Dec. 1, 2010-Jan. 21, 2011). Where appropriate, this strategy was updated in response to comments and new information.

The success of the strategy outlined in this document depends on the collective efforts of the NNI agencies and their priorities and resources. The strategy forms one component of the ongoing facilitation and coordination by the NSET Subcommittee and the NEHI Working Group of a multifaceted, multi-agency NNI EHS research program.

Structure of the Research Strategy Document

This document provides the concepts, frameworks, research needs, and activities that will assist agencies in making strategic decisions about their nanotechnology EHS research programs. Structurally, the nanoEHS research needs are organized into six chapters (Chapters 2–6), covering five of the core nanoEHS research categories — (1) Nanomaterial Measurement Infrastructure, (2) Human Exposure Assessment, (3) Human Health, (4) the Environment, and (5) Risk Assessment and Management Methods — and a new, sixth core category, informatics and modeling, followed by a final chapter on the means to effectively move nanoEHS research forward.

These five core research categories are strongly interrelated and synergistic, as illustrated in Figure 1-4. The risk of nanomaterials to both humans and the environment is the product of exposure and hazard. Thus, science-based risk assessment and risk management requires data that address research needs in human exposure, human health, and the environment. The generation and organization of a vast body of required data that are accurate, precise, and reproducible requires both a comprehensive nanomaterial measurement infrastructure and predictive modeling and informatics capabilities. This EHS strategy is predicated on both concurrent and sequential progress in all six research categories.

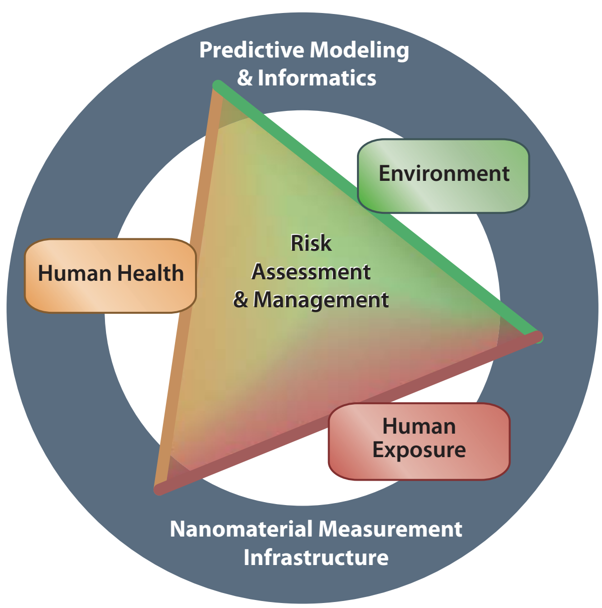

Figure 1-4. Interrelationship of core research areas of the 2011 NNI EHS Research Strategy.

Source: Debra Kaiser, NIST. N.R. Fuller of Sayo-Art provided revised image graphics.

Each of the five research category chapters contains a set of goals, revised research needs to achieve those goals, and an analysis of ongoing research in the category. The term "revised research needs" in these chapters refers specifically to changes made to the research needs in the 2008 NNI EHS Research Strategy as a result of stakeholder input and analysis of the current state of the science. As part of the revision process, some of the 2011 nanoEHS research needs were reordered to reflect the sequence in which the research is conceptualized and accomplished. In response to stakeholder comments, and after careful consideration, the NEHI Working Group has eliminated the heat diagrams that were used in the 2008 EHS Research Strategy.[8] To be meaningful, prioritization, or timing and staging of research, are components of an implementation plan and should be developed within agency missions and appropriations, as guided by this NNI EHS Research Strategy.

New in the 2011 NNI EHS Research Strategy is the section (Chapter 7) describing the newly defined research area of informatics and modeling, and its critical role in organizing the expanding nanoEHS knowledge base, and the section (Chapter 8) promoting timely and effective achievement of strategic NNI nanoEHS goals.

Life cycle assessment has an increased emphasis in the 2011 NNI EHS Research Strategy. A life cycle assessment approach (Figures 1-2, 1-3, and 1-5) presents an opportunity to mitigate potential adverse human and environmental impacts of nanotechnology. Adding a life cycle approach to the NNI EHS Research Strategy integrates practical and applied research with the basic research needed to accomplish the goals of the NNI and its EHS Research Strategy.

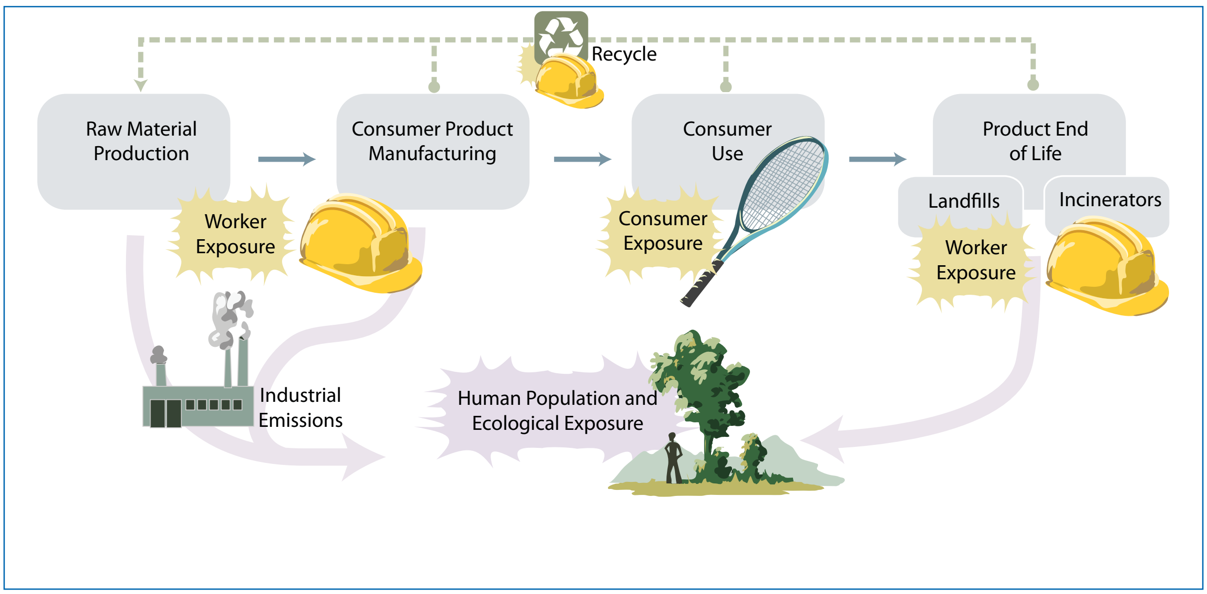

Figure 1-5. The life cycle perspective on risk assessment. Life cycle assessment supports sound product development, responsible nanomanufacturing (scaling up), and protection of public health.

Source: EPA 100/B07/001, February 2007, http://epa.gov/osa. N.R. Fuller of Sayo-Art provided revised image graphics.

8. *National Nanotechnology Initiative Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* (NSET/NSTC, Washington, DC, 2008; http://www.nano.gov/NNI_EHS_Research_Strategy.pdf), Figures 3, 5, 7, 9, and 11 on pages 18, 24, 31, 36, and 42, respectively.

Also new in the 2011 NNI EHS Research Strategy is the inclusion of ethical, legal, and societal implications of EHS research. ELSI considerations are deeply embedded in the NNI's commitment to responsible development of nanotechnology (NNI Strategic Plan Goal 4; see Introduction, p. 2 and Figure 1-2). How nanotechnology research and applications are introduced into society; how transparent decisions are; how sensitive and responsive policies are to the needs and perceptions of the full range of stakeholders; and how ethical, legal, and social issues, including environmental justice, are addressed will determine public trust and the future of innovation driven by nanotechnology. The NNI seeks to generate ELSI knowledge and insights through (1) research in the areas of public perception and understanding of expected benefits, anticipated risks, and safety that can help society assess potential impacts of nanotechnology and possible responses; (2) scientific meetings and workshops at the local, state, national, and international levels; and (3) public engagement activities to identify stakeholder perspectives on nanoEHS and ELSI issues.

ELSI considerations are woven throughout the research chapters of this document to inform research planning and data and product management at all levels, and they are linked to the ELSI objectives outlined in the Goal 4 section of the 2011 NNI Strategic Plan (see also Chapter 8 of this document, Table 8-1). Additionally, EHS research fits within the larger NNI area of societal dimensions, which includes considerations of who in society is most likely to benefit most from nanotechnology, and who is most likely to incur any adverse impacts.

The final chapter of this document, Chapter 8, The Path Forward, is aimed at effectively focusing the NNI agencies' EHS research efforts. It includes a section on targeting and accelerating research by introducing criteria for prioritizing nanomaterials for EHS research; expanding standard measurements, terminology, and nomenclature; defining key concepts to maximize data quality; recognizing approaches to stratify knowledge for risk assessment; and highlighting the need for partnership and international engagement. These are followed by a section linking the 2011 NNI EHS Research Strategy with the goals and objectives of the 2011 NNI Strategic Plan. Finally, Chapter 8 addresses implementation and coordination of the NNI EHS Research Strategy and dissemination of the knowledge gained through the EHS research efforts of the NNI agencies.

2. Nanomaterial Measurement Infrastructure

Overview

A comprehensive measurement infrastructure consisting of a suite of complementary tools for accurate, precise, and reproducible measurements is critical for reliable assessment of exposure and hazards for humans and the environment across all life cycle stages of engineered nanomaterials (ENMs) and nanotechnology-based, or nanotechnology-enabled, products (NEPs). The 2011 NNI EHS research category Nanomaterial Measurement Infrastructure (NMI) restructures and expands upon the measurement-focused research category Instrumentation, Metrology, and Analytical Methods (IMA) described in the 2008 NNI EHS Strategy. The new category title reflects the foundational role that measurement tools play in supporting and enabling the research needs in the other research categories, such as by evaluating and understanding effects, processes, and mechanisms related to exposure and hazards.

The "supporting infrastructure and tools," set out as part of Goal 3 of the NNI Strategic Plan, include measurement protocols, standards, instruments, models, and data. These measurement tools enable the accurate, precise, and reproducible measurements essential for science-based risk assessment and management of ENMs and NEPs. Such tools should provide the appropriate level of traceability[9] and precision required for risk-relevant ENM characterization.

The various types of measurement tools covered in this research category are defined as follows:

- ***Protocols*** are well-defined procedures, methods, or assays that may require the use of reference materials and controls, as well as methods for data analysis.
- ***Standards*** as used in this document refers to internationally recognized reference materials and certified reference materials,[10] developed by organizations such as the National Institute for Standards and Technology (NIST), and consensus-based documentary standards published by national and international standards development organizations such as the International Organization for Standardization (ISO) and ASTM International.
- ***Instruments*** are new or improved measurement apparatuses that may be broadly transferred to and adopted by other organizations.
- ***Models*** are representations that support interpretation of nanomaterial measurements. *Note*: predictive models of effects or structure–activity relationships are covered in other research categories.
- ***Data*** are "benchmark" data that have been measured using validated protocols and reference materials (if relevant) or other well-characterized test materials.

9. Traceability is a term to describe the process by which a measurement instrument has been calibrated using a reference material and how and the degree to which its property values are traceable to the fundamental units of the International System (SI) of units of weight and measure (e.g., the meter for length and the kilogram for mass).

10. ISO Committee on Reference Materials (REMCO), see http://old.iupac.org/standing/on/remco/ISO_REMCO_for_Teamwork12_July2006.pdf.

Relevant media for measurement include all media through which humans and the environment could be exposed, as well as media utilized for *in vitro* and *in vivo* testing: environmental matrices (e.g., air, water, soil, sediment, and sludge); biological matrices (e.g., blood, tissue, and other fluids); and buffers and cell culture media. ENM and NEP life cycle stages to be included in measurement activities span ENM production and NEP manufacture, use, and disposal or recycling.

There are several issues that cut across the five NMI research needs and that pose formidable challenges for the development of accurate, precise, and reproducible measurement tools for ENMs and NEPs. These tools are essential for comprehensive characterization of nanomaterials so that measurements are not questioned and specific studies are not duplicated. Requiring that measurements be performed in various media adds significant complexity to the design of instruments, the packaging and handling of reference materials, and the specificity of protocols. Determining the large number of risk-relevant properties of each ENM-NEP-media system is time-intensive, and can only be made feasible through the development of high-throughput, high-content-generating instruments and protocols. Real-time, in-field testing of exposure media requires new instrumentation concepts and novel approaches to the development of protocols and reference materials. Significant efforts are needed for national and international harmonization and validation of measurement tools. Finally, greater collaboration between academia, government, and the private sector is essential to establish a comprehensive measurement infrastructure.

Of the various types of measurement tools, the needs for reference materials (RMs) and protocols are perhaps of greatest immediacy. Because the time and cost associated with certification of RMs is significantly high, there is a short-to-intermediate need for "study" materials that are designed for specific applications and are well-characterized and widely available, preferably in a centralized repository.

A database that includes all available measurement tools would be a valuable resource for all environmental, health, and safety assessments of ENMs and NEPs.

Goals

- Develop measurement tools to detect and identify engineered nanoscale materials in products and relevant matrices and determine their physico-chemical properties throughout all stages of their life cycles.
- Develop measurement tools for determination of biological response, and to enable assessment of hazards and exposure for humans and the environment from engineered nanomaterials and nanotechnology-based products throughout all stages of their life cycles.

Research Needs as of 2011

#1. Develop measurement tools for determination of physico-chemical properties of ENMs in relevant media and during the life cycles of ENMs and NEPs, focusing on:

- Physical dimensions and morphology: size, size distribution, characteristic dimensions, shape
- Internal structure: atomic-molecular, core-shell

- Surface and interfacial properties: surface charge, zeta potential, surface area and structure, elemental composition, surface-bound molecular coatings and conjugates, reactivity
- Bulk composition: elemental or molecular composition, crystalline phase(s)
- Dispersion properties: degree and state of dispersion
- Mobility and other transport properties: diffusivity and transport in biological and environmental matrices

#2. Develop measurement tools for detection and monitoring of ENMs in realistic exposure media and conditions during the life cycles of ENMs and NEPs, focusing on:

- Sampling and collection of ENMs
- Detecting the presence of ENMs
- Quantity of ENMs: concentration based on surface area, mass, and number concentrations
- Size and size distribution of ENMs
- Spatial distribution of ENMs
- Discriminating ENMs from ambient nanomaterials such as combustion products and welding fumes
- Discriminating multiple types of ENMs, e.g., metals and metal oxides

#3. Develop measurement tools for evaluation of transformations of ENMs in relevant media and during the life cycles of ENMs and NEPs, focusing on:

- Agglomeration and de-agglomeration
- Dissolution and solubility
- Adsorption of natural organic matter and bioconstituents
- Oxidation and reduction
- Deposition of ENMs on surfaces

#4. Develop measurement tools for evaluation of biological responses to ENMs and NEPs in relevant media and during the life cycles of ENMs and NEPs, focusing on:

- Adequacy of existing assays
- New assays or high-throughput, high-content assays
- Correlation of biological responses with physico-chemical properties
- Surface reactivity at the interfaces between ENMs and biological receptors
- Biomarkers of toxicological response

#5. Develop measurement tools for evaluation of release mechanisms of ENMs from NEPs in relevant media and during the life cycles of NEPs, focusing on:

- Release by fire, combustion, and incineration
- Release by mechanical degradation, such as abrasion, deformation, and impact
- Release by dissolution of matrix material
- Release by chemical reactions of matrix material
- Release by photo-induced degradation of matrix material
- Release by consumer interactions, such as spraying, mouthing, and swallowing
- Release by interactions with biological organisms in the environment

Comparative Analysis of Projects

The NNI agencies reported 78 projects for this research category in the FY 2006 nanoEHS data call and 42 projects in the FY 2009 data call. The restructuring of this research category can partly account for the decrease in projects; subject matter experts have noted an increase over the past few years in research on measurement tools, particularly on protocols and reference materials. All of the FY 2009 projects are strongly relevant to nanoEHS research and represent well the Federal effort in this research category. The FY 2006 and FY 2009 projects were mapped onto the newly defined research needs; the resulting distributions by number of projects and funding are presented in Table 2-1.

Although the number of projects and funding for research needs #1–3 apparently decreased between FY 2006 and FY 2009, the distributions of projects and funding did not change greatly, with most funding distributed between research needs #1 and #2. Measurement tools for evaluation of biological responses to ENMs and NEPs and release mechanisms of ENMs from NEPs were not identified explicitly in the FY 2006 and FY 2009 data calls; hence, there are few or no projects reported for research needs #4 and #5. However, there is considerable interest within many Federal agencies directed towards these research needs. In addition, measurement tool development is a secondary activity in some projects reported in other research categories, for example, the Human Health research category.

Two projects reported in the FY 2009 data call were determined to be of benefit to the NMI research category but did not support a specific research need: (1) an interdisciplinary training program for ENM characterization; and (2) an approach for independent validation of commercially derived ENM analyses.

Gaps for Future Investment

The underpinning nature and importance of a nanomaterial measurement infrastructure requires a significant increase in effort by Federal agencies to establish this infrastructure in a comprehensive manner. Elements of such an infrastructure are beginning to be put into place, particularly in some aspects of research needs #1 and #2, as noted by the funding distribution in Table 2-1. However, significantly greater emphasis is required to develop the full suite of essential measurement tools in research needs #1 and #2, identified as necessary for science-based risk assessment and management of ENMs and NEPs.

Table 2-1. Analysis of Projects Related to the Nanomaterial Measurement Infrastructure Category of EHS R&D, FY 2006 & FY 2009*

Research Need	FY 2006		FY 2009		Change
	Reported funding in $K (% of total)	Number of projects (% of total)	Reported funding in $K (% of total)	Number of projects (% of total)	Funding in $K (number of projects
1. Develop measurement tools for determination of physico-chemical properties of ENMs in relevant media and during the life cycles of ENMs and NEPs	9,891 (37.4%)	25 (32.0%)	4,758 (42.2%)	18 (42.8%)	-5,133 (-7)
2. Develop measurement tools for detection and monitoring of ENMs in realistic exposure media and conditions during the life cycles of ENMs and NEPs	12,396 (46.8%)	36 (46.2%)	4,315 (38.3%)	14 (33.3%)	-8,081 (-22)
3. Develop measurement tool for evaluation of transformations of ENMs in relevant media and during the life cycles of ENMs and NEPs	2,845 (10.7%)	14 (17.9%)	1,229 (10.9%)	6 (14.3%)	-1,616 (-8)
4. Develop measurement tools for evaluation of biological responses to ENMs and NEPs in relevant media and during the life cycles of ENMs and NEPs	---	---	579 (5.1%)	2 (4.8%)	+579 (+2)
5. Develop measurement tools for evaluation of release mechanisms of ENMs from NEPs in relevant media and during the life cycles of NEPs	---	---	---	---	
Multiple: Projects that capture multiple needs	1,300 (4.9%)	2 (2.6%)	0	0	-1300 (-2)
Other: Not captured above but of benefit to the research category	50 (0.2%)	1 (1.3%)	400 (3.5%)	2 (4.8%)	+350 (+1)
TOTALS	**26,482**	**78**	**11,281**	**42**	**-15,201 (-36)**

* Agencies supporting research in this category: EPA, FDA, NIOSH, NIST, NSF

Substantial effort should also be allocated to developing the critical measurement tools for research needs #3, #4, and #5, for which there is currently little to no funding. Based on stakeholder inputs from the four EHS workshops, the most immediate and greatest need that cuts across all five research needs areas is the development of protocols and reference materials.

Rationale for the 2011 Research Needs and Changes from 2008

The research needs for the NMI research category have been changed substantially from those in the IMA research category of the 2008 EHS strategy, as illustrated in Figure 2-1. The rationale for the 2011 NMI research needs is detailed in following subsections.

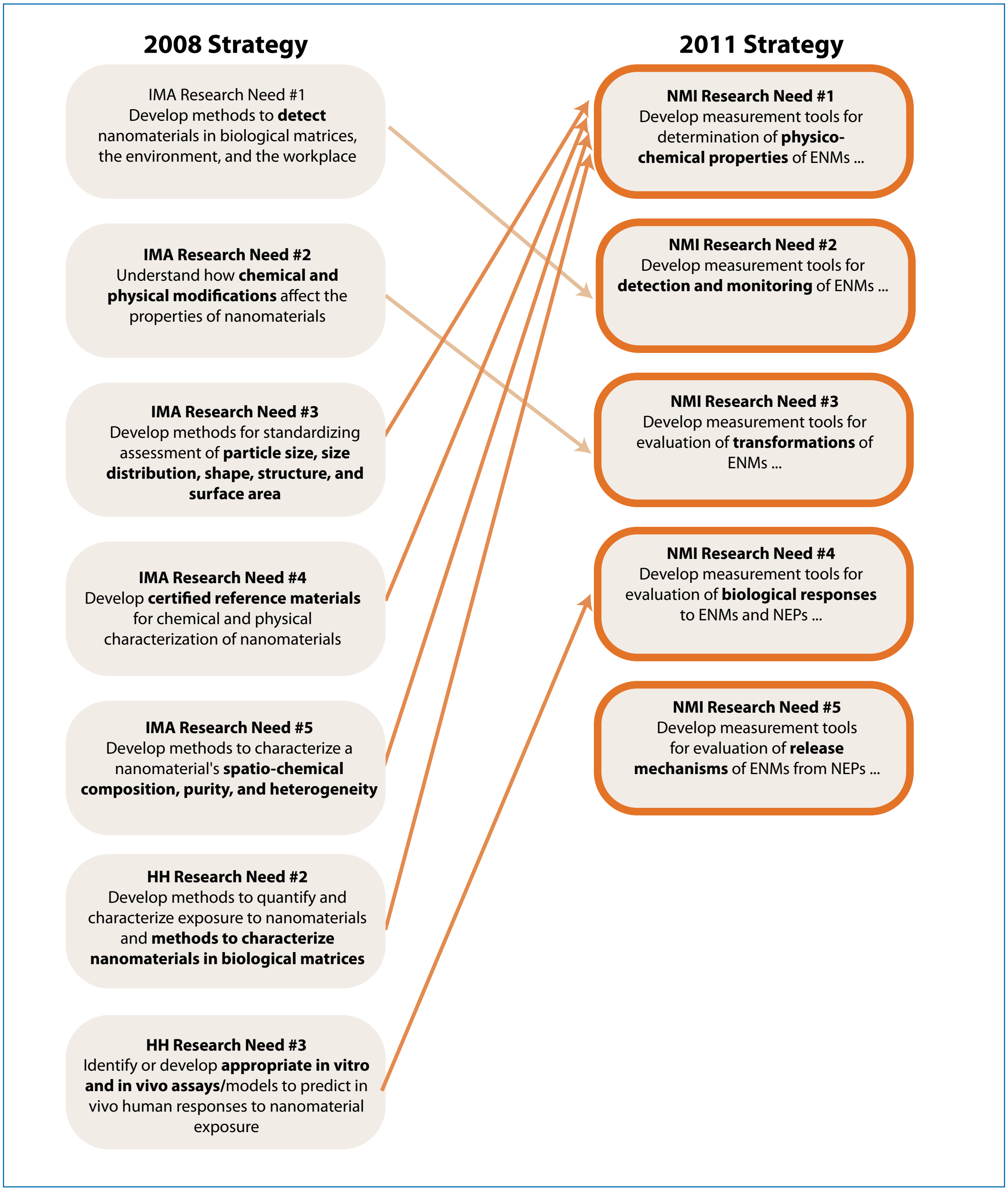

Figure 2-1. Comparison of the IMA research needs in the 2008 NNI EHS Research Strategy (left) with the NMI research needs in the 2011 NNI EHS Research Strategy (right). The arrows indicate mapping of the 2008 IMA research needs to the 2011 NMI research needs.

- Three of the five IMA research needs concerning physico-chemical properties of ENMs have been consolidated into one NMI research need, and the scope of the key properties in this need has been expanded.
- The IMA research need concerning detection of ENMs maps to the NMI research need on detection and monitoring, and the scope of the need has been expanded.
- The IMA research need concerning chemical and physical modifications of ENMs maps to the NMI research need on transformations, and the scope of the need has been expanded to cover the key transformation processes.
- Some aspects of the 2008 Nanomaterials and Human Health research needs concerning method development are included in the NMI research need #4 on biological responses.
- A new research need on release of ENMs from NEPs was included in the 2011 NMI research category to address growing awareness and concerns about such releases during manufacture, use, and disposal or recycling of NEPs.

The five 2011 NMI research needs encompass the ENM physico-chemical properties or parameters identified as essential for EHS assessment by various domestic and international groups, including the Minimum Information on Nanoparticle Characterization (MinChar) Initiative, the ISO, and the Organisation for Economic Co-operation and Development (OECD).

Research Need #1: Develop measurement tools for determination of physico-chemical properties of ENMs in relevant media and during the life cycles of ENMs and NEPs

Overview

Accurate, precise, and reproducible determination of the physico-chemical properties of ENMs in relevant media has been consistently identified by the nanoEHS community as a high-priority research need, and it is the critical initial phase of ENM characterization prior to risk or fate assessment. Insufficient or inaccurate upstream physico-chemical characterization of ENMs is a significant barrier to understanding the underlying mechanisms of biological response to ENMs and is detrimental to the reproducibility and accuracy of published toxicity studies. Furthermore, fundamental material properties such as particle size, shape, and surface chemistry are deterministic with respect to biological response (e.g., cell uptake, toxicity) and fate (e.g., absorption, distribution, metabolism, and excretion [ADME] ecosystem-wide effects). Therefore, the relevance of this research need is both cross-cutting and integral to the objectives of the core research categories described elsewhere in this document.

Existing technologies for the measurement of physico-chemical properties are mature and widely available, but many lack specificity for ENMs or have not been validated for measurement conditions relevant to EHS applications. Critical needs exist for rapid and high-throughput analysis, validated protocols for sample preparation and measurement, reference materials relevant to nanoEHS research, and measurement tools applicable to complex biological and environmental matrices over the entire life cycles of ENMs and NEPs.

Analysis of Current Projects

The agencies reported 18 projects for this research need in 2009: 16 by NIST, and one each by the National Science Foundation (NSF) and the National Institute for Occupational Safety and Health (NIOSH). Of these projects, the distribution of projects by sub-research need and measurement tool type is as follows:

- ***Physical dimensions and morphology:*** 3 projects on protocols and reference materials, and 2 projects on high-resolution microscopy methods
- ***Internal structure:*** 4 projects on neutron diffraction and scattering, transmission electron microscopy, and optical methods
- ***Surface and interfacial properties:*** 3 projects on electron microscopy, ion mass spectrometry, and Auger electron spectroscopy methods
- ***Bulk composition:*** 3 projects on 3D chemical imaging methods, X-ray microanalysis methods, and single-particle mass spectrometry instrumentation
- ***Mobility and other transport properties:*** 1 project on a single-nanoparticle tracking method
- ***Cross-cutting:*** 2 projects covering reference materials and protocols for two or more sub-research needs

Research Need #2: Develop measurement tools for detection and monitoring of ENMs in realistic exposure media and conditions during the life cycles of ENMs and NEPs

Overview

Detection and monitoring of ENMs in a specific environment require the collection of samples of realistic exposure media under exposure conditions, e.g., samples of air from a manufacturing plant or samples of soil from a disposal site. Similarly, detection of ENMs in humans requires sampling or visualization of actual biological matrices, e.g., blood or tissue. Quantitative methods for detection and monitoring of ENMs have been consistently identified by the nanoEHS community as a high-priority research need and thus constitute a vital component of the overall nanoEHS risk assessment approach and a prerequisite for developing scientifically valid estimates of exposure.

Existing technologies for detection and monitoring of ENMs in the workplace are nonspecific, limited to airborne measurement, and have limited application beyond the workplace. Similarly, existing technologies for detection and monitoring of ENMs in humans and the environment lack specificity for ENMs or have not been validated for relevant measurement conditions. Hence, a critical need exists for measurement tools to detect and monitor ENMs: for example, real-time or near real-time instruments, including personal monitors, for specific and sensitive measurement of a range of ENM physico-chemical properties in relevant media.

Analysis of Current Projects

The agencies reported 14 projects for this research need in 2009: 5 by NIOSH, 8 by NSF, and one by NIST. Of these projects, the distribution by sub-research need and measurement tool type is as follows:

- ***Sampling and collection of ENMs:*** 1 project on aerosol sampling instruments
- ***Detecting the presence of ENMs:*** 9 projects on novel instruments and methods in various media
- ***Determining the quantity of ENMs:*** 2 projects on real-time instruments and methods and models to determine specific surface area and mass in air samples
- ***Determining the size and size distribution of ENMs:*** 1 project on a standard method to measure ENM size in air samples
- ***Determining the spatial distribution of ENMs:*** 1 project on electron-microscopy-based methods for imaging the distribution of ENMs in two and three dimensions

Research Need #3: Develop measurement tools for evaluation of transformations of ENMs in relevant media and during the life cycles of ENMs and NEPs

Overview

Interactions of an ENM with its surrounding media often result in transformations that alter its form and physico-chemical properties. Transformation processes such as dissolution and agglomeration affect exposure and hazards of the ENMs to humans and the environment. Determination of the extents and rates of transformation processes in realistic exposure media and conditions has been consistently identified by the nanoEHS community as a critical component of nanoEHS studies.

Assessing ENM transformations requires a thorough evaluation of both ENMs and surrounding media. Measurement tools for media evaluation are relatively mature and therefore may be readily adapted to this nanoEHS application. There are some existing technologies to measure the extents and rates of transformations of micro- to macroscale materials; however, these technologies lack specificity for ENMs or have not been validated for measurement conditions relevant to EHS applications. Transformations of ENMs result in changes in physico-chemical properties as a function of time; thus, measurement tools for evaluating transformations are dependent on the availability of tools for research need #1 on physico-chemical properties and research need #2 on detection and monitoring. A critical need exists for measurement tools to detect and monitor the progress of transformations, including real-time instruments and quantitative methods and reference materials.

Analysis of Current Projects

The agencies reported 6 projects focused primarily on the development of measurement tools for evaluation of transformations: 5 by NIST and 1 by NSF. Of these projects, the distribution by sub-research need and measurement tool type is as follows:

- ***Agglomeration and de-agglomeration:*** 1 project on advanced, *in situ* synchrotron and neutron scattering methods

- ***Dissolution and solubility:*** 2 projects focused on protocols and models for silver nanoparticles
- ***Adsorption of natural organic matter and bioconstituents:*** 1 project on microbalance-based methods
- ***Oxidation and reduction:*** 2 projects on optical and scanned probe microscopy methods

A number of 2009 projects included above for research needs #1 and #2 concern measurement tools that are applicable to evaluation of transformations. In addition, a number of projects reported for the Environment research category have measurement tool development as a secondary objective or as a prerequisite for the generation of experimental data.

Research Need #4: Develop measurement tools for evaluation of biological responses to ENMs and NEPs in relevant media and during the life cycles of ENMs and NEPs

Overview

Quantitative assays for the evaluation of toxic responses have been consistently identified by the nanoEHS community as a high-priority research need. The lack of quantitative *in vitro* and *in vivo* assays with specificity for ENMs and relevance to biological systems has been identified as a significant barrier to understanding human responses to ENMs; determining the mechanisms responsible for toxicity at the molecular, cellular, tissue, organ, and whole-body levels; and determining ENM uptake, adsorption, and dose effects. In the absence of quantitative assays, the accuracy and reproducibility of published toxicity studies cannot be ascertained. Quantitative assays are also required to evaluate possible beneficial biological responses, e.g., ENMs acting as antioxidants in cells.

Many assays have been developed to evaluate toxic responses to chemicals; however, there are no methods to test the adequacy and extensibility of these assays for ENMs. Critical needs exist for such methods, as well as new high-throughput assays for generating large amounts of information, also known as high-content assays. The correlation of toxic responses to physico-chemical properties is essential for extrapolating data obtained for one ENM-media system to other similar ENM-NEP-media systems and for developing predictive models. Determination of surface reactivity, i.e., interactions of ENMs with proteins and other molecular species in the human body, is critical to the evaluation of biological response, as are validated biomarkers.

Analysis of Current Projects

The agencies reported 2 projects focused primarily on the development of measurement tools for evaluation of biological responses: one each by NIST and the Food and Drug Administration (FDA). Of these projects, the distribution by sub-research need and measurement tool type is as follows:

- ***New assays:*** 1 project on an assay for photochemical generation of hydroxyl radical
- ***Surface reactivity:*** 1 project on mass spectrometry-based methods to assess DNA damage due to ENMs

It is expected that some projects reported for the Human Health research category have measurement tool development as a secondary objective or a prerequisite for the generation of experimental data; these projects are not included here.

Research Need #5: Develop measurement tools for evaluation of release mechanisms of ENMs from NEPs in relevant media and during the life cycles of NEPs

Overview

The use of ENMs in NEPs has increased dramatically in recent years. ENMs can be released from NEPs during manufacturing, use, and disposal or recycling, posing risks of human and environmental exposure to ENMs. Despite the increased presence of ENMs in commercial intermediates, industrial components, consumer products, and other NEPs such as medical devices, little is known about the extent to which ENMs are released from NEPs as a function of use or about the rates of release. These mechanisms include those active during fire, combustion, or incineration; mechanical degradation; dissolution; chemical reaction or photo-induced degradation of the NEP matrix containing the ENMs; consumer interactions with NEPs; and interactions of NEPs with biological organisms. For example, ENMs can be released by a consumer spraying an ENM-containing aerosol product or by the frictional degradation of ENM-coated clothing during regular wear. After disposal, NEPs undergo various physico-chemical degradation processes, such as mechanical crushing of waste, photo-induced breakdown by sunlight, or extraction of ENMs into wastewater by matrix dissolution or chemical reaction, that result in the release of ENMs.

Analysis of Current Projects

More effort is needed for all research in this revised category: research need #5 is a newly defined research need, so no relevant projects were reported in the FY 2009 data call. However, there is work underway at NIST and at the Consumer Product Safety Commission (CPSC) to evaluate ENM release mechanisms from NEPs due to incineration, mechanical degradation, and consumer interactions.

Example of Progress in NanoEHS Research: Gold Nanoparticle Standards

A critical first measurement for all nanoEHS research studies is nanomaterial size, because size affects physico-chemical and biological properties and thus exposure to and hazards to humans and the environment. NanoEHS research has suffered from a lack of reliable nanoscale measurement standards, both to ensure consistency of data from one lab to the next and to verify the performance of measurement instruments and analytic techniques. In January 2008, the National Institute of Standards and Technology issued its first reference materials (RMs) for nanomaterials targeted for the nanoEHS and biomedical research communities—literally "gold standards" for determining the size of nanoparticles (Figure 2-2). The new reference materials, gold spheres nominally 10 nm, 30 nm, and 60 nm in diameter, were developed in cooperation with the National Cancer Institute's Nanotechnology Characterization Laboratory (NCL). The RM dimensions were measured using six independent methods commonly used by researchers. Over 400 RM units have been sold to industry, government agencies, and universities, including 37 international sales. The RMs have been used in development of NIST-NCL protocols (http://ncl.cancer.gov/working_assay-cascade.asp) and ASTM International consensus standards (http://astm.org/COMMIT/SUBCOMMIT/E56.htm).

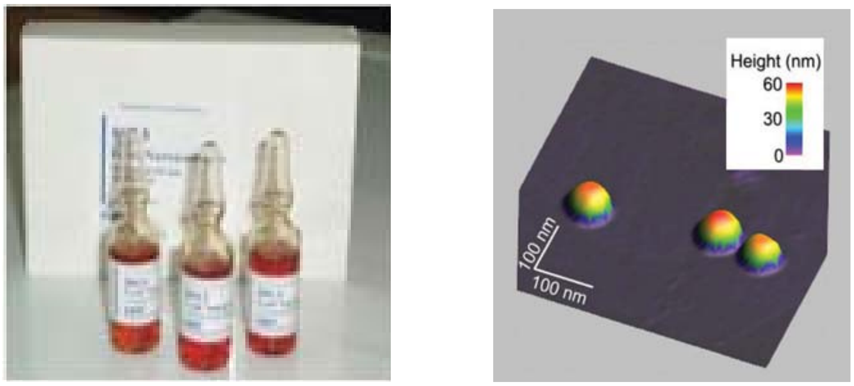

Figure 2-2. **(Left) NIST gold nanoparticle reference materials (RMs) 8011–8013. (Right) Atomic force microscopy image of 60 nm gold reference material nanoparticles.**

Source: NIST, http://www.nist.gov/srm/index.cfm. Image: J. Grobelny.

3. Human Exposure Assessment

Overview

The number of products in commerce and under development that contain nanomaterials has grown rapidly to include products such as plastics, metals, ceramics, surface coatings, creams, sprays, cosmetics, electronics, clothing, drugs, medical devices, and medical imaging aids. Exposure potential for nanomaterials can be expected to be strongly dependent on industrial manufacturing and processing methods, the nanomaterial state and its physico-chemical properties, and the nanomaterial applications. Hence, research on potential exposure must evaluate whether, and to what degree, exposure will occur for each nanomaterial or NEP at each stage of its life cycle. The 2011 NNI EHS research category Human Exposure Assessment addresses these and related issues. Characterization of exposure involves use of appropriate methods and tools for measuring or estimating exposure to nanomaterials in various media and organisms. As described in the Chapter 8 subsection, "Targeting and Accelerating NanoEHS Research," a life cycle analysis approach may be useful to express the range of exposure likelihoods and potential areas of focus for research. As the likelihood of exposure for key population segments is determined, care should be taken in determining what constitutes a "key segment" of the population, who is empowered to define groups of people, and what implications may arise from placing people in particular categories. In addition, subpopulations among the "general population" that are disproportionally exposed or more vulnerable to impacts from exposure should be identified.

Life cycle considerations should include the characterization of exposure to nanomaterials for use in risk assessment and/or risk management. Where nanomaterials are effectively embedded in the product matrix, such as computer circuit boards, the potential for exposure during routine use of the product is unlikely because the embedded nanomaterials are not available for exposure. However, potential exposure of workers during the manufacture of such materials, including during any subsequent activities like milling, machining, sanding, and grinding of the matrix, must still be considered, as should potential exposure of workers, the general public, and consumers during reasonably foreseeable misuse and as a result of recycling or disposal at the end of product life.

Because of the relative newness of nanotechnology, very little exposure data related to engineered nanomaterials, and only a few analyses of workplace exposures based on emission measurements and consumer exposures based on modeling estimates, have been reported in the scientific literature. Much of the needed exposure data and analyses will be enabled through linkages to the Nanomaterial Measurement Infrastructure research needs (Chapter 2), wherein measurement tools are being developed for physico-chemical properties, detection and monitoring, transformations, and releases of nanomaterials in the workplace and from products.

With untested materials entering commerce, exposure assessment and health surveillance of exposed groups have added importance for identifying potential hazards that should be studied. Toxicology and other health studies provide predictions on safe exposure levels that need to be validated through exposure assessment and health surveillance. This work is complicated by workforce fluctuation. The production industry is comprised of many startups that either fail or are purchased by larger companies, creating difficulties in tracking exposed workers. The rapidly changing nature of the field increases the difficulty of this task; researchers are continuously finding new and better ways to incorporate nanomaterials into a large array of products. This means that inferior or less profitable applications are constantly being phased out, resulting in shifting exposure scenarios. This suggests that industries that are end-users of nanomaterials might prove to be the best subjects for exposure investigations. These challenges also make international harmonization of exposure assessment methodologies and international collaboration in conducting health surveillance studies critically important.

Specific requirements to achieve significant progress in the Human Exposure Assessment research category include the following:

- Development of methods or approaches to identify potential sources, characterize the exposure scenario, and measure actual exposure to nanomaterials
- Collection of data and information on the life cycle and variables that affect exposure to nanomaterials
- Collection and dissemination of data and development of databases for health surveillance and exposure to nanomaterials
- Development of models to estimate exposures to specific nanomaterials

Goals

- Identify potential sources, characterize the exposure scenarios, and quantify actual exposures of workers, the general public, and consumers to nanomaterials.
- Characterize and identify the health outcomes among exposed populations in conjunction with information about the control strategies used and exposures to determine practices that result in safe levels of exposures.

Research Needs as of 2011

#1. Understand processes and factors that determine exposures to nanomaterials:

- Conduct studies to understand processes and factors that determine exposure to engineered nanomaterials
- Develop exposure classifications of nanomaterials and processes
- Develop internationally harmonized and validated protocols for exposure surveys, sample collection and analysis, and reporting through existing and newly created international frameworks
- Develop comprehensive predictive models for exposures to a broad range of engineered nanomaterials and processes
- Characterize process- and task-specific exposure scenarios in the workplace

#2. Identify population groups exposed to engineered nanomaterials:

- Systematically collect and analyze information about nanomaterial manufacture, processing, and direct use in commercial and consumer products over time to discern geographic areas where engineered nanomaterials may be emitted into the environment, consumed in the form of ingredients of products, and/or disposed of in solid waste, wastewater, etc.
- Conduct population-based surveys to obtain information on use patterns for consumer products
- Identify potential subpopulations that are more susceptible to exposure to engineered nanomaterials than others
- Develop quantitative assessment methods appropriate for target population groups and conduct assessments of those population groups most likely to be exposed to engineered nanomaterials

#3. Characterize individual exposures to nanomaterials:

- Expand currently available exposure assessment techniques to facilitate more accurate exposure assessment for ENMs at benchmark concentration levels using feasible methods
- Develop new tools through national and international surveys to support effective exposure characterization of individuals
- Characterize and detect nanomaterials in biological matrices and conduct studies to understand transformations of nanomaterials during transport in the environment and in human bodies
- Conduct studies to examine emissions and human contact during normal use and after wear and tear have degraded a product, as well as during repeated exposures
- Develop engineered nanomaterials exposure assessment models based on identified critical exposure descriptors
- Develop databases to contain the collected data and information

#4. Conduct health surveillance of exposed populations:

- Establish a program for the epidemiologic investigation of physician case reports and reports of suspicious patterns of adverse events
- Establish exposure registry and medical surveillance programs for workers
- Analyze injury and illness reporting in existing programs

Comparative Analysis of Projects

Project data ascribed to the Human Exposure Assessment research category in FY 2006 and FY 2009 are shown in Table 3-1. For ease of comparison, FY 2006 projects are shown categorized by the new 2011 research needs. A mapping between the 2008 and 2011 needs is provided in Figure 3-1. (The 2011 NNI EHS Research Strategy incorporates environmental exposure research into the Environment research category, while the 2008 strategy addressed human and environmental exposure together.) Since FY 2006, there was an almost three-fold increase in total funding and in the number of projects for the Human Exposure Assessment research category and for its individual research needs areas. In addition, previously unfunded research need #2 and #4 (both the 2008 Human and Environmental Exposure Assessment category and the 2011 Human Exposure Assessment category) are now supported by agencies.

Table 3-1. Analysis of Projects Related to the Human Exposure Assessment Category of NanoEHS R&D, FY 2006 & FY 2009*

Research Need	FY 2006		FY 2009		Change
	Reported Funding in $K (% of total)	Number of projects (% of total)	Reported Funding in $K (% of total)	Number of projects (% of total)	Funding in $K (number of projects)
1. Understand processes and factors that determine exposures to nanomaterials	265 (23%)	3 (60%)	902 (27%)	5 (36%)	+637 (+2)
2. Identify population groups exposed to engineered nanomaterials	--	--	1100 (33%)	1 (7%)	+1,100 (+1)
3. Characterize individual exposures to nanomaterials	879 (77%)	2 (40%)	1242 (38%)	7 (50%)	+363 (+5)
4. Conduct health surveillance of exposed populations	--	--	45 (1%)	1 (7%)	+45 (+1)
Multiple: Projects that capture multiple needs	--	--	--	--	
Other: Not captured above but of benefit to the research category	--	--	--	--	
Total	**1,144**	**5**	**3,289**	**14**	**+2,145 (+9)**

*Agencies supporting research in this category (FY 2009): CPSC, EPA, NIOSH, NSF

Gaps for Future Investment

Research activities in this category remain low relative to the other four NNI EHS research categories. Therefore, more efforts are needed for all research needs in this category for the specific topics identified in this document. A major remaining gap is the limited funding for research need #4 to conduct health surveillance of exposed populations. Public health surveillance is an ongoing activity with well-established methods for collecting both health and exposure data. None of the ongoing exposure registry and medical surveillance activities is currently targeted to engineered nanomaterials, although all would be capable of collecting health data from exposed groups. Development of health surveillance projects with international partners would leverage funding and study populations, thus accelerating our understanding of human exposures and potential adverse health effects.

Rationale for the 2011 Research Needs and Changes from 2008

In order to reflect research progress achieved in the last three years, incorporate public recommendations, and recognize common challenges across population groups and exposure environments, the 2008 Exposure Assessment research needs have been updated as follows:

1. Understand processes and factors that determine exposures to nanomaterials (2008 research need #5 was expanded to include the general population and consumers, and reordered as research need #1)
2. Identify population groups exposed to engineered nanomaterials (2008 research need #2 was expanded to include workers and reduced to exclude environments, which are covered in the Environment research category)
3. Characterize individual exposures to nanomaterials (2008 research needs #3 and #1 have been merged and refocused on individual exposures)
4. Conduct health surveillance of exposed populations (2008 research need #4 was reduced to exclude environments, which are covered in the Environment research category)

These changes are shown graphically in Figure 3-1. The ordering of research needs mirrors the sequence of exposure data generation and prerequisites, rather than priority ranking.

Research in the Human Exposure Assessment category is closely interconnected with research in the other four core EHS research categories. Development of techniques to measure exposure conducted under the Nanomaterial Measurement Infrastructure category (Chapter 2) is critical for obtaining exposure data. Environmental exposure information generated under the Human Exposure Assessment category can be utilized by the Environment category (Chapter 5); likewise, an understanding of environmental fate and transport and transformation is needed to characterize human exposure to nanomaterials from air, water, landfill, and other releases into the environment from industrial, processing, and use facilities. Exposure data can guide the design of toxicological experiments to generate dose–response data in the vicinity of possible exposure levels under the Human Health category (Chapter 4), and correlations between exposures and health observed in health surveillance programs in the Human Exposure Assessment category can be investigated through targeted toxicological experiments and as such, are relevant to the Human Health category. Similarly, mechanistic toxicology studies in the Human Health category can facilitate exposure characterization with toxicologically relevant metrics. Exposure assessment data is necessary in risk assessments and can also provide feedback on the effectiveness of the risk mitigation measures conducted under the Risk Assessment and Management Methods category (Chapter 6).

Figure 3-1. Comparison of the Human and Environmental Exposure Assessment research needs in the 2008 NNI EHS Research Strategy (left) with the Human Exposure Assessment research needs in the 2011 NNI EHS Research Strategy (right). The arrows indicate mapping of the 2008 research needs to the 2011 research needs. Note that several of the 2008 research needs here map to an Environment research need.

Research Need #1. Understand processes and factors that determine exposures to nanomaterials

Overview

Processes and factors that affect exposures to engineered nanomaterials in the workplace can occur at the macro level (e.g., across industry sectors), mid level (e.g., among organizations in an industry sector), and micro level (e.g., among specific operations). Research gaps include macro-level data on which sectors to target for exposure monitoring, mid-level data on manufacturing processes and techniques that could influence exposures within a sector, and micro-level data on non-carbon nanomaterials and tasks and activities that produce an intermediate or nanotechnology-enabled product. Factors that affect exposures among the general population and consumers are not well understood. Critical research gaps include characterization of process and task-specific exposure in the workplace, data on emission sources (types, rates, locations, etc.), manufacture of NEPs (processes, types of nanomaterials, etc.), and consumer product use habits (type of use, frequency, etc.). Key barriers for this research need include (1) identification, measurement, and characterization of nanomaterials during their life cycles; (2) information on variables that affect exposures; and (3) development and international harmonization of exposure assessment methodologies appropriate for epidemiological studies, studies of the effectiveness of control technologies, and other research areas.

Recommendations for Changes

The 2008 NNI EHS Research Strategy emphasized three topics for this research need: (1) exposure classification of nanomaterials, (2) exposure classification of processes, and (3) predictive models of workplace exposure. Progress is being made toward understanding these research topics, and new topics are emerging. Applying a life cycle approach is recommended to make it clear that work to understand processes and factors that modify exposures in the workplace, among the general population, and among consumers is complementary, informs the remaining research needs in the Human Exposure Assessment research category, and is interdependent with all other research categories.

Analysis of Current Projects

Five FY 2009 projects were identified under research need #1. Two projects, funded by NIOSH, focus on dustiness that will provide information on the physical behavior of some classes of nanomaterials. Two projects, funded by the U.S. Environmental Protection Agency (EPA), investigate effects of physicochemical parameters on exposure potential in the environmental media and determinants of exposure to platinum-containing nanomaterials among the general population. The last project, funded by NSF, is a supplement to an existing research center devoted to studying exposure pathways of nanoparticles from synthesis to biological systems, including exposures to people, with a particular focus on aerosolized nanoparticles.

Research Need #2. Identify population groups exposed to engineered nanomaterials

Overview

No projects were identified for this research need in the 2008 NNI *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research*. Publicly available studies are underway to identify workers who are potentially exposed to nanomaterials in industrial settings. Over the last two years, there has been an increasing recognition that consumers may use products that contain or are made using nanomaterials. Since 2005, the EPA has received over 100 premanufacture notices for nanomaterials under Section 5 of the Toxic Substances Control Act. In addition to these products, nanomaterials are also used in a variety of medical products.

Key barriers for identifying population groups exposed to engineered nanomaterials include (1) the difficulties in collecting and disseminating of information on populations potentially exposed to engineered nanomaterials while protecting confidential business information and personal privacy; (2) the lack of data on the life cycles of nanomaterials, including sources, pathways, and routes of potential exposure, and the form of the material to which the person is exposed; and (3) the lack of existing databases to enable the collection and dissemination of information.

Recommendations for Changes

As described in the report of the February 2009 NNI *Human and Environmental Exposure Assessment Workshop*,[11] data may already exist with which to begin identifying populations potentially exposed to engineered nanomaterials. Existing data such as that available in insurance companies, tracking of consumer use of nanomaterials, information on manufacture and sale of nanomaterials, information from the EPA's New Chemicals Program, information on patients seeking medical attention, worker exposure registries, and information from researchers all may prove helpful in identifying or evaluating consumer and general population exposure scenarios. Collection of this type of information and data may serve as a mechanism for obtaining relevant data to identify populations potentially exposed to nanomaterials and to determine whether any segments of the population are disproportionately susceptible or vulnerable to adverse impacts. While some of this data may be personal or confidential business information, efforts should be made to make as much information as possible publicly available within established procedures for protecting information. There should be an expectation that the private sector will provide adequate information to enable policymakers and members of the public to understand and make decisions regarding possible exposures to nanomaterials.

Analysis of Current Projects

One project (funded by EPA) was identified under research need #2. This project is a collaborative initiative with several United Kingdom partners that proposes integrated model(s) of fate, behavior, bioavailability, and effects; validates and refines the models; and develops methods and tools to detect, assess, and monitor for nanomaterials in biological and environmental samples.

Research Need #3. Characterize individual exposures to nanomaterials

Overview

Since 2008, there has been increasing recognition that consumers may use products that contain or are made using engineered nanomaterials. In addition to managing worker exposures, understanding and, where necessary, reducing potential exposures to the general public and consumers from use of engineered nanomaterials is critical for promoting public health; however, the mechanisms of exposure to engineered nanomaterials resulting from contact with nanotechnology-enabled products are not fully understood. Although some existing models can be used to predict environmental releases of nanomaterials and potential worker and general population exposures, such estimates are generic, conservative, or not specific to nanomaterials.

Key barriers to characterizing individual exposures to engineered nanomaterials include:

1. Limitations in existing sampling and analysis methods and the limited availability and usage of instrumentation to measure exposure, including measurement of multiple metrics by use of one instrument

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11. *Human and Environmental Exposure Assessment: Report of the National Nanotechnology Initiative Workshop*, February 24–25, 2009, Bethesda, Maryland (NSET/NSTC, Washington, DC, 2011; http://www.nano.gov/publications-resources).

2. Inability to collect, store, and disseminate data useful in characterizing releases of and human exposures to nanomaterials
3. Limited information on the life cycles of nanomaterials and potential exposure sources and pathways
4. Paucity of data to characterize releases and potential exposures while protecting confidential business information and personal privacy
5. Lack of standardized protocols for sample collection, analysis, and reporting of results that are necessary to facilitate intercomparison of study results
6. Few or inadequately tested models for assessing exposure to specific nanomaterials

Recommendations for Changes

As described in the report from the February 2009 NNI Workshop on Human and Environmental Exposure Assessment, data with which to characterize general population and consumer exposures are limited, although there are data available with which to begin characterizing worker exposures.

Research is needed to characterize occupational and consumer exposures resulting from repeated use (e.g., abrasion and strain) and reasonably foreseen misuse conditions and accidents (e.g., breakage and combustion). Some initial work has been done to determine how abrasion can cause the release of titanium dioxide and silver nanoparticles from substrates, but more work is needed to address this potential exposure scenario.

In addition, research is needed to enable characterization of general population exposure from emissions occurring during manufacture, processing, use, and disposal of nanomaterials. Exposure is also affected by the cross-cutting issue of aggregation/agglomeration, since exposure to nanomaterials will not simply be to the primary particle but also to clusters of different-sized particles that could change the relevant concerns for dermal, oral, or inhalation exposure. In particular, research is needed to examine exposure in vulnerable populations such as children, the elderly, and immunocompromised persons who may be more susceptible to potential adverse health effects resulting from exposure to nanomaterials.

Analysis of Current Projects

Seven FY 2009 projects were identified under research need #3. Four research projects are being conducted by NIOSH, one is being conducted by CPSC and NIST, and two are being conducted by EPA. These research projects include workplace monitoring for carbon nanofibers and nanotubes, the feasibility of industry-wide studies of workers exposed to nanotubes, a titanium dioxide (TiO_2) nanoparticle exposure study, nanotechnology field evaluations for worker exposure, exposure and fire hazard assessment of nanoparticles in fire-safe consumer products, investigation of techniques for physical and chemical evaluation of nanoparticles in the environment, and evaluation of current sampling and analysis of nanoparticles in the atmosphere.

In FY 2010 CPSC, EPA, and NIOSH developed a collaborative project to investigate the exposure potential from the use of nanosilver-enabled products by the public and workers. The objectives of this work include the development of protocols for evaluating the presence of nanosilver and the potential releases from treated products. For those articles that contain nanosilver, the chemical form and physico-chemical properties (morphology, size, chemistry) of material released from the products during simulated use activities will be evaluated using appropriate analytical techniques.

Research Need #4. Conduct health surveillance of exposed populations

Overview

Health surveillance, that is the collection, analysis, and dissemination of health information, is a basic tool used in Federal, state, and local public health protection activities. The information can be used to characterize the extent of health and safety problems, identify opportunities to prevent adverse effects, plan for delivery of services to mitigate effects, and identify associations between adverse effects and possible causes that can serve as hypotheses for further research. Integrations of health surveillance data with exposure assessment data and identification of exposed populations would allow adequate determination of the impact of ENMs on human health. Key to surveillance is the dissemination to and use of data by those who need it to protect health and safety. Health surveillance can focus on a specific adverse outcome to identify risk factors (i.e., the NIOSH Adult Blood Lead Epidemiology and Surveillance Program) or on a specific risk factor to identify adverse outcomes. There are established procedures for ensuring that personal information is protected in surveillance programs, and those practices must be put in place for any such programs instituted for nanomaterials. Also, while certain individuals may be disproportionately exposed to nanomaterials, so too may specific groups (e.g., certain age groups utilizing specific products), and surveillance programs should take this into account.

While no fundamental barriers exist to meeting this research need, there are challenges to overcome: (1) attracting the health surveillance community of researchers to nanotechnology, which may require significant outreach; (2) identifying groups with well-defined exposure characteristics or health outcomes known to be associated with exposure, which is needed for most effective surveillance; (3) developing new targeted medical screening tests such as those for cardio-vascular and pulmonary effects; (4) standardizing data collection, format, and terminology to improve efficiency and effectiveness; and (5) collecting information about nanomaterial use in consumer products, which would allow existing poison control and emergency room surveillance programs to identify opportunities for investigation.

Recommendations for Changes

To overcome these challenges and knowledge gaps, instituting a program for the epidemiologic investigation of physician case reports and reports of suspicious patterns of adverse events should be considered. Recent examples of nanomaterial exposure and unexpected health events reported in the literature show that astute physicians can identify sentinel events and patterns of events and that investigating the causal factors for these events can provide insight into whether production and use of nanoscale engineered materials are creating undue risks that can be controlled.[12]

12. Y. Song, X. Li, X. Du, Exposure to nanoparticles is related to pleural effusion, pulmonary fibrosis, and granuloma, *Eur Respir J.* 34(3), 559-67 (2009); M. Wu, R.E. Gordon, R. Herbert, M. Padilla, J. Moline, D. Mendelson, V. Litle, W.D. Travis, J. Gil, Case report: Lung disease in World Trade Center responders exposed to dust and smoke: Carbon nanotubes found in the lungs of World Trade Center patients and dust samples, *Environ Health Perspect*. 118(4), 499-504 (2010).

To allow for analysis of the health and exposure data to identify possible associations between the two, exposure registry and medical surveillance programs for workers should be established. Selected groups of workers and others who are currently exposed to nanomaterials should be included in an exposure registry to facilitate medical surveillance of their health over time. Health surveillance in the workplace can be particularly effective because employment processes already generate records on job duties, locations, exposures, and health status that can be used to establish exposure registry and medical surveillance programs. These records may be augmented with special medical and exposure monitoring studies if sufficient data are not already being generated by company safety and health protection programs. Suspicious health events or patterns of events can be investigated to identify possible associations with exposure. Specific steps to facilitate establishing such registries include (1) characterizing what nanotechnology workers do, to facilitate creation of exposure registries; (2) providing guidance as to how companies might develop registries and medical surveillance programs; and (3) initiating a project to demonstrate the value of routine analyses of health and exposure data.

Evaluation is needed of existing injury and illness reporting programs for consumer exposures to determine the feasibility and utility of their use for identifying adverse outcomes associated with specific nanomaterials. As in occupational exposure reporting, a key question is whether the programs collect information that allows for the identification of events associated with nanomaterials. Another potential resource is risk management programs operated by manufacturers and insurers; these collect loss and claim data that can identify injuries and illnesses associated with nanotechnology activities. Access to this information may identify opportunities for further investigation of the likely causes of apparent associations.

Analysis of Current Projects

At the 2009 NNI exposure assessment workshop, no existing projects to gather health information from nanomaterial-exposed cohorts were identified. However, analysis of FY 2009 projects shows one funded by NIOSH that provides nanotechnology surveillance and epidemiology for workers exposed to nanomaterials.

Example of Progress in NanoEHS Research: Occupational Guidelines

To protect workers and responsibly move nanotechnology forward, NIOSH has developed three parallel research efforts to (1) conduct foundational toxicology research, (2) measure nanomaterials in workplace air, and (3) evaluate control approaches and personal protective equipment. Findings from field investigations and laboratory research (e.g., see Figure 3-2) are integrated into the NIOSH guidance, *Approaches to Safe Nanotechnology: Managing the Health and Safety Concerns Associated with Engineered Nanomaterials* (http://www.cdc.gov/niosh/docs/2009-125/). This guidance identifies nanotechnology occupational safety and health issues; makes recommendations on occupational safety and health best practices in the production and use of nanomaterials; facilitates dialogue between NIOSH, industry, labor, and academia; responds to requests for authoritative safety and health guidelines; and identifies information gaps and areas for future study and research. This document is widely utilized by industry; is cited by trade associations, unions, and other nongovernmental organizations; and has been used by international organizations as a template for their guidance documents.

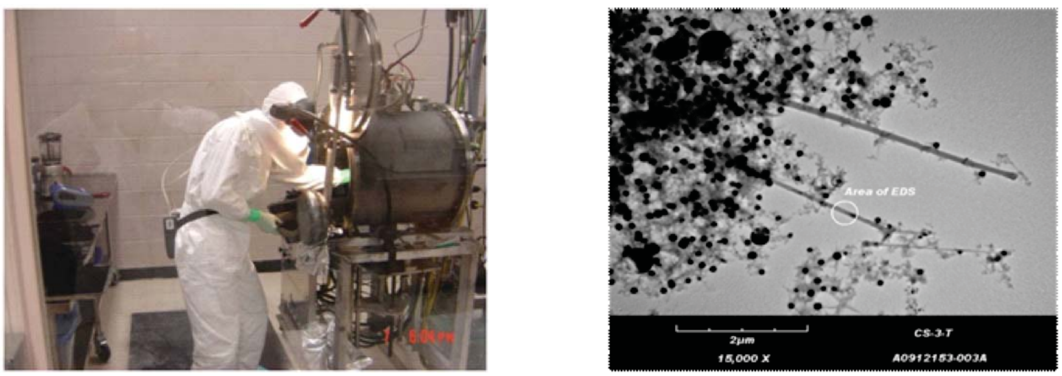

Figure 3-2. (Left) A researcher harvests single-walled carbon nanotubes from a carbon arc reactor. (Right) A TEM image of nanotubes collected in the researcher's personal breathing zone during nanotube harvesting.

Source: National Institute for Occupational Safety and Health.

4. Human Health

Overview

The 2011 Human Health category of EHS research needs is designed to systematically examine exposure, uptake, distribution, metabolism, excretion, and effects of nanomaterials in *in vitro* and *in vivo* models and relate their physico-chemical properties to nanomaterial biological response at the molecular, cellular, tissue, and whole-organism levels. Data from *in vitro* and *in vivo* models will be extrapolated to the human response in healthy, vulnerable, and susceptible individuals and populations. When integrated with data from other sections of the NNI EHS Research Strategy, they will provide the information necessary to understand the human health risk of exposure to nanomaterials and support development of evidence-based guidance to protect human health.

While there has been progress in understanding human responses to nanomaterials, researchers have not yet achieved the critical data sets needed to understand fully the risk of exposure and develop science-based nanotechnology-related health and safety guidelines and support for regulatory decision making. To advance this research through an integrated Federal strategy, the NEHI Working Group reviewed the status of nanotechnology-related human health research and solicited stakeholder comments, leading to the identification of six areas of research needed to achieve the two goals set forth for human health.

Accurate assessment of physico-chemical properties of engineered nanomaterials is critical to realizing the human health goals. Through linkages to the Nanomaterials Measurement Infrastructure research needs (Chapter 2), measurement tools to determine physico-chemical properties and create reliable and reproducible assays and methods[13] are being developed and applied in human health research to understand more precisely the physico-chemical property or subset of properties that regulate absorption, distribution, metabolism, and excretion (ADME) of nanomaterials and cause specific biological responses. An understanding of these property–response or dose–response relationships is essential for accurate, science-based decision analysis by regulatory agencies and development of robust predictive models that will improve nanomaterial design, maximize biocompatibility, and minimize adverse health and environmental effects.

This 2011 NNI EHS Research Strategy expands the concept of human health research to include healthy individuals, vulnerable populations with acute and chronic disease, and developmentally sensitive populations such as fetuses, children, and the elderly. Airborne particulate research involving sensitive and vulnerable populations has demonstrated differences in the uptake, metabolism, and excretion components of the exposure–response paradigm that could shift risk management guidelines for particular populations. Further explanation is provided in the newly crafted research need #6.

Another cross-cutting thread in the design of nanotechnology-related human health research is the need to define more accurately the concept of exposure across the life cycles of nanomaterials and

13. The concept and process of validation has scientific discipline-specific definitions and criteria to identify validated assays and methods. Therefore, the term "reliable and reproducible" is used in place of the term "validated" when referring to assays and methods in this chapter.

nanotechnology-enabled products. Human Exposure Assessment (Chapter 3) considers population-based exposure measurements, whereas the Human Health research needs build on these data at the individual level by characterizing and analyzing exposure for each exposure route (research need #2) and at and in tissues at the port of entry (research need #4). Transport, biotransformation, and sequestration of ENMs in secondary tissues are examined in research need #1. Inherent in the life cycle concept and applicable to all human health research is the longitudinal examination of exposures to nanomaterials across life cycle stages from R&D material to large-scale production, product incorporation, use, and disposal.

Furthermore, research on human health often involves complex, interrelated concepts that are investigated most efficiently and effectively by research programs conducted in parallel rather than serially. This construct challenges the development of a linear series of research needs; however, when woven together, the Human Health research needs provide the critical framework to provide relevant, high-quality data.

Goals

- Understand the relationship of physico-chemical properties of engineered nanoscale materials to *in vivo* physico-chemical properties and biological response.
- Develop high-confidence predictive models of *in vivo* biological responses and causal physico-chemical properties of ENMs.

Research Needs as of 2011

#1. Identify or develop appropriate, reliable, and reproducible in vitro *and* in vivo *assays and models to predict* in vivo *human responses to ENMs:*

- Establish a system to develop and apply reliable and reproducible *in vitro* and *in vivo* test methods
- Evaluate the degree to which an *in vitro* response correlates with an *in vivo* response
- Evaluate the degree to which *in vitro* and *in vivo* models predict human response
- Translate structure–activity relationship and other research data into computational models to predict toxicity *in silico*

#2. Quantify and characterize ENMs in exposure matrices and biological matrices:

- Determine critical ENM measurands in biological and environmental matrices and ensure the development of tools to measure ENMs in appropriate matrices as needed
- Determine matrix and/or weathering effects that may alter the physico-chemical characteristics of the ENM measurands
- Identify key factors that may influence the detection of each measurand in a particular matrix (e.g., sample preparation, detection method, storage, temperature, solvents/solutions)

- Characterize and quantify exposure for all exposure routes using *in vivo* models to identify the most likely routes of human exposure
- Identify biomarkers of exposure and analytical methods for their determination

#3. Understand the relationship between the physico-chemical properties of ENMs and their transport, distribution, metabolism, excretion, and body burden in the human body:

- Characterize ENM physico-chemical properties and link to mechanisms of transport and distribution in the human body
- Understand the relationship of the physico-chemical properties of ENMs to the mechanisms of sequestration in and translocation of ENMs out of the exposure organ and secondary organs, and to routes of excretion from the human body
- Determine the metabolism or biological transformation of ENMs in the human body

#4. Understand the relationship between the physico-chemical properties of ENMs and uptake through the human port-of-entry tissues:

- Characterize ENMs at and in port-of-entry tissues, including nontraditional routes of entry such as the ear and eye, and identify mechanisms of ENM uptake into tissues
- Determine the relationship of ENM physico-chemical properties to deposition and uptake under acute exposure conditions and under chronic exposure conditions
- Translate data on ENM properties and uptake to knowledge that may be used to intentionally redesign ENMs for optimum human and environmental safety and product efficacy

#5. Determine the modes of action underlying the human biological response to ENMs at the molecular, cellular, tissue, organ, and whole-body levels:

- Determine the dose response and time course of biological responses at the primary site of exposure and at distal organs following ENM exposure
- Understand the mechanisms and molecular pathway(s) associated with ENM biology within cellular, organ, and whole-organism systems
- Link mechanisms of response with ENM physico-chemical properties and employ this information in the design and development of future ENMs
- Develop translational alternative *in vitro* testing methods for the rapid screening of future ENMs based on mechanism(s) of response that are predictive of *in vivo* biological responses

#6. Determine the extent to which life stage and/or susceptibility factors modulate health effects associated with exposure to ENMs and nanotechnology-enabled products and applications:

- Determine the effect of life stage and/or gender on biological response to ENMs

- Establish the role of genetic and epigenetic susceptibility on the biological response to ENMs in the context of life stage and/or susceptibility factors
- Understand mechanistically the influence of preexisting disease on the biological response to ENMs in the context of life stage and other susceptibility factors
- Identify exposure conditions that make susceptible individuals more vulnerable to the health effects associated with ENMs and nanotechnology-enabled applications
- Establish a database that contains published, peer-reviewed literature, occupational and consumer reports, and toxicological profiles that describe altered responses to ENMs and nanotechnology-enabled applications in susceptible animal models or individuals following exposure

Comparative Analysis of Projects

The FY 2009 investment for human health research projects increased by $17.6 million and 17 projects since FY 2006, with funding from two additional agencies, CPSC and FDA. The average investment per project has increased from approximately $240,000 per project in FY 2006 to $350,000 per project in FY 2009. The increase is distributed across the Human Health research needs, with the exception of research need #3 on the distribution and fate of nanomaterials in the body. This decrease is due to a change in agency reporting of nano-biomedical projects that only partially support nanoEHS research. The increase in funding reflects in part the American Reinvestment and Recovery Act funding across most research needs.

Three projects have broad research scopes that address multiple human health research needs, and 15 are reported as "other" because their research themes are tangentially related to nanoEHS research and provide some benefit to the general knowledge base. The FY 2006 and FY 2009 projects were mapped onto the newly defined research needs; the resulting distributions by number of projects and funding are presented in Table 4-1.

Table 4-1. Analysis of Projects Related to the Human Health Category of NanoEHS R&D, FY 2006 & FY 2009*

Research Needs	FY 2006		FY 2009		Change
	Reported funding in $K (% of total)	Number of projects (% of total)	Reported funding in $K (% of total)	Number of projects (% of total)	Funding in $K (number of projects)
1. Identify or develop appropriate, reliable, and reproducible *in vitro* and *in vivo* assays and models to predict *in vivo* human responses to ENMs.	975 (4%)	6 (6%)	5,170 (12.4%)	17 (14.5%)	+4,195 (+11)
2. Quantify and characterize ENMs in exposure matrices and biological matrices.	2,895 (12.1%)	13 (13%)	7,900 (19%)	19 (16.2%)	+5,005 (+6)
3. Understand the relationship between the physico-chemical properties of ENMs and their transport, distribution, metabolism, excretion, and body burden in the human body.	7,758 (32.4%)	30 (30%)	2,700 (6.5%)	7 (6%)	-5,058 (-23)
4. Understand the relationship between the physico-chemical properties of ENMs and uptake through the human port-of-entry tissues.	2,722 (11.4%)	11 (11%)	3,800 (9.1%)	13 (11.1%)	+1,078 (+2)
5. Determine the modes of action underlying the human biological response to ENMs at the molecular, cellular, tissue, organ, and whole-body levels.	9,590 (40%)	39 (39%)	17,870 (43%)	40 (34.2%)	+8,280 (+1)
6. Determine the extent to which life stage and/or susceptibility factors modulate health effects associated with exposure to ENMs and nanotechnology-enabled products and applications.	--	--	1,330 (3.2%)	3 (2.6%)	+1,130 (+3)
Multiple: Projects that capture multiple needs	--	--	1,160 (2.8%)	3 (2.6%)	+1,160 (+3)
Other: Not captured above but of benefit to the research category	35 (0.1%)	1 (1%)	1,680 (4%)	15 (12.8%)	+1,680 (+14)
TOTALS	**23,975**	**100**	**41,610**	**117**	**+17,635 (+17)**

* Agencies supporting research in this category: DOD, CPSC, EPA, FDA, NIH, NIOSH, NIST, NSF

Gaps for Future Investment

While continued investment across all human health research needs is necessary to achieve the goals outlined in this chapter, the fate of nanomaterials in the body (research need #3) and the responses of vulnerable and susceptible populations (research need #6) require near-term attention.

Rationale for the 2011 Research Needs and Changes from 2008

Against the backdrop of research progress and stakeholder recommendations from the 2009 NNI Workshop on Nanomaterials and Human Health,[14] the Human Health research needs have been revised in the 2011 NNI EHS Research Strategy as indicated in Figure 4-1. The order of the research needs mirrors the sequence of research and data generation and prerequisites, rather than priority ranking.

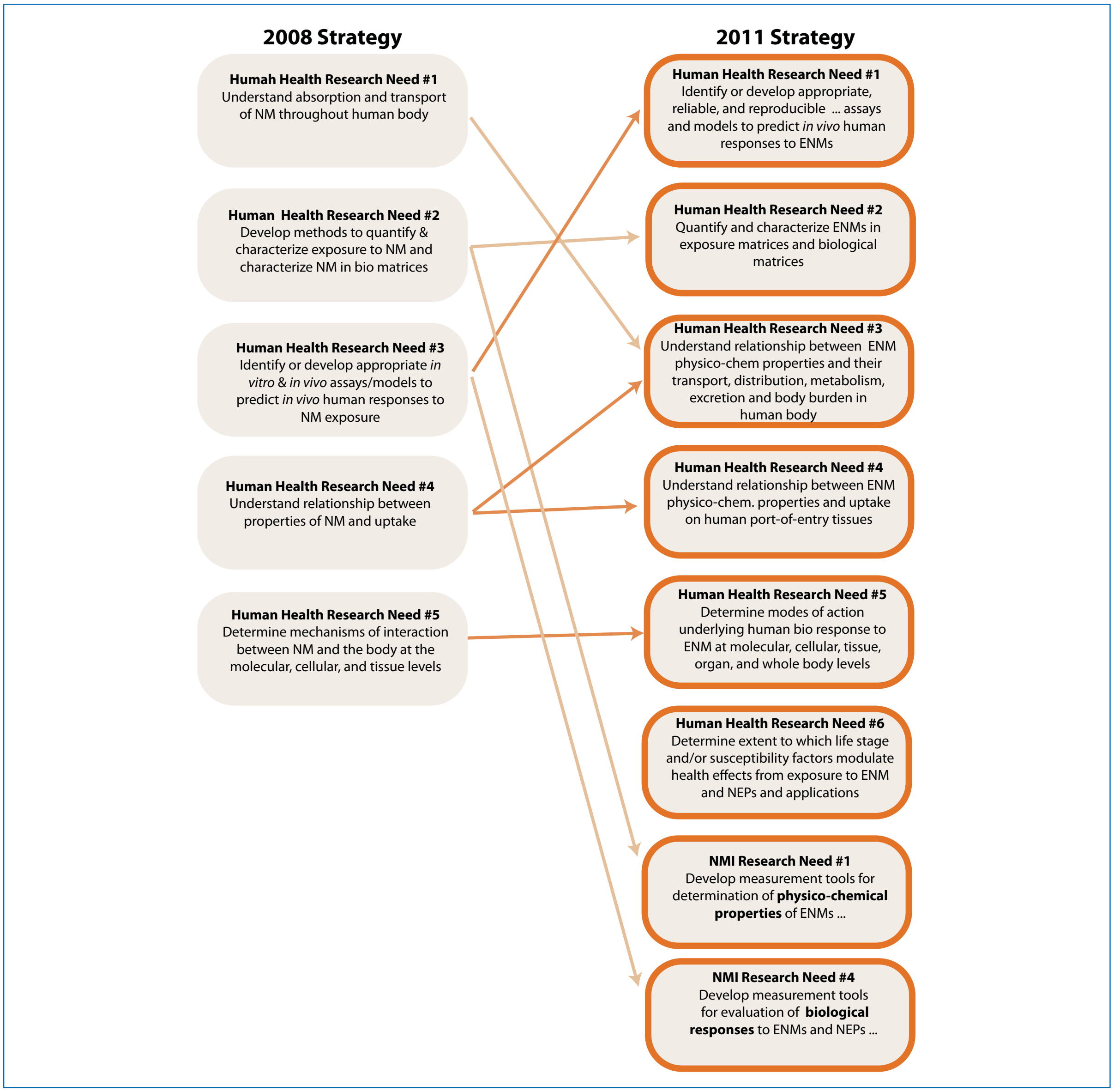

Figure 4-1. Comparison of the Nanomaterials and Human Health research needs in the 2008 NNI EHS Research Strategy (left) with the Human Health research needs in the 2011 NNI EHS Research Strategy (right). The arrows indicate mapping of the 2008 research needs to the 2011 research needs. Note that two of the 2008 research needs map in part to the Nanomaterial Measurement Infrastructure (NMI) research category, that 2011 adds a sixth research need, and that the ordering shifted between 2008 and 2011.

14. *Nanomaterials and Human Health & Instrumentation, Metrology, and Analytical Methods, National Nanotechnology Initiative Workshop, November 17–18, 2009* (NSET/NSTC, Washington, DC, 2011; http://www.nano.gov/publications-resources).

Research Need #1. Identify and develop appropriate, reliable, and reproducible in vitro *and* in vivo *assays and models to predict in vivo human responses to ENMs*

Overview

In order to predict the behavior of ENMs in humans, it is essential to have in place reliable and reproducible *in vitro* and *in vivo* test methods and models that accurately assess ENM distribution and kinetics in the human body and to develop approaches to translate these data to humans. Developing the ability to predict with a high confidence level the biological effects of ENMs in exposed humans from *in vitro* tests is an iterative process, requiring first the evaluation of the adequacy of traditional *in vitro* and *in vivo* tests for ENMs, followed by the determination that the *in vitro* results reflect the *in vivo* response quantitatively and qualitatively. This process should culminate in the assessment of the degree to which the models mimic human exposure conditions and predict the human response to ENMs. Therefore, efforts should focus on accurate methods of exposure and endpoints that are known to be similar in animal models and humans. This research need will greatly benefit from the Nanomaterial Measurement Infrastructure effort (Chapter 2) to develop high-throughput screening methods for *in vitro* research that could reliably replace *in vivo* systems and from the Human Exposure Assessment research (Chapter 3) on dose metrics and routes of exposure.

Recommendations for Changes

At the 2009 NNI human health public workshop, the eight components of the 2008 Human Health research need #3 were found to be redundant within that research need or between other NNI research needs. The original eight bullet points have been refocused and consolidated into three bullets and distributed to Human Health research need #1 in the 2011 NNI EHS Research Strategy.

New test methods and high-throughput screening technologies were incorporated into the 2011 Human Health research need #1 to emphasize the need to develop and apply a system to establish reliable and reproducible *in vitro* and *in vivo* test methods. (Workshop participants considered the development of high-throughput screening technologies to be a long-term, lower priority because it will require significant work to develop high-throughput screening technologies that can reliably replace *in vivo* systems, and this component was dropped.)

The 2008 research need #3 bullet to evaluate the degree to which *in vitro* and *in vivo* models predict human response is left unchanged in the 2011 research need #1, but it is identified as a long-term and low priority because animal models only approximate the anatomy and physiology of humans.

Additionally, workshop participants recommended that the term "validate" be avoided due to the potential for confusion over what criteria and protocols are required to fully validate test methods. In lieu of "validation," the 2011 wording is "reliable and reproducible," to more accurately reflect the desired properties of these test methods.

Analysis of Current Projects

Seventeen FY 2009 projects were identified as relevant to predicting the behavior of ENMs in humans, more than double the number of FY 2006 projects under this research need. Using the four 2011 subordinate points identified for Human Health research need #1, almost all of the funded research fits currently under the first point to develop and apply a system to establish reliable and reproducible *in vitro* and *in vivo* test methods. Only two projects are relevant to the third point to translate structure–activity relationships and other research data into computational models to predict toxicity *in silico*. No projects were identified as relevant at this time to the second bullet, suggesting that the field has not progressed sufficiently to translate data and models to the prediction of human response. Clearly, this is a critical gap that needs to be filled in the near term to improve understanding of the relevance of the *in vitro* and *in vivo* test methods to human health. The outcome of those efforts would inform and drive development of the third point, that is, to start building the computational models to predict toxicity *in silic*o.

Research Need #2. Quantify and characterize ENMs in exposure matrices and biological matrices

Overview

Carefully measuring the quantity and properties of ENMs at the site of biological uptake and impact is critical to identifying and understanding the relationship between exposure, uptake, and biologically effective dose. Measurement data are needed to support an ENM exposure framework for linking sources to effects. Biomarkers of exposure have been recognized as important tools for understanding the relationship between exposure, uptake, and disposition in the body.

This priority research need focuses on methods to quantify and characterize ENMs in environmental matrices that may contact the human body, and to determine the uptake, transport, disposition, and concentration in appropriate human biological compartments. Biological matrices are complex environments that may change the surface chemistry of nanoparticles; for example, lung surfactant proteins may be applied to ENMs post-synthesis to prevent agglomeration during use. Technologies that measure physical properties such as particle size and surface area within an organism are critical to evaluating exposure, fate, and biological effects over various dose–response paradigms. Analytical methods, particularly those that would enable the integration of exposure across exposure routes, need to be explored. Additionally, it may be insufficient to report only mass measurement of nanomaterials for data analysis, because other physical and chemical parameters are required to fully understand the biological behavior of ENMs.

Recommendations for Changes

The 2008 NNI EHS strategy document presented the need for techniques to characterize ENMs *in vivo*, and to evaluate the toxicity of these materials in the dose–response paradigm. The results of the 2009 NNI human health workshop emphasized the critical need to understand the relationship between exposure and dose. Therefore the 2011 EHS Research Strategy has been refocused to include identifying ENMs *in vivo* and in matrices outside of the body, such as in air and food, that may subsequently enter the body and reach target organs, tissues, and cellular components. Current methods that characterize ENMs in biological or environmental media are unable to measure either physical or chemical transformations of ENMs. Identifying and adequately describing these changes is a key factor in translating exposure and uptake to biological impact.

Tools and methods developed under this research need will enable mechanistic studies that can be performed *in vitro* and *in vivo*, as well as support research to determine changes in particle properties that result from interactions between exposures and biological matrices. Collaboration between physical chemists, physiologists, toxicologists, and pathologists will be important so that diverse scientific approaches can be applied to characterize multiple types of ENMs in diverse biological matrices. Applying the tools and methods to catalog transformation of ENMs through time, uses, and micro-environments will enable analysis of measurement uncertainty and production of accurate data. Use of informatics and data transfer tools should be encouraged between measurement researchers and those studying effects.

Analysis of Current Projects

Nineteen projects were reported in FY 2009 for this research category: 2 by EPA, 4 by NIOSH, 2 by NSF, and 11 by the National Institutes of Health National Institute of Environmental Health Sciences (NIH/NIEHS). This represents an increase of six projects since FY 2006. The FY 2009 projects represent a wide range of approaches, from assessments of toxicity at the cellular level and the properties that impact observed effects, to projects that use personal sampling for characterizing ENM exposures through nasal and oral routes. Several studies investigated the relationship between the physico-chemical properties of ENMs and their observed cellular impact, and one study examined nanomaterial bioavailability and biopersistence.

While these studies address most of the topics under this research need for one or more nanomaterials, additional studies will be necessary to fully quantify and characterize the diverse classes and categories of nanomaterials in biological and exposure matrices. Areas of further study should include development of biomarkers of exposure and high-throughput screening methods for exposure assessment, the effects of factors such as storage and impact of solvents and solutions during ENM toxicity studies, and route-specific *in vivo* investigations correlated with biomarkers and biological effects. Models and methods are needed to determine linkages between exposure sources and health effects. Interactions between measurement researchers, biologists, and toxicologists should be encouraged to meet this research need.

Research Need #3. Understand the relationship between the physico-chemical properties of ENMs and their transport, distribution, metabolism, excretion, and body burden in the human body

Overview

This research need focuses on the deposition, translocation, and fate of nanomaterials throughout the body in order to provide information on the bioaccumulation and potential body burden resulting from repetitive low-level exposures to ENMs. This work will continue to draw upon biomedical and environmental research to examine ENM biokinetics and transport mechanisms, because these applications provide useful safety data. Projects in this area may investigate, for example, (1) the physico-chemical properties of ENMs that enhance or impede transport through the biological barriers, blood, cells, and organs; (2) transport through intracellular compartments and cytoplasm; and (3) the role of ENM–protein interactions in the uptake transport of ENMs within these biological systems. This research will provide critical information on the properties and mechanisms regulating ENM uptake, translocation, and fate in biological systems at the molecular, cellular, and organ levels in order to develop biokinetic models that predict ENM biological exposure and fate. This research focuses on (1) the transport and distribution of nanomaterials throughout the body, including metabolic pathways and excretion; and (2) body burden, including biotransformation, sequestration, and effects of nanomaterial exposure and absorption, especially for sensitive tissues such as the nerves, blood vessels, and bone marrow. Nanomaterials research in this need area will continue to draw on the experimental and *in silico* biomedical research on the design of nanomaterials for improved drug delivery and imaging.

Recommendations for Changes

In 2008, the Nanomaterials and Human Health research need included the absorption and transport of ENMs and did not include research on the distribution, metabolism, excretion, and body burden of ENMs.

Coordination and integration of imaging and analytical methods will allow distinction between ENMs and their physico-chemical properties and will enhance systematic mass balance analysis over the time course from exposure to sequestration, as well as analysis of biological responses. Stable radioactive isotopic tracing approaches should be employed to enhance sensitivity and selectivity of the imaging and analytical tools.

Finally, the identification of dose–response, or structure–activity, relationships and the impact of ENMs on cell function are limited. Little information is currently available on the effect of ENM surface functionalization on metabolism intracellular and intra-organ translocation and dissolution of ENMs into their component elements/chemicals, and biologically mediated changes in the material properties. More progress is needed to identify generalized principles of ENM interaction with biological systems, protein opsonization, and ENM dissolution. The differences in experimental results using *in vitro* and *in vivo* models and the relationship of data from these experimental systems to human exposures need to be determined so that *in vitro* and *in vivo* data can be interpreted meaningfully.

Analysis of Current Projects

Thirty FY 2006 projects were determined to be in alignment with this research area (2008 EHS Research Strategy research need #1), for total funding of $7.8 million. Seventeen projects addressed this research need directly, and 13 had a relevant research component. Topics included the investigation of ENM physico-chemical characteristics governing absorption through the respiratory tract; physico-chemical properties that enhance or impede transport through blood, tissues, intracellular compartments, and cytoplasm; and intracellular and extracellular forces that stabilize or destabilize ENMs and properties that allow them to coexist benignly with the immune and reticuloendothelial systems.

Only seven FY 2009 projects in the Federal portfolio were identified as aligned with 2011 Human Health research need #3. These projects, funded by NIH (through the National Institute of Environmental Health Sciences, the National Institute of Child Health and Human Development, and the National Institute of Dental and Craniofacial Research), NIOSH, and NSF, totaled nearly $2.7 million. Four of the FY 2009 projects examined sequestration of ENMs in the exposure organ and/or secondary organs, and one study characterized distribution of ENMs within alveolar tissue. Another characterized ENM surface properties and mechanisms of transport in the placenta. The final project addressed general toxicological assessments for ENMs within the context of the National Toxicology Program. One of the projects was funded by the American Recovery and Reinvestment Act (ARRA) of 2009, with the result that ARRA funds accounted for almost 15 percent of the total investment for this research need for the year ($350,000). Nevertheless, considerably fewer projects are reported for FY 2009 than for FY 2006, primarily due to a redistribution and reorganization of research priorities, in particular, as was reported in the 2008 human health research needs #3 – #5.

There remains significant opportunity for further research to promote understanding of the relationship between the physico-chemical properties of ENMs and their transport, distribution, metabolism, body burden, and excretion from the human body. There were no studies to address mechanisms of translocation of nanomaterials from one organ to a secondary organ, address mechanisms of biotransformation, or examine excretion routes of nanomaterials from the human body. Gastrointestinal and ocular exposures also remain understudied.

Research Need #4. Understand the relationship between the physico-chemical properties of ENMs and uptake through the human port-of-entry tissues

Overview

The research encompassed by research need #4 focuses on the processes by which ENMs enter the human body. Developing an understanding of the physico-chemical properties of ENMs that can aid or prevent uptake is critical to forming a complete picture of ENMs and human health. The term "uptake" is used in this strategy as an inclusive term to encompass interactions of ENMs at cellular boundaries in port-of-entry tissues resulting from processes such as deposition, adsorption, and absorption. Research need #4 specifically correlates the physico-chemical properties of ENMs with uptake at the cellular level in relevant biological models and fluids.

The current studies in this research area lack technical specificity on the relationships between nanoparticle characterization, transformation at cellular boundaries, and uptake mechanisms. There has been considerable attention paid to pulmonary exposure. Although there have been recent advances in aspiration techniques and aerosol generation, historical instillation methods that bypass the upper respiratory tract are still employed. These instillation methods change the dose rate and distribution of materials *in vivo* and have limited value for risk assessment. ENM interactions with biological barriers at the port of entry, as well as the effects of biological coatings on ENMs such as surfactants and lipoproteins, should also be studied to understand the influence of these materials on cellular uptake.

Recommendations for Changes

To expand consideration of exposure and uptake in this report, these are divided between research needs #3 and #4: research need #3 describes the research associated with physico-chemical properties of nanomaterials and their distribution, metabolism, excretion, and body burden, while research need #4 describes the research associated with physico-chemical properties of nanomaterials and their uptake. There has been more research and progress in the past several years on uptake of nanomaterials than on assessment of distribution, metabolism, excretion, and body burden. However, many of the studies of uptake have been performed *in vitro* with various cell types that are considered to be models of organ uptake in the simplest sense.

Analysis of Current Projects

Thirteen projects were identified in the FY 2009 Federal portfolio to align with research need #4. Compared to the projects listed in the FY 2006 Office of Management and Budget data call, the FY 2009 projects more explicitly seek to connect nanomaterials' physico-chemical properties with uptake and to leverage that knowledge for design of more biocompatible ENMs and development of biomarkers of exposure; 8 projects were in this area. Two projects examined the relationship between ENM properties and acute exposure, deposition, and uptake; 2 focused on intentionally designed ENMs to optimize safety and efficacy; and 1 focused on the identification of biomarkers of exposure.

Research gaps are evident in the FY 2009 portfolio with respect to research to understand uptake at port-of-entry tissues. There were no projects identified that studied the relationship between ENM properties and chronic exposure, deposition, and uptake, nor were there any projects identified to examine nontraditional port-of-entry tissues such as ear, nose, and eye. Because most of the research was focused in a single area, there were clear gaps in the portfolio, providing significant opportunities for further research to promote understanding of the relationship between ENM properties and their uptake.

The existing, limited studies lack technical specificity on characterization and exposure, such as physico-chemical characteristics of the nanomaterials, transformation of ENMs at the interfaces where the nanomaterial meets the cellular border, and mechanisms of the particle's cellular uptake. Additional studies are needed on mechanisms of cell-specific uptake in tissues and organs on ports of entry and ENM interactions, and on the effects of biological molecules covering the nanomaterial surface. Also, studies are needed on inhalation designed for use in risk assessment. Ultimately, there is a desire for acute studies to better identify the need for, and inform the design of, studies and risk assessments.

Research Need #5. Determine the modes of action underlying the human biological response to ENMs at the molecular, cellular, tissue, organ, and whole-body levels

Overview

This research will provide fundamental understanding of the key events and processes that mediate the biological response and alter function and pathology associated with interaction of ENMs at the molecular, organelle, cellular, and organ/tissue levels of biological organization. By employing physico-chemically distinct ENMs, diverse routes of exposure, and dose metrics that reflect realistic human exposure conditions (Chapter 3), research in this area will enable the identification of common and diverse molecular mechanism(s) mediating biological responses for similar or different ENMs. Data from such inquiries will provide cell-, tissue-, and organ-specific responses and will aid in developing a predictive testing approach based on mechanistic information.

Given the multitude of ENMs under development and the alteration of biological behavior by minute changes in ENM structure and composition, a high-throughput, high-content assay tool is critical to timely evaluation of ENM safety. Development of this tool is described in Nanomaterial Measurement Infrastructure (NMI) research need #4 (see Chapter 2) and applied to model systems under this research need. These methods, combined with *in vitro* and *in vivo* systems, will also lead to identification of the biomarkers that demonstrate biological response to acute or chronic ENM exposure and that link these exposures and responses to health effects.

Recommendations for Changes

In response to participant input at the November 2009 public NNI Workshop on Human Health and Instrumentation, Metrology, and Analytical Methods and to recent developments in the field, research need #5 and supporting specific bullets have been modified from the 2008 NNI EHS Research Strategy. The research need is refocused to state, "Determine the *modes of action* underlying the human biological response" to ENMs. The focus of the research was recast to identify critical research endpoints and distinguish between dose–response relationships and relationships between nanomaterial physico-chemical properties and bioactivity. This links biological mechanisms to nanomaterials' physico-chemical properties, information that can be employed in the design and development of future nanomaterials.

Emphasis on determining the relationship of biological response, or modes of action, in animal models to human response was expanded in response to the public workshop recommendations to specify the routes of exposure that require evaluation and to couple this with specifying the time course for exposure dose and response. The language in the research need #5 bullets now incorporates these three concepts into four bullets and evaluates the biological response to ENMs at the primary site of exposure and at the distal organ level following pulmonary or dermal exposure, ingestion, or intravenous administration.

Analysis of Current Projects

The FY 2006 EHS project portfolio was rich in evaluation of nanomaterials for targeted drug delivery and medical imaging. These studies contributed to the basic foundation for the understanding of interactions of nanoparticles with biological fluids, proteins, and cell membranes. In FY 2006, projects directly evaluating nanotoxicology were in their early stages, and research gaps existed. Review of the FY 2009 portfolio of Federal projects identified 40 projects related to nanotoxicology research that examined dose–response relationships, mechanisms and pathways of biological response, linkage of mechanisms to ENM physico-chemical properties, and development of alternative testing methods for rapid screening. Current projects are concentrated primarily on pulmonary and dermal exposure routes, and evaluate pulmonary, cardiovascular, neurological, reproductive, and dermal endpoints, as well as tumorigenesis and mutagenesis. Most of the studies addressing the elucidation of molecular response pathways are evaluating the role of oxidant generation. Additional projects involve evaluation of particle/biological matrix interactions, particle/cell interactions, and effects of size, shape, and surface reactivity on bioactivity. A few projects include methods development for alternative rapid screening tests.

High-priority areas for future investment include the relationship between the structure of ENMs and their biological effects; development of EHS predictive capability based on ENM physico-chemical properties; improved and specific testing regimens, for example, predictive *in vitro* screening tests or mechanistic information needed to develop biomarkers; the relationship between acute/high-dose-rate exposures versus chronic/low-dose-rate exposures; and improved studies of systemic effects of ENMs, for example, effects of pulmonary or dermal exposure on the carcinogenic potential of ENMs.

Research Need #6. Determine the extent to which life stage and/or susceptibility factors modulate health effects associated with exposure to ENMs and nanotechnology-enabled products and applications

Overview

Life stage and host susceptibility factors are critical in regulating all aspects of biological responses associated with exposure to chemicals and environmental pollutants, including health effects, dosimetry and biokinetics, mechanism of injury, dose metrics, and dose–response relationships. These factors play critical roles in susceptibility where young and old individuals with preexisting diseases are most susceptible to the adverse health effects associated with environmental exposures. In addition, exposure to elevated levels of particulate air pollution is associated with adverse developmental effects such as premature births, birth defects, and low birth weights. There also exists the environmental justice concern for people who are disproportionally exposed to pollution and therefore are more vulnerable to the addition of potential new stressors such as ENMs. Recent studies have shown that some ENMs (1) enhance the sensitization and exacerbate challenge phases in mouse allergy models, (2) exacerbate atopic dermatitis, and (3) exacerbate pulmonary and cardiovascular toxicity in older animals.

Recommendations for Changes

Understanding the role that life stages and/or susceptibility factors play in biological response to ENM exposure is critical to achieving effective protection of the occupational work force and the general public; this is a new research need that was supported by participants at the 2009 NNI Workshop on Human Health and Instrumentation, Metrology, and Analytical Methods. Research for this new need should include developmental and health effects associated with all life stages, including pregnancy and pre- and post-gestational development, and altered susceptibility to exposures that may be associated with preexisting diseases. The spectrum of research should include dosimetry, biokinetics, dose–response metrics, and mechanisms of biological responses following different routes of exposure to ENMs.

Analysis of Current Projects

A review of Federally funded projects in FY 2009 to examine nanotechnology-related human health effects revealed that 3 out of 117 projects (or 3 percent of projects) were conducting research to identify the extent to which life stage and/or susceptibility factors play a role in modulating health effects associated with exposure to ENMs and nanotechnology-enabled products. Specifically, the 3 projects examined the impact that life stage (1 project) or preexisting pulmonary disease (2 projects) have on the biological response to ENMs. This paucity of research represents a significant gap in our knowledge, and future nanotechnology health effects research should increase resources to fully understand the relationship of life stage and host susceptibility factors to the human responses to ENM exposure. These data are essential to allow for effective risk assessment and management decisions that are protective of both the occupational work force and the general public.

Example of Progress in NanoEHS Research: Dermal Exposure to Sunscreens

Early concern about the safety of nanomaterials focused on the use of nanoscale materials in skin products, especially in sun block, products that are increasingly used by the general public. Nanoscale titanium dioxide and zinc oxide, through their ability to act as sunblock agents in sunscreens, can reduce skin cancer from cell damage caused by solar radiation. Concern arose about the ability of nanoscale materials to penetrate the skin and enter the body. Through a focused research program that examined both acute and chronic exposure of skin to sunscreen formulation (with or without nanoparticles, on intact skin), FDA, the NIEHS National Toxicology Program, and National Cancer Institute Nanotechnology Characterization Laboratory determined that intact skin provided a barrier to application of a nanomaterial-containing sunscreen formulation (Figure 4-2).

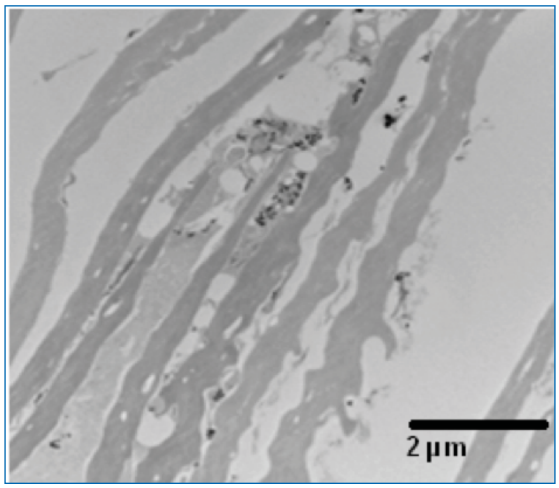

Figure 4-2. Electron microscope image of titanium dioxide particles in stratum corneum following administration of nanoscale TiO_2. No significant dermal penetration of titanium dioxide from sunscreen formulations containing nanometer and submicrometer-size titanium dioxide particles was observed.

Source: N. Sadrieh, A. M. Wokovich, N.V. Gopee, J. Zhen, D. Haines, *et al.*, Lack of significant dermal penetration of titanium dioxide (TiO_2) from sunscreen formulations containing nano- and submicron-size TiO_2 particles. *Toxicological Sciences* 115, 156-166, 2010.

5. Environment

Overview

The 2011 Environment EHS research category encompasses research to identify, understand, and control the potential effects of engineered nanomaterials on both relevant ecological receptors such as fish and the ecosystems that they occupy, and research on fate and transport of engineered nanomaterials that leads to a better understanding of the mechanisms by which nanomaterials enter, remain in, degrade, and are transported through environmental media. Understanding these potential environmental implications is critical to implementing good product stewardship.

Releases of engineered nanomaterials have the potential to occur at any stage during the product life cycle. Characterization of physico-chemical properties of specific nanomaterials underpins understanding of how they will move, deposit and accumulate, and transform in environmental matrices and under the often-changing conditions in which they may be released. Transformation of these materials via biological and/or photochemical processes, contact with water, or other processes may reduce environmental persistence and help to determine exposure concentrations. These concentrations, along with other modifying factors and the receptors that are present, shape potential exposures.

Effects in exposed organisms again tie back to fundamental physico-chemical properties, as well as to a host of other factors such as exposure route, detoxification mechanisms in the organism, and sensitivity of the species. Product life cycle offers many potential points of entry into the environment. Fundamental studies of the potential hazards from nanomaterials, such as those involving single species tests performed for regulatory decision making, should be guided by a view of how nanomaterials behave in environmental systems. To understand ecosystem-wide effects, the sources (production/use/disposal), the pathways, and the key environmental receptors need to be understood.

Inventory databases of production and use information should be developed and coupled with nanoparticle properties of interest, including information on persistence, toxicity, transformations, and phase distributions. Populating such databases implies a shared responsibility and commitment by industry and government to make information available that, while addressing confidential business information needs, also provides the public with information on how much of what kinds of materials are being produced for what uses.

Source, pathways, and receptor exposures will be influenced by the fate and transformation of nanoparticles, which can be assessed in microcosms and/or mesocosms. Differences between nanomaterial behavior in the laboratory and in the environment should be better understood in the near term and should be correlated with appropriate in-laboratory dosing methods. Testing for adverse effects should consider not only the parent nanoparticle, but also transformation products and other toxic chemicals associated with nanoparticles in the environment. Whole effluent testing may be useful to better understand adverse effects of nanoparticles within a realistic background. Surrogate biomarkers such as oxidative stress genes can be considered as markers of exposure and effects.

Technical barriers impede progress in research on environmental fate and effects of ENMs. Methods or approaches must be developed to identify, characterize, and measure exposure to nanomaterials, and to follow their path and transformation through the environment and accumulation in organisms. Approaches may be needed for quantifying nanomaterials in test situations where the concentration may not be adequate for measurement by conventional means. Improved models for predicting environmental release and exposure to nanomaterials require more empirical data and mechanistic understanding of processes. Research on environmental transport is hampered by a limited understanding of particle coating chemistries and formulations used for consumer product applications, and by limited analysis of sources that may release nanomaterials, such as industrial point sources and consumer non-point sources.

Research in the Environment category provides significant information for other categories. Transport and transformation research informs the Human Exposure Assessment and Human Health categories, as it does the environmental exposures and effects on individuals or ecosystems within the Environment research category. Although research on human health and on effects on individuals of a species often pursues different paths, the results provide valuable counterpoints to each other. Exposures to workers, consumers, and the general population are included in the Human Exposure Assessment chapter; environmental exposures are included in this chapter.

Progress in overcoming the technical barriers to research progress in this category will be enabled through linkages to the Nanomaterial Measurement Infrastructure research needs wherein measurement tools are being developed for physico-chemical properties, detection and monitoring, and transformations of nanomaterials. The evaluation of exposure depends on understanding of transport, transformation, and the life cycle of the nanomaterial, as well as on species-specific biological and ecological information. Understanding effects on individuals of a species, populations, communities, and ecosystems (including abiotic effects) depends on understanding how these fate processes alter materials prior to their interactions with ecosystem receptors. Risk assessment ultimately depends on information from each of these research areas, and it also informs, in an iterative process, where information gaps exist in each area.

Goal

- Understand the environmental fate, exposure, and ecological effects of engineered nanomaterials, with priority placed on materials with highest potential for release, exposure, and/or hazard to the environment.

Research Needs as of 2011

#1. Understand environmental exposures through the identification of principal sources of exposure and exposure routes:

- Manufacturing processes and product incorporation
- Life cycle of technology and exposures subsequent to product manufacturing

- Analytical approaches to measure temporal changes in nanoparticle properties throughout the life cycle
- Models to estimate releases
- Environmental receptors for exposure assessments

#2. Determine factors affecting the environmental transport of nanomaterials:

- Determine key physico-chemical properties affecting transport
- Determine key transport and fate processes relevant to environmental media
- Develop new tools and adaptations of current predictive tools to accommodate the unique properties of nanomaterials

#3. Understand the transformation of nanomaterials under different environmental conditions:

- Identify and evaluate nanomaterial properties and transformation processes that will reduce environmental persistence, toxicity, and production of toxic products
- Determine the rate of aggregation and long-term stability of agglomeration/aggregation and the long-term stability of these aggregates and agglomerates
- Develop tools to predict the transformations or degradability of nanomaterials

#4. Understand the effects of engineered nanomaterials on individuals of a species and the applicability of testing schemes to measure effects:

- Test protocols
- Dose–response characterization
- Uptake/elimination kinetics, tissue/organ distribution
- Mode/mechanism of action, predictive tools
- Tiered testing schemes/environmental realism

#5. Evaluate the effects of engineered nanomaterials at the population, community, and ecosystem levels:

- Population
- Community
- Other ecosystem-level effects
- Predictive tools for population-, community-, and ecosystem-level effects

Comparative Analysis of Projects

The FY 2006 and FY 2009 projects were mapped onto the newly defined research needs; the resulting distributions by number of projects and funding are presented in Table 5-1.

Gaps for Future Investment

Much of the research in the Environment core EHS research category depends on improvements in the ability to quantify and characterize nanomaterials and to differentiate manufactured nanomaterials from naturally occurring background particles in the environment. Enhancing predictive capabilities will require investments in databases of nanomaterial properties, environmental modifications, and sources; development/refinement of testing schemes; improved understanding of nanomaterial behavior and fate; and improved understanding of potential receptors, exposures, and effects in individuals and ecosystems.

Rationale for the 2011 Research Needs and Changes from 2008

The 2008 research needs have been reordered to reflect the risk assessment process and updated as follows, and as indicated in the section above, Research Needs as of 2011. Research need #5 in particular was changed to clarify its scope and incorporate public recommendations from the October 2009 NNI Workshop on Nanomaterials and the Environment and Instrumentation, Metrology, and Analytical Methods.[15] The sections below on individual research needs describe changes to the bullets. The order of the research needs was changed to better reflect the risk assessment process, as indicated in Figure 5-1.

The report from the 2009 NNI Nanomaterials and the Environment & Instrumentation, Metrology, and Analytical Methods Workshop recommended research to:

- Understand exposure as it relates to determining environmental risk and
- Consider life cycle analysis as part of the evaluation of releases from manufacturing sites and other major waste streams in the near and medium term.

15. *Nanomaterials and the Environment & Instrumentation, Metrology, and Analytical Methods: Report of the National Nanotechnology Initiative Workshop, October 6-7, 2009*, Arlington, VA (NSET/NSTC, Washington, DC, 2011; http://www.nano.gov/publications-resources).

Table 5-1. Analysis of Projects Related to the Environment Category of EHS R&D, FY 2006 & FY 2009*

Research Need	FY 2006		FY 2009		% Change
	Reported Funding ($K) and % of total	Number of projects	Reported Funding ($K) and % of total	Number of projects	Funding in $K (number of projects)
1. Understand environmental exposures through the identification of principal sources of exposure and exposure routes	250 (2%)	1	250‡ (0.6%)	2	0 (+1)
2. Determine factors affecting the environmental transport of nanomaterials	4,490 (38%)	22	1,315‡ (3.0%)	4	-3,175 (-18)
3. Understand the transformation of nanomaterials under different environmental conditions	2,433 (21%)	9	5,065‡ (11.6%)	16	+2,632 (+7)
4. Understand the effects of engineered nanomaterials on individuals of a species and the applicability of testing schemes to measure effects	351 (3%)	5	715‡ (1.6%)	4	+364 (-1)
5. Evaluate the effects of engineered nanomaterials at the population, community, and ecosystem levels	115 (1%)	1	0	1	-115 (0)
Multiple: Projects that capture multiple needs			36,337+ (83.2%)	27	+36,337 (+27)
Other: Not captured in needs above but of benefit to the research category	4,089 (35%)	11	0	0	-4,089 (-11)
Total	**11,728**	**49**	**43,682**	**54**	**+31,954 (+5)**

*Agencies supporting research in this category (FY 2009): EPA, NSF, DOD/USAF, NIFA, DOE, NIST
‡ Funding attributable to projects that met the requirement for that research need and no other
+ Funding for projects associated with more than one research need

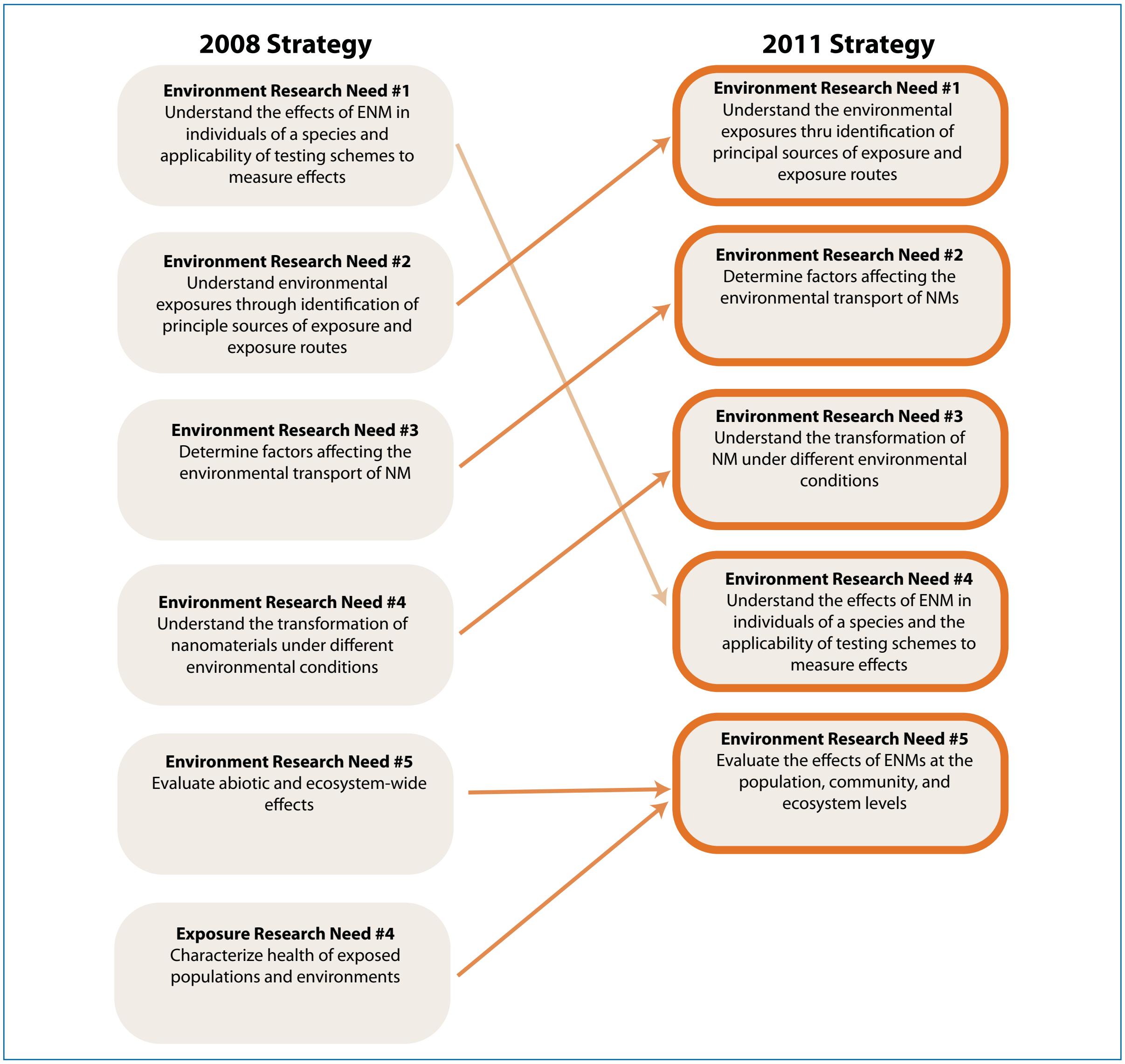

Figure 5-1. Comparison of the Nanomaterials and the Environment research needs in the 2008 NNI EHS Research Strategy (left) with the Environment research needs in the 2011 NNI EHS Research Strategy (right). The arrows indicate mapping of the 2008 research needs to the 2011 research needs.

Research Need #1. Understand environmental exposures through the identification of principal sources of exposure and exposure routes

Overview

The environmental exposures research need addresses sources of nanomaterials and their routes to the environment and environmental exposure, and helps to identify environmental receptors. To understand sources of nanoparticles, exposure pathways, and environmental exposures, the entire life cycle of a nano-enabled technology must be considered.

One of the fundamental components in understanding a potential risk is characterizing the exposure to a stressor. Exposure, uptake, and accumulation of nanomaterials may result in toxicity and other effects. The variety of nanotechnologies and products gives rise to a wide range of potential releases (both accidental and routine) to the environment throughout product life cycles. While some existing models can be applied to predict environmental concentrations of nanoparticles in air, surface water, groundwater, sediments, and soil, the precision and reliability of such estimates are limited by the lack of nanomaterial-specific laboratory and field validation studies that examine variability in space and time. Such studies are hampered by the inability of current methods to analyze nanomaterials in environmental samples. To be successful, the integration of life cycle information and exposure assessment must be coordinated across disciplines and also across organizations (including industry, government, nongovernmental organizations, and academia), as recommended by the President's Council of Advisors on Science and Technology.

Recommendations for Changes

The October 2009 NNI workshop also recommended research to develop models that can predict various aspects of engineered nanomaterial fate, distribution, exposure routes, transformations, and interactions with organisms and ecosystems.

Further discussion identified improved analytical tools, generation of an inventory of nanomaterial production and use, and routes of waste management as missing in the research topography. In addition to clarification of these points in the exposures research need, a new bullet was added for identification of environmental receptors for exposure assessments.

Analysis of Current Projects

Funding associated with the analysis of nanomaterial releases and exposures as part of a technology or for the analysis in the environment has increased. In 2006, the one project related to environmental exposures totaled $250,000. In 2009, 2 related projects totaled over $250,000, and 12 more contained elements that pertained to the research need and are reported in the "Multiple Research Needs" line in Table 5-1. Although life cycle approaches are an important research requirement, research that directly addresses this need is minimal.

While several projects focus on analysis of materials, there is limited research on the life cycles of nanomaterials and releases, and no research on manufacture, processing, use, or disposal of manufactured nanomaterials, including identification of future trends and ways to minimize potentially harmful environmental exposures. Additional gaps include identification of environmental receptors for exposure assessments and development of cost-effective environmental monitoring approaches. There is one project with an emphasis on evaluating current modeling capabilities for predicting environmental releases and exposures.

Research Need #2. Determine factors affecting the environmental transport of nanomaterials

Overview

Research on transport of nanomaterials through the environment includes consideration of fundamental chemistry and physical properties (formation and stabilization) as well as the contribution of these properties to transport and fate in various environmental matrices and scenarios (e.g., aquatic, atmospheric, and terrestrial). The physical and chemical properties that govern nanoparticle transport and fate are not always constant, unique values, but rather are best represented as populations of values that vary over time. Recent research has shown that critical nanoparticle characteristics change over time and that bioactivity and transport vary with respect to different size classes of nanoparticles. These studies have highlighted the importance of nanomaterial characterization and the dynamic nature of nanomaterials dispersed in aquatic systems. These complexities in nanomaterial composition complicate efforts to adapt existing transport models to accommodate the properties of nanoparticles and predict their movement in the environment.

As the report from the Nanomaterials and the Environment & Instrumentation, Metrology, and Analytical Methods Workshop (2009) highlights, examination of transport requires understanding of the potential sources of nanomaterials, or incorporation of a life cycle perspective that considers the sources and their points of entry into the environment.

Recommendations for Changes

The wording of the bullets for the environmental transport research need has been clarified but not changed substantively.

Analysis of Current Projects

In FY 2006, five agencies funded 22 projects on environmental transport in several relevant environmental media. In FY 2009 there are four research projects to understand key physico-chemical properties affecting transport being supported by EPA, DOD and the Department of Energy (DOE). Three of these are characterizing the effect of cerium oxide nanoparticles in diesel fuel additives, commercially available silver nanoparticles, and suspensions of fullerenes; the use of organic nanoparticles for heavy metals remediation; and the leaching of silver nanoparticles from consumer products and subsequent transport through the environment. An additional 9 projects include environmental transport components and are included under "Multiple Research Needs."

There also is research funded through NSF focusing on the transport and retention of carbon nanotubes in soils, water, municipal waste water systems, and aquatic ecosystems, and the study of aggregation behavior, deposition, and sediment infiltration of nanoparticles in lake water, river water, groundwater, and seawater. EPA, NSF, and DOE are funding transport studies on C60 fullerenes, metal oxide nanoparticles, and zero-valent iron in contaminated soils.

Finally, there are research projects involving modification and validation of currently used transport models for specific types of nanoparticles being funded by and conducted through EPA, NSF, and DOE. This research includes modeling of the dissolution of silver nanoparticles in aqueous solutions, analyzing nanoparticle stability and mobility, and modeling of the transport of combusted nanomaterials and their effect on regional-scale air quality.

Research Need #3. Understand the transformation of nanomaterials under different environmental conditions

Overview

This research need focuses on developing, refining, and evaluating experimental and modeling tools for evaluating the effects of biotic and abiotic transformations on exposure to manufactured nanomaterials and their absorption by environmental organisms in water, sediments, and soil. The research will reduce uncertainties in risk assessment by determining and predicting the forms of manufactured nanomaterials to which organisms are exposed.

Transformations play an important role in determining exposure concentrations and the form of nanomaterials to which organisms are exposed. These transformations may be benign or beneficial to the environment, as well as deleterious. Biological and/or photochemical processes may transform nanomaterials by degrading and thus reducing environmental persistence. Engineered nanoparticles, through transformations, may cause adverse effects, such as the generation of toxic reactive oxygen species by photochemical transformation of nanoscale titanium dioxide, or nanoparticles may bind environmental substances and be used for environmental remediation. Additionally, under certain environmental conditions, nanomaterials may agglomerate into micrometer-scale particles or partition into soil and water and display more limited mobility and bioavailability. They may also bind to other contaminants in the environment.

Recommendations for Changes

The 2008 EHS Research Strategy included three bullets for this research need: key physico-chemical properties affecting transformation, key transformation processes, and development of predictive tools. Many of the key physico-chemical properties affecting transformation and the key chemical processes driving those processes have been identified since 2008. To reflect this progress and incorporate the recommendations of the workshop, the bullets have been refocused as indicated in the Research Needs as of 2011 section.

Development of tools to predict the transformations or degradability of nanomaterials remains a need. Such efforts should focus on determining nanomaterial characteristics that make them susceptible to enzymatic and photo-transformations. These tools should also predict rates of agglomeration and stability, given key nanomaterial characteristics.

Analysis of Current Projects

The nine FY 2006 projects reported in the 2008 NNI strategy document primarily focused on the reactivity of nanomaterials as used for catalysis. In FY 2009, 16 projects were identified by agencies as contributing to this research need, of which 14 were considered applicable to support for transformation and related research needs. Three of these projects were focused on the agglomeration of nanomaterials after release into the environment. These projects focused on transformations ranging from microbial to photochemical transformations in aquatic systems to those occurring in the atmosphere. One project focused on developing single-walled carbon nanotubes using green chemistry principles. Several projects focused on developing or optimizing the use of nanomaterials to remediate contaminated groundwater and decontaminate drinking water, but they did not evaluate the safety of nanomaterials to environmental receptors or function; thus, these projects are not relevant to this research need or to the EHS Research Strategy. Little of the work addresses developing predictive tools for transformation.

Research Need #4. Understand the effects of engineered nanomaterials in individuals of a species and the applicability of testing schemes to measure effects

Overview

Research in Environment research need #4 focuses on potential adverse effects of engineered nanomaterials on individuals of aquatic and terrestrial species. These include effects in numerous species tested under current test guidelines and protocols, including freshwater and marine vertebrates and invertebrates, both benthic and pelagic, and a range of metallic and carbon-based engineered nanomaterials. Endpoints used to assess toxicity range from genomic and molecular, to whole-organism, to mortality assessed in individuals or as changes in population growth or structure. A key focus of this research area is evaluating the applicability or adequacy of current test guidelines and protocols for assessing effects of nanomaterials on individuals of a species. This research area also focuses on nanomaterial uptake, translocation among tissues and organs, elimination, and the kinetics associated with these processes.

Research in this area has revealed generally moderate or low levels of acute toxicity and limited translocation of nanomaterials from potential uptake sites to other organs or tissues. This suggests that production of reactive oxygen species may be a mechanism of action common to several classes of nanomaterials. These generalities do not apply for every specific material, test system, or species. Such examples illustrate that nanomaterials need to be evaluated on a case-by-case basis.

Research in Environment research need #4, effects on individuals of a species, has focused primarily on acute effects of ENM exposures in pelagic aquatic species. Less research has been completed on nonaquatic species, on very early life stages or full life cycle assessments, or on uptake and translocation. Exposure and effect levels have generally been reported using bulk (concentration) metrics. In addition, the tested materials are predominantly either feedstock materials likely to undergo modification prior to use or product application, or are specially produced for the effects research being undertaken. While test results based on these materials are essential for understanding basic questions concerning nanomaterial behavior in test systems and potential toxicity, it remains unclear how well these materials represent those that have the greatest potential to reach natural environments. Similarly, acute testing in systems having relatively low complexity is also useful as a starting point for addressing fundamental toxicity questions, but has limited ability to predict effects or responses in more complex test systems or over longer exposure periods. While chronic or longer-term testing has received little focus, initial research involving biomarkers (including genomics, proteomics, and indicators of oxidative stress) suggests that detectable responses may occur in lower, chronic-level exposures. These responses might provide a basis for development of rapid screening approaches; this is a critical need given the large number of nanomaterials likely to require testing.

The paucity of research in this area can be attributed to the absence of readily available methods or the requirement for acquisition of such data in existing test guidelines and protocols. Complex test systems such as microcosms and mesocosms offer more realistic assessment, relative to simple beaker or growth media studies, of the complex and simultaneous fate and biological effects that could occur in natural environments. Some research has focused on high-throughput testing and standard acute and chronic testing protocols. Confirmation of the validity of standard test methods is important, as is high-throughput testing focused on early, initiating events in toxic pathways and early developmental stages.

Recommendations for Changes

In order to reflect research progress achieved in the last three years, to incorporate public recommendations, to better explain the content of the science, and to fill recognized gaps in the research needs, four modifications have been made to the research need #4 sub-bullets. These are listed in the section above, Research Needs as of 2011.

The first of these changes is the addition of a specific bullet on uptake/elimination, kinetics, and tissue/organ distribution. This topic was identified in the 2008 EHS Research Strategy and considered by participants in the October 2009 NNI workshop, Nanomaterials and the Environment & Instrumentation, Metrology, and Analytical Methods, to be a major component of high-throughput screening in order to understand tissue dose when evaluating initiating events in toxic pathways. The bullet, "tiered testing schemes," was modified to "tiered testing schemes/environmental realism" to incorporate testing nanomaterials in complex systems, such as natural river systems and micro- and mesocosms. This modification also identifies a major cross-cutting issue within the Environment research category, that complexity in effects testing will require an understanding of transport and transformation processes, as well as the need to quantify and characterize nanomaterials in complex media. The bullet, "mode of action leading to predictive tool development," has been modified to accommodate a greater focus on alternative testing based on mechanisms of action as well as more traditional mode-of-action endpoints. Finally, the "test protocols" research need bullet has been reordered and refocused to acknowledge the importance of identifying and remedying inadequacies in current methods for testing nanomaterials by development of new test protocols.

Analysis of Current Projects

Four projects in FY 2009 were focused on some aspect of Environment research need #4; funding for these projects totaled $715,000. In addition, under the "multiple" category, there were four more projects that contributed to this and to other related research needs. Funding was fairly evenly distributed among the bullets, although uptake/elimination kinetics received about 43% of the total funding, compared with 11% to 17% for research in other sub-needs. It is important to point out that none of the funding for the Centers for the Environmental Implications of Nanotechnology at Duke University (CEINT; http://ceint.duke.edu), and UCLA (CEIN; http://cein.ucla.edu) is included here; rather, it is included under the funding category, "Multiple" (see section at the end of this chapter, Projects Capturing Multiple Needs).

The OMB FY 2009 data call includes research on mechanisms of nanoparticle uptake into cells, tissues, and organs, and research on the effect of nanomaterials on the performance of individual organisms, including their reproduction, growth, and survival that contributes to predictive capabilities. Research systems include terrestrial (plant-soils-microbes), freshwater (algae-invertebrates-fish), and marine (algae-invertebrates) food webs. Two additional research projects in research need #4 address methods for characterization and quantification of nanomaterials in environmental media while also focusing directly on effects of nanomaterials on DNA function.

Funding was fairly evenly distributed among the bullets and suggests that currently funded research properly targets many of the needs identified in the October 2009 NNI workshop report.

Research Need #5. Evaluate the effects of engineered nanomaterials at the population, community, and ecosystem levels

Overview

The Environment research need #5 focuses on effects of engineered nanomaterials beyond those found in individuals of a species and includes effects on populations, communities, and ecosystems, including abiotic components and processes. Effects on populations and communities reflect individual responses but incorporate aspects of population-level and community-level functions (for example, density-dependent mortality and predation). Research need #5 also encompasses abiotic components and processes in ecosystems that might be affected by nanomaterial exposure. These might include interaction of hydrophobic nanomaterials with organic material such as dissolved organic carbon, or alteration of carbon cycling and energy flow through ecosystems, including effects of photoreactive nanomaterials in aquatic systems and the influence of natural organic material on the physiological effects of nanomaterials. This research area also includes a focus on higher-level abiotic effects that might include alteration of air quality and natural photo-oxidative or catalytic processes.

Limited research indicates that microcosms and/or mesocosms offer more realistic study environments and can improve understanding of nanomaterial behavior. Studies with greater realism give enhanced understanding of issues such as receptor exposure in various media, relative sensitivities of different species of organisms, relative impacts of different nanoparticles in the same system, and selection of receptors that best indicate ecosystem-wide effects such as impacts on nutrient cycling. Valuable information will come from comparisons of nanomaterial impacts on individuals (laboratory studies) with community-level results from microcosm, mesocosm, and field studies. Terrestrial systems are infrequently studied, with more research focused on terrestrial mammals than on avian species and plants. Also understudied are nanoparticle effects on nutrient and water cycling, or on biomass production.

Recommendations for Changes

In response to multiple stakeholder input, an additional bullet on predictive tools has been added. The section above, Research Needs as of 2011, shows the rewording of the research needs in the Environment core research category to increase the clarity of the bullets. The pace for much of this research should be increased in the nearer term relative to that identified in the 2008 NNI EHS Research Strategy.

Analysis of Current Projects

In FY 2006, there was 1 project totaling $115,000 related to this research need. In FY 2009, there was 1 project (Environmental Impacts of Nanomaterials in Engineered Water Systems) focused on this research need, and two other large projects supported this and other research needs.

Projects Capturing Multiple Research Needs

Two large projects were within the Centers for the Environmental Implications of Nanotechnology at Duke University and UCLA. These centers were funded at a total level of $7.8 million in FY 2009. The work of the centers spans many research needs, including ones within the scope of other chapters. CEIN funding applies to all five research needs in the Environment chapter as well as to research needs in other chapters and cannot be compared with totals in the FY 2006 data call. The CEIN research explores the impact of libraries of engineered nanomaterials on a range of cellular life forms, organisms, and plants in terrestrial, fresh water, and seawater environments. Fundamental research on the behavior of nanoscale materials in laboratory and complex ecosystems covers nanomaterial transport, transformation, fate, exposure, and ecotoxicological impacts and ecosystem functional responses (e.g., biogeochemical cycling) over a range of length scales and complexity using macrocosms, microcosms, and bench-scale experiments. The work also characterizes natural and incidental nanomaterials in the environment, including structural and reactivity differences between natural and synthetic nanomaterials of the same chemical composition, and measurement methods for environmental nanoparticles. Risk assessment and fate models assess the environmental implications of nanomaterials, including life cycle factors.

Example of Progress in NanoEHS Research: Nanosilver Case Study

In August 2010, the U.S. Environmental Protection Agency released a draft case study document for external review, *Nanoscale Silver in Disinfectant Spray* (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=226723), organized around a comprehensive environmental assessment framework that integrates a product life cycle perspective with the risk assessment paradigm and addresses environmental fate and transport, exposure-dose, ecological and human health, and other potential impacts of nanoscale silver in a spray product. The intent of this case study is to describe what is known and unknown about silver nanoparticles in a selected application to help identify and prioritize scientific and technical information that will support long-term assessment efforts. The study notes, for example, that the behavior of engineered nanoparticles is greatly influenced by the properties of the particles and the composition and chemistry of the surrounding environment (e.g., see Figure 5-2). This influence may also extend to the toxicity of nanoparticles; some evidence exists that particle size and surface properties affect the toxicity of silver nanoparticles. These efforts are helping to refine an integrative, multidisciplinary strategic approach to research on nanomaterials and may be used to inform decisions that reduce the risk of unintended consequences from nanotechnology R&D.

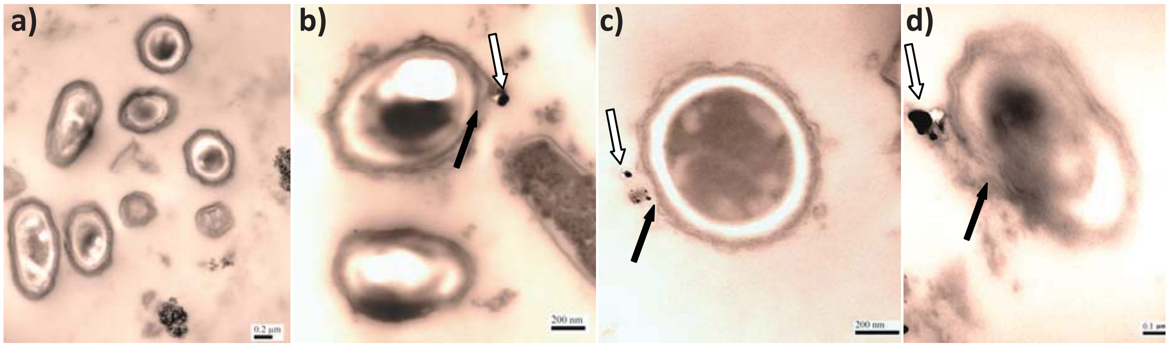

Figure 5-2. TEM images of gram-positive bacteria *(Bacillus)* cells exposed to silver nanoparticles: (a) unexposed cells, (b–d) cells exposed to branched polyethyleneimine silver nanoparticles that vary from highly negative surface charge to highly positive. White arrows indicate silver nanoparticles (b–d); black arrows (b–d) indicate damage to cell membranes. The positively charged silver nanoparticles exhibited the highest toxicity and caused bacterial death at all investigated concentrations, whereas the most negatively charged particles exhibited the least toxicity.

Source: EPA.

6. Risk Assessment and Risk Management Methods

Overview

Risk assessment (RA) involves the application of analytical tools, data, and expert knowledge to the evaluation of potential exposure of humans and the environment to nanomaterials and the hazards that exposure might engender. Risk management methods (RMM) for nanotechnology identify and implement strategies to address potential hazards.

A number of national and international activities relevant to RA and RMM (combined, RAMM)—the fifth NNI core EHS research category—are focused on characterizing a set of standard nanomaterials, identifying a standard battery of tests to estimate safety and toxicity, and standardizing a range of approaches to better inform and quantify potential risks. Most projects are in early stages of development, and the overall state of the science appears to indicate we are still in the process of learning about nanotechnology, collecting information, and evaluating how best to incorporate findings into risk assessment and risk management approaches. In addition, research activities to understand and manage risk relevant to (1) nanomaterial measurement infrastructure, (2) human exposure assessment, (3) human health, and (4) the environment are incorporated into RAMM. For example, activities in the physical sciences (including nanomaterials characterization, environmental transformation, identification of chemical properties, etc.) and in risk assessment and risk management may not be entirely separate; rather, information flows freely among physical research, risk assessment, and risk management methods. As a result, current research efforts aim to address these questions across several distinct, yet related, disciplines.

An effective risk management framework involves increasing use of all relevant information to guide risk-based decisions and management. The risk assessment process incorporates the best available data on the potential health effects of a nanomaterial and the exposure potential to humans and to the environment; thus, the data needs described in previous chapters and the quality of the results of studies in measurement, exposure assessment, human health, and the environment directly impact the reliability of risk estimates. In addition to quantifying risk to the extent possible, risk management (1) employs basic scientific information; (2) uses comparative risk assessments for different nanomaterials with different properties, applications, or intended uses that can affect and result in different risk parameters and decision making; (3) integrates life cycle evaluations; and (4) considers ethical, legal, and societal implications (ELSI) such as stakeholders' values, communication needs, and other aspects of decision analysis. Risk research will play an important role in understanding these factors and integrating them into an effective risk management schema.

Important inputs from several sources have led to the research need areas outlined in the RAMM core nanoEHS research category. These sources include the March 2010 NNI capstone workshop, Risk Management Methods & Ethical, Legal, and Societal Implications of Nanotechnology; other Federally sponsored environmental, health, and safety workshops; agency missions (including those of regulatory agencies); input from the public and from a variety of other stakeholders; and input from risk assessors and managers in all sectors. In some cases, research needs reflect the ongoing targets from the 2008 EHS Research Strategy, such as the importance of risk characterization information; in other cases, new research needs have been identified, such as the integration of risk assessment from multiple scenarios to aid in decision making. All the research needs incorporate information from the wide variety of sources and wide range of stakeholders and areas of expertise indicated above.

RAMM is relevant to all research categories within the 2011 NNI EHS Research Strategy, and vice versa. For example, one significant area of input derives from the NMI focus on developing measurement tools to determine physico-chemical properties of ENMs in relevant media and during the life cycles of ENMs and NEPs for risk characterization information. Critical to developing effective strategies to minimize adverse impacts of ENMs to populations and the environment and to manage any potential undesirable effects of this emerging technology are adequate assessment of the biological effects of nanomaterials; of the release and fate of the materials in the environment, indoors, and in occupational settings; and ultimately, of exposure and uptake into living organisms and humans and the ultimate risk of harm to these receptors.

Goal

- Increase available information for better decision making in assessing and managing potential risks from nanomaterials, including using comparative risk assessment and decision analysis; life cycle considerations; and additional perspectives such as ELSI considerations, stakeholders' values, and additional decision makers' considerations.

Research Needs as of 2011

#1. Incorporate relevant risk characterization information, hazard identification, exposure science, and risk modeling and methods into the safety evaluation of nanomaterials:

- Characterization, fate, and release of nanoparticles throughout the life cycles of NEPs
- Development of predictive models on accumulation, migration, and release of nanoparticles throughout the life cycles of NEPs
- Safety of the nanoparticles throughout the life cycles of the NEPs
- Comprehensive and predictive models to assess the potential risks of nanoparticles during the manufacturing and life cycles of nanotechnology-enabled products, with inputs from research on human and environmental exposures and on nanomaterial properties

#2. Understand, characterize, and control workplace exposures to nanomaterials:

- Dissemination and implementation of effective techniques and protocols to measure exposures in the workplace
- Identification and demonstration of effective containment and control technologies including for accidents and spills

- Development of an effective industry surveillance system
- Design and deployment of a prospective epidemiological framework relevant to exposure science
- Systematic approaches for occupational risk modeling

#3. Integrate life cycle considerations into risk assessment:

- Establishment of a nanotechnology-specific taxonomy for life cycle stages
- Integration of risk assessment, life cycle analyses, and decision-making approaches into regulatory decision-making processes
- Application of adaptive management tools based on monitoring/implementation to evaluate life cycle analysis implementation
- Development of case studies, e.g., green chemistry, nanomaterials selection, nanomaterials acquisition processes, illustrating application of these risk management methods

#4. Integrate risk assessment into decision-making frameworks for risk management:

- Development of comparative risk assessment and formal decision-analytical methods as opposed to "absolute" risk assessment strategies
- Application of formal decision-analytical methods to prioritize risk management alternatives
- Use of gap analysis and value of information analysis to identify research needs
- Integration of stakeholder values and risk perceptions into risk management processes
- Application of an integrated decision framework through case studies in risk management decision making

#5. Integrate and standardize risk communication within the risk management framework:

- Development and use of standardized terminology in risk communications
- Early information-sharing on hazards and risk among Federal agencies
- Development of appropriate risk communication approaches for agency-specific needs

Comparative Analysis of Projects

Overall FY 2009 investment in the RAMM research category is primarily focused on risk characterization information, workplace exposure and exposure of other population subgroups, life cycle assessment, and informed decision making, with emphasis on standardization and integration of risk communication within the risk management framework. A new research need, integration of risk assessment into decision making frameworks for risk management, was not identified previously; it represents a new area for nanoEHS research, because independent research activities need to be thoughtfully combined in more sophisticated models for evaluation and risk management.

The FY 2009 research investment tracks closely to the FY 2006 balance of funding reported in the 2008 NNI EHS Research Strategy, but with increased investment in risk characterization information, hazard identification, exposure science, and risk modeling and methods for the development and evaluation of nanomaterials. Another area with increased investment is understanding, characterizing, and controlling workplace exposures to nanomaterials. Investments in FY 2009 comparable to those made in FY 2006 have been made in integrating life cycle considerations into risk assessment and management and integrating and standardizing risk communication into the risk management framework. The FY 2006 balance of funding identified six projects that capture multiple needs. In contrast, all FY 2009 projects were categorized within the 2011 strategy's research needs. The FY 2006 and FY 2009 projects were mapped onto the newly defined research needs, as shown in Figure 6-1; Table 6-1 presents the resulting distributions by number of projects and funding.

Table 6-1. Analysis of Projects Related to Risk Assessment and Risk Management Methods Category of NanoEHS R&D, FY 2006 & FY 2009*

Research Needs	FY 2006		FY 2009		Change
	Reported Funding in $K (% of total) †	Number of projects (% of total)‡	Reported Funding in $K (% of total)	Number of projects (% of total)	Funding in $K (number of projects)
1. Incorporate relevant risk characterization information, hazard identification, exposure science, and risk modeling and methods into the safety evaluation of nanomaterials	132 (4%)	1	1,767 (50%)	6	+1,635 (+5)
2. Understand, characterize, and control workplace exposures to nanomaterials	495 (15%)	4	1,267 (36%)	10	+772 (+6)
3. Integrate life cycle considerations into risk assessment	396 (12%)	2	300 (8%)	4	-96 (+2)
4. Integrate risk assessment into decision-making frameworks for risk management	—	—	—	—	—
5. Integrate and standardize risk communication within the risk management framework	231 (7%)	1	200 (6%)	1	-31 (0)
Multiple: Projects that capture multiple needs	2046 (62%)	6	—	—	-2,046 (-6)
Other: Not captured in the needs above but of benefit to the category	—	—	—	—	—
TOTAL	**3300**	**14**	**3534**	**21**	**+234 (+7)**

*Agencies supporting research in this category (FY 2009): EPA, FDA, NIOSH, NSF
† Funding estimates track to related research needs in FY 2006
‡ Number of projects track to related research needs in FY 2006

Gaps for Future Investment

As the use of nanomaterials increases rapidly, it is of vital importance that the risk assessment community understands the complexities of the issues surrounding the manufacture, use, and disposal of nanomaterials, the potential of environmental and occupational exposure to human populations, as well as potential adverse health outcomes. For this to happen, it is necessary for the scientific community to understand the needs of risk assessors for information such as risk characterization, and what research will provide that information; also, researchers need to know the decision contexts within which their research findings will be applied. Risk management of nanomaterials requires more information about the human and ecological effects of exposure to a variety of nanomaterials.

Rationale for the 2011 Research Needs and Changes from 2008

Research focused on the range of uses of a nanomaterial across its life cycle, and the risk assessment methods and tools used to evaluate each stage of the life cycle, may use different measurement tools. Also, comparing the use of nanomaterials under different circumstances aids in applying what is learned to new applications, including predictive modeling for potential exposure and hazard case scenarios.

Due to the wide variety of regulations, legal standards, and other rules pertaining to nanomaterials used in different products or circumstances, risk assessment and management strategies may need to change as they focus on various life cycle stages. As a result, the following research needs have been identified that are general enough to be applied to a variety of nanomaterial uses under different conditions and environments, and yet specific enough to identify key phases of the life cycles of nanomaterials during development and use. The research needs presented in the RAMM research category are listed in the order that reflects steps of risk assessment and management, rather than priority ranking. As indicated in Figure 6-1, there are changes in the wording and sequence of the 2011 key research needs in risk assessment and risk management methods as compared to 2008, based on multiple inputs from stakeholders and experts in the field.

Figure 6-1. Comparison of the Risk Management Methods research needs in the 2008 NNI EHS Research Strategy (left) with the Risk Assessment and Risk Management Methods research needs in the 2011 NNI EHS Research Strategy (right). The arrows indicate mapping of the 2008 research needs to the 2011 research needs.

Research Need #1. Incorporate relevant risk characterization information, hazard identification, exposure science, and risk modeling and assessment methods into the safety evaluation of nanomaterials

Overview

RAMM for nanotechnology requires an adequate knowledge of the interactions of nanomaterials with humans and the environment, not only during the manufacture of nanomaterials, but also during their life cycles. The 2008 NNI EHS Research Strategy placed a majority of RAMM research emphasis on airborne particles and controls of inhalation exposures at the workplace. Such emphasis has provided valuable data for assessing the potential EHS risks of nanotechnology during the manufacture and use of engineered nanomaterials. However, nanomaterials are increasingly incorporated into a variety of product classes and used in a wide range of environments. The fate of these nanomaterials alone or when used in products, and their EHS effects during the whole life cycle, are largely unknown. For example, the properties of an ENM influence its behavior in the body and safety profile, whereas slight alterations can fundamentally change both parameters. Observations indicate (1) nanomaterials are increasingly used in many large-volume industries such as construction, automobiles, and textiles, and the number of people, including sensitive populations such as children, who are exposed to these types of nanomaterial or products containing such materials is also very high; and (2) long, continuous human exposure during the entire service life of the products is also an important factor to consider.

Yet, little data currently exist on the use of nanomaterials in products or on the potential risks of nanomaterials during service and post service (e.g., in landfills) in nanotechnology-enabled products. The lack of such data severely hinders our ability to intelligently assess and manage the potential risks of nanomaterials; this includes insufficient data on (1) the effects of exposed media on physico-chemical properties, toxicity, and fate of nanomaterials; and (2) interactions between nanomaterials and the exposed environments (e.g., hydrolysis, photodegradation, thermodegradation, erosion, and abrasion). For example, in the presence of ultraviolet light, pollutants, water, electrolytes, and oxygen, many types of nanomaterials are likely to be oxidized, transformed, or modified, which would lead to different EHS effects, hence potential risks, as compared to their natural states in isolation.

Recommendations for Changes

In 2008, the NNI focused on two areas for this research need: (1) information on flammability and reactivity of nanomaterials, and (2) hazard information for risk management. Progress has been made in these two categories for pristine nanomaterials; however, a comprehensive awareness of potential benefits and risks of exposure requires similar reliable data for ENMs and NEPs across the entire life cycle using relevant biological and exposure media. Additional recommended areas of research include:

- Data on characterization, fate, and human and environmental exposure across the product life cycle
- Development of models to describe and predict the accumulation, migration, release, and population exposure to nanomaterials from products under different exposure conditions
- Analysis of toxicity of nanoparticles released during the life cycle of a nanomaterial or NEP
- Comprehensive models to assess the potential risks of nanomaterials across the product life cycles, including human and environmental exposure data and release potential

Analysis of Current Projects

Research to provide greater understanding about nanomaterials for better risk assessment has been substantially increased between FY 2006 and FY 2009. Such research is especially important to developing the rapidly expanding field of risk assessment and management, understanding the evolving state of scientific knowledge, and applying it to new uses. For example, in FY 2006, only one project on development of risk characterization information was undertaken among U.S. Federal agencies, but in the FY 2009 data call, six projects related to this topic were listed across several government agencies, including projects focused on the applicability and predictability of genotoxicity of nanomaterials; release and migration studies in food packaging; explosion hazards of carbonaceous nanoparticles; incorporating ethical decisions into nanomanufacturing research; development of greener synthesis strategies for nanomaterials; and efforts relevant to detecting and characterizing nanomaterials in biological matrices.

Although a stronger emphasis on addressing research need #1 has been made in the past few years, a greater effort should be focused on developing robust data on nanomaterial properties and potential exposures and hazards for nanomaterials that are used in consumer products and found in the environment during their total life cycles. For example, new developments in the field mean that attention must be paid to the emerging science needed to enable nanoEHS efforts to better predict and prepare for the new types of products that may be seen in the near future. Risk characterization data should offer sound risk assessment and effective strategies to manage the risks of new nanomaterials.

Research Need #2. Understand, characterize, and control workplace exposures to nanomaterials

Overview

Mitigation of exposure is a key goal of risk management across the life cycle of an engineered nanomaterial. During the manufacture or use of engineered nanomaterials, exposure controls can be in the form of engineering solutions, administrative controls, or procedural approaches. The 2008 NNI EHS Research Strategy identified the need to gain information on how to identify and better characterize worker populations with the potential for exposure, develop and refine methods to characterize exposures, and develop tools to control workplace exposures.

Recommendations for Changes

As more nanotechnology-enabled products move to commercialization, there are increasing opportunities to develop knowledge of the nature and scope of the worker population that has the potential to be exposed. Specific areas that require additional emphasis include developing an epidemiologic framework that can be used to evaluate workers who use nanomaterials; collecting business and industrial surveillance data to identify and describe the nanomaterials workplace; and incorporating nanomaterial-specific examples into incident investigation, reporting, and tracking systems. Additional research needs in the workplace include developing a streamlined model program for tracking nanomaterials workers; identifying the control and containment approaches that can be applied to nanomaterials; and use of historical experiences from the pharmaceutical, cosmetics, and dry powder pigment industries to identify candidate control technologies. Future needs may include identifying and demonstrating the effectiveness of modern containment technologies for safe handling and transport through the life cycle, investigating the effectiveness of different work practices for exposure mitigation, and strengthening current research on personal protective equipment and respiratory protection. Finally, there is a need to develop and disseminate case studies showing the successful containment and control applications in nanomaterial facilities in order to identify the best design practices for facilities and processes that can engineer out potential exposures.

Analysis of Current Projects

Key research needs in this area can be divided into two categories: (1) control technologies and (2) industry surveillance.

The 2008 NNI EHS Research Strategy included projects to conduct exposure characterization studies; as these studies progress, conditions that cause environmental releases and worker exposures are being identified. The 2009 OMB data call identified 4 projects distributed between NIOSH, EPA, and NSF that investigated various aspects of workplace characterization, environmental impact, risk management methods, and impact on other population subgroups. One project by NIOSH deployed a team of field investigators to visit nanomaterial manufacturing and product incorporation sites to gain a better understanding of actual workplace exposure scenarios and to evaluate the effectiveness of any controls that might be in place. Other projects funded by NSF and EPA sponsored centers or workshops that focused on the high-rate manufacture of nanomaterials. As these nanomanufacturing processes are developed, key information will be captured on their potential for emission of nanomaterial and possible human or environmental exposure. Knowledge gained on manufacturing processes has been used to identify opportunities for additional research on mitigating human and environmental exposures and risks. To meet the need for developing a risk management approach in the absence of complete hazard data, NIOSH has continued its efforts to explore the utility of applying control banding to nanomaterial processes. This effort was conducted in parallel with research to evaluate the effectiveness of protective clothing and respiratory protection equipment. These projects have laid a good foundation for filling knowledge gaps; however, research is still needed to demonstrate the effectiveness of various types of containment and control technologies for nanomaterial manufacturing processes.

Because nanomaterials are products or key product ingredients, not process contaminants, historical contaminant control and removal approaches may not be appropriate. Preliminary investigations have identified some conventional controls that are effective, but the number of scenarios evaluated to date is limited. Research is needed to provide an effective logic model for selecting the most appropriate type of containment or control based on the material and the processes. More workplace investigations are needed to identify and evaluate containment and control approaches that are effective, as are laboratory-based studies that evaluate different containment and control schemes and optimize their performance.

As nanomaterials continue to be developed for commercial application, the number of workers involved in their manufacture and use will continue to grow and become more diverse. A systematic approach to gather and evaluate that information is needed to develop a more realistic view of the potential impact of nanomaterials on the workplace. Developing an effective industry surveillance system to capture that data will require collaboration and cooperation between government agencies and the private sector. Designing and deploying a prospective epidemiological framework, which is described in the Human Exposure Assessment category, will be needed to evaluate and characterize the exposure experience of the workers. Applied research that results in the types of guidance and recommendations called for in this research need should be an area for future investment. Project outcomes that have a prospective impact on reducing emissions and exposures to engineered nanomaterials will support responsible development of the technology.

Research Need #3. Integrate life cycle considerations into risk assessment

Overview

Consideration of nanomaterial life cycle has been a standing recommendation, beginning with the 2008 NNI research need to determine the stages of the product's life cycle that may introduce potential for EHS risks.[16] The 2008 NNI EHS Research Strategy also lists green design as an important consideration, without linking it to life cycle analysis. In the 2011 revised NNI EHS Research Strategy, life cycle and green design considerations are linked, and the scope of this research is expanded to include the design of nanomaterials with maximal benefit and minimal risk to public health and the environment. The limited information collected over the last several years on nanomaterial risk at different life cycle stages has highlighted numerous data gaps.

Recommendations for Changes

In the 2008 NNI EHS Research Strategy, this research need focused specifically on risk management methods for nanomaterials, with no clear discussion of the role of risk assessment or decision making. Much of the funding has been focused on the overarching issues related to general risk management. With the research funded since FY 2006, it is now possible to focus future research more precisely on both risk assessment and risk management, linking them to specific regulatory decision making. Research priorities in the 2011 NNI EHS Research Strategy have been developed after consideration of the NNI agency missions, the best use of currently available scientific information, as well as the values and information expressed by stakeholders and the public.

Analysis of Current Projects

Although NIOSH or NSF funded the FY 2006 projects under this research need, the most recent work has been funded by EPA and includes risk assessment research. Four FY 2009 projects identified in this category have a component to assess the sustainability of the nanomaterial manufacturing processes used in the project: three focus on life cycle assessment for specific uses of nanomaterials, and one focuses on green chemistry use in manufacturing.

The first project is a multicomponent, holistic life cycle assessment for decision support and enhanced sustainability though the provision of tools that reduce the environmental costs of processes and products. The second project, a life cycle assessment case study on lithium ion batteries, is a partnership between two EPA offices, industry, and others to provide specific insights into environmental improvements in batteries and general insights into how life cycle analysis can be used to design more environmentally benign nanotechnology-enabled products. The third project, a pilot case study, is evaluating a nontraditional approach to assessing sustainability and life cycle implications of nanoscale carbon fibers in windmill blades. This comparative thermodynamic assessment of a nanocomponent and related life cycle inventory, if successful, could be developed for a wide range of applications. The last ongoing project is developing nanoparticle synthesis using a high-efficiency reactor and is intended to demonstrate the use of a continuous process to increase the production efficiency (yield, energy savings,

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16. *The National Nanotechnology Initiative: Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials* (NSET/NSTC, Washington, DC, 2006; http://www.nano.gov/NNI_EHS_research_needs.pdf), p. 54.

and time savings) of producing nanoparticles. Such a process would also reduce potential releases and therefore, risks to people and the environment.

Although these projects are focused on life cycle assessment, due to the nature of the research, each is focused on a single nanomaterial application. The remaining projects expand life cycle assessment to include ethical, legal, and societal issues and a core facility that supports this type of assessment of nanomaterials and products. Decision analysis methodology has not been included in some risk assessment processes and represents a key data gap. The addition of this decision analysis methodology will help highlight the key data needs for determining risk related to nanomaterial production, use, and disposal.

Research Need #4. Integrate risk assessment into decision-making frameworks for risk management

Overview

The diversity of nanomaterials in production and use has led to uncertainty about the further development, selection, and application of risk methodologies. There is general agreement among the NNI stakeholder communities that nanomaterials, for the near term, need to be assessed on a case-by-case basis—an approach that challenges time and resources. This 2011 RAMM research need aims to integrate risk assessment information with multiple data sources to better inform all stakeholders and help expedite the evaluation of new applications of nanomaterials.

Whereas the objective of traditional risk assessment is often an absolute risk characterization, a decision-directed approach emphasizes comparative bases for relative assessment of alternative materials with varying material properties and life cycle properties. Data needs may be less critical because the decision-directed approach is comparative and is bounded by the limited number of alternatives and decision criteria assessed by criteria-specific metrics. Development of comparative risk assessment and decision-analytical frameworks to assess nanomaterial risks and support management decisions is thus an important extension of the 2008 Risk Management Methods research category.

Recommendations for Changes

Significant information collection efforts funded by governments and industry worldwide have resulted in a large volume of data on nanomaterial fates and effects, but their applicability to risk management and policy decisions has been limited. As this work has progressed, it has become clear that there is a need to focus and prioritize research efforts to evaluate relative risks and benefits associated with nanomaterials. There also exists a growing body of academic literature illustrating application of formal decision-analytical approaches (e.g., multi-criteria decision analysis) and value-of-information analysis to nanomaterial risk management, and the 2011 NNI EHS Research Strategy capstone workshop[17] specifically discussed the use of these methods for risk management. These developments since 2008 are reflected in the new RAMM research need #4.

17. *Risk Management Methods & Ethical, Legal, and Societal Implications of Nanotechnology: Report of the National Nanotechnology Initiative Workshop, March 30-31, 2010, Arlington, VA* (NSET/NSTC, Washington, DC, 2011; http://www.nano.gov/publications-resources).

One way to aid nanoEHS research efforts is to recognize synergies available through the integration of risk assessment and life cycle analyses into decision frameworks. The emergence of new nanomaterials and uncertainties associated with their properties requires integrating technical evaluations of nanomaterial properties with values and decision-maker objectives as part of this process. Developing formal decision-analytical methods and tools and their application will focus the gathering of information on risk-based decision needs. Although there are currently no ongoing NNI-funded projects on the use of decision analysis with nanomaterials, there exists a growing body of academic literature illustrating the application of formal decision-analytical approaches to nanomaterial risk management. One example is the Risk Governance Framework of the International Risk Governance Council (IRGC, http://www.irgc.org/), which developed as a comprehensive risk governance framework tool that incorporates many societal aspects and communication needs and is aimed at framing nanomaterial governance as a decision problem. Another example is the 2008 joint North Atlantic Treaty Organization/ EPA and DOD workshop "Nanomaterials: Environmental Risks and Benefits and Emerging Consumer Products"[18] that reviewed multiple risk assessment frameworks and illustrated the application of formal decision-making tools in multiple settings.

There is a need to integrate stakeholder values in the risk management process in a transparent way. The emerging risk management tools should be evaluated by stakeholder groups, and value and barriers for their applications in different settings should be assessed. Stakeholder engagement and decision analysis could be used for mapping risk perception and tolerance by different stakeholder groups. Decision-making approaches could be used to quantify values that stakeholders place on different resources and to integrate these values with technical information to select risk management alternatives.

Analysis of Current Projects

Although currently there are no ongoing NNI-funded projects on the application of decision analysis to nanomaterials, it has been specified as the ultimate goal in several funded projects.

Given the issues specific to nanomaterials, particularly the variability in risks among similar nanomaterials based on their surface coatings, method of production, and specific formulation, decision analysis frameworks would greatly inform future risk assessments. Case studies incorporating decision analytics into the risk assessment process will inform the data needed for future risk assessments and will assist in streamlining data needs for risk assessment. This simplification of data needs will lead to a decrease in extraneous data collection related to specific nanomaterials and move forward risk assessment of many nanomaterials.

Research Need #5. Integrate and standardize risk communication within the risk management framework

Overview

Risk communication is an integral and ongoing process for risk analysis of nanomaterials and is an essential part of informing stakeholders (e.g., workers, consumers, and the general public) at each stage of the risk assessment and risk management process. Effective risk communication is fundamental for

18. Igor Linkov, Jeffery Steevens, eds., *Nanomaterials Risks and Benefits, Proceedings of the NATO Advanced Research Workshop on Nanomaterials: Environmental Risks and Benefits,* Faro, Portugal 27–30, April 2008 (NATO Science for Peace and Security Series C: Environmental Security, Springer, Heidelberg / Dordrecht, 2008).

developing trust among the various nanotechnology stakeholders and is interconnected with the ELSI and life cycle considerations for nanotechnology. Risk communication is most effective if undertaken in a systematic and timely way that can be enhanced by using common terminology and by early sharing of risk information among Federal agencies. Risk communication should also be appropriately tailored to the targeted audience. As a result, different approaches may be used to communicate risk(s) by Federal and state agencies, academia, and industry stakeholders with the goal of fostering the development of an effective risk management framework.

Recommendations for Changes

The need for standardized two-way risk communication approaches was identified in the 2008 NNI EHS Research Strategy. Opportunities for communication are diverse, and different Federal agencies use a variety of approaches to communicate with and disseminate health and safety information to the public and other stakeholders, taking into account the needs of target audiences. These approaches include websites, technical publications, guidances, public meetings, and presentations. Since 2008, various agencies have initiated risk communication projects, yet there is still limited information among stakeholders regarding nanotechnology hazards, risks, and benefits. This can be attributed, at least in part, to a lack of effective risk communications.

The process for enabling and enhancing risk communications across Federal agencies can begin with developing standardized terminology to describe nanotechnology, promoting early information-sharing on hazards and risks, and developing risk communication approaches for agency-specific needs. While the various regulatory agencies have methods available for communicating with stakeholders, specific sectors, such as consumers and industry, can further benefit from understanding agencies' approaches in order to evaluate what may be required from them or what is in their best interests. The ultimate benefit is for stakeholders and agencies to have a better understanding of the risks and benefits from nanotechnology and of the best ways to manage them.

Analysis of Current Projects

The one FY 2009 research project is funded through NSF. This collaborative research project is investigating the societal aspects of nanoscale science and engineering (NSE), combined with public engagement, to improve deliberation and decision making about NSE. Its goal is to develop new ways of organizing the production of knowledge, and to develop and test new processes of anticipatory governance to meet the emerging promises and challenges of NSE.

Additional gaps remain, and needs have been identified related to risk communication research: identifying location and volume of nanomaterials produced in order to direct where risk communication efforts are needed; promoting early identification and sharing on hazard and risk; and developing an integrated approach to research, cooperation, and communication strategies to direct efforts toward responsible and sustainable growth of nanotechnologies. Progress in this research need will assist the transparency of other research needs in the RAMM category of nanoEHS research.

Finally, success in communicating ELSI and risk assessment findings will aid in increasing transparency and public understanding of safety issues surrounding the development, use, and disposal of nanomaterials.

Example of Progress in NanoEHS Research: Risk Characterization of Nanomaterials in Spray Products

Government-sponsored risk assessment activities have assessed the safety of nanomaterials in cleaning and disinfecting products. Nanoscale titanium dioxide, when exposed to ultraviolet (UV) light, acts as a photocatalyst to eliminate potentially harmful microorganisms and the accumulation of dirt on the surfaces of materials such as glass. These products may be used by consumers in the home environment and by workers who apply these materials, for example, to the surfaces of windows in office buildings. Through a collaborative effort, NIOSH and CPSC have examined the potential exposure of consumers and industry workers to nanomaterials released into the air during the use of these products, and the characteristics of this exposure. A testing method was developed in 2009 that includes use of a chamber simulating a controlled indoor environment and incorporating a series of instruments to characterize nanomaterial releases (Figure 6-2). This experimental process addresses the critical need for gathering risk characterization information on consumer products, exposure assessment methods, and exposure data that can be used to evaluate potential health risks that may result from the use of these spray products. This method will be publicly available to guide industry and consumer groups in the development and evaluation of spray products that may contain nanomaterials.

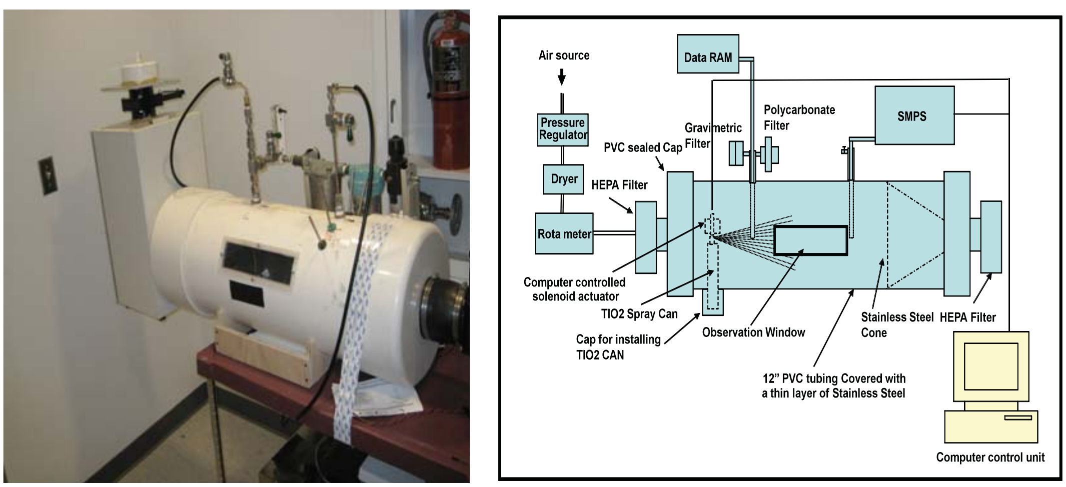

Figure 6-2. (Left) Nanoparticles-containing spray can aerosol; (Right) Characterization, exposure assessment, and generator design.

Source: B.T. Chen, A. Afshari, S. Stone, M. Jackson, D. Schwegler-Berry, D.G. Frazer, V. Castranova, T.A. Thomas, Nanoparticles-containing, spray can aerosol: Characterization, exposure assessment, and generator design, *Inhal. Toxicol.* 22, 1072-1082, 2010.

7. Informatics and Modeling for NanoEHS Research

To attain the goals of the NNI EHS Research Strategy, an interagency nanoinformatics infrastructure and a strategy for rapidly expanding and integrating that infrastructure are urgently needed. Expanding informatics capabilities will aid development, analysis, organization, archiving, sharing, and use of data that is acquired in nanoEHS research projects in the core categories described in the previous five chapters. Thus, informatics and modeling have been identified as a sixth core research category. Effective management of reliable, high-quality data will also help support advanced modeling and simulation capabilities in support of future nanoEHS R&D and nanotechnology-related risk management. Research needs to achieve these informatics and modeling goals are described below.

Enhance Quality and Availability of Data

Data Acquisition

Interlaboratory studies (ILS) have repeatedly emphasized three essential needs for improving data quality: (1) development and validation of standard protocols having positive and negative controls to check for interference by the specific nanomaterial being tested; (2) informal interlaboratory testing in development of standard protocols; and (3) formal ILS to establish the uncertainty and traceability[19] associated with use of those protocols. Related efforts seek to establish guidelines for minimum reporting requirements regarding the range of quantitative assays used to characterize nanomaterials. In addition, there is a need to acquire data generated during method development and validation that establish the robustness and ruggedness of standard protocols. These data provide a measure of the sensitivity of the method to changes in experimental parameters, procedures, and materials, and would aid in developing more robust methods. Finally, reporting guidelines regarding the extent of validation attained by the laboratory performing the method should be established—whether full or partial validation was attained, if the result is a single laboratory measurement, or if it has been corroborated by another laboratory. Until these needs are met, published data will continue to be of limited value, referencing basic techniques and assay types rather than documented protocols, with assays modified or amended arbitrarily, and without sufficient characterization of the nanomaterial being studied.

Improvements in data reliability and reproducibility can be effected quickly by leveraging the widespread use of wireless and video-enabled devices by the public and by standards development organizations to capture protocol detail through videos and to create training materials for their use. Relatively modest resources would also be required to establish repositories to store, aliquot, ship, and monitor the study materials for ILS, and to establish a registry system to provide unique identifiers for each type and lot of material. The more daunting obstacle is the lack of incentives for participation in the standards development and ILS processes by academics and by government scientists and regulators. Putting new incentives in place for participation by all stakeholders, combined with a modest investment in infrastructure, would provide the means to achieve significantly more reliable and reproducible data.

19. See footnote 9.

Data Analysis

The need for sensitivity analysis in conjunction with error and uncertainty analysis is urgent for hazard and exposure estimation and the rational design of nanomaterials. Because the last decade has seen large improvements in synthesis control and separation techniques, purer and more monodisperse nanomaterials are becoming available for detailed analysis of the sensitivity of their properties to changes in their surrounding media and environment. Collaborative multidisciplinary projects to develop mappings of structure–property spaces for select nanomaterials with monodisperse components would provide design reference data. These efforts would provide focal points for collaborative efforts in nanomaterial design, including curation of datasets with known uncertainties and errors, the use of sensitivity analysis to predict changes in nanomaterial properties, and the development of computational models to augment and elucidate experimental data. Identifying regions in which small changes in nanomaterial structures lead to large differences in their properties (high sensitivity) and/or large uncertainty and error in the data or models would provide a quantifiable measure of the need for greater understanding of the underlying mechanisms and help target priority areas for additional research and funding.

Data Sharing

Improved data sharing is a crucial need to accelerate progress in nanoscience by removing the barriers presented by the current "siloed" data environment. Because data must be curated by those who have the most intimate knowledge of how it was obtained and analyzed and how it will be used, a central repository to facilitate sharing is not an optimal solution. However, federating database systems through common data elements would permit rapid semantic search and transparent sharing over all associated databases, while leaving control and curation of the data in the hands of the experts. The use of nanomaterial ontologies to define those data elements, together with their computer-readable logical relationships, can provide a semantic search capability.

A number of pilot systems and applications have been developed as initial demonstrations of capability to elicit user requirements for database federation. As examples, the NanoParticle Ontology (NPO; http://nano-ontology.org) provides a consistent mapping among nanoparticle structure and property data, and nano-TAB (http://is.gd/eaviO) provides a nanotechnology extension to the ISA–TAB format for data acquisition and sharing. The staged, iterative development of an open-source infrastructure compatible with the current Network for Computational Nanotechnology (NCN; http://www.ncn.purdue.edu/) and amenable to public/private partnerships should be initiated, with governance of the effort by the participating agencies and partners. This would permit the nanotechnology community to improve, adapt, and extend the pilots and applications that are now available or being developed.

Expand Theory, Modeling, and Simulation Capabilities

Structural Models of Nanomaterials

A nanomaterials data bank is needed to develop, validate, and archive 3D nanomaterial molecular structures. This data bank would act as an archive and data processing center for freely available structural data and would accept structural models from depositors as part of the journal publication process, provide data-checking and validation services, and archive models. In turn, these models could be used in blinded validation studies to improve computational models of nanomaterials in different biological environments. The Collaboratory for Structural Nanobiology (CSN; http://csn.ncifcrf.gov/csn; see example at the end of this chapter) is such a data bank and includes a 3D model builder to rapidly develop fully three-dimensional molecular models for complex nanomaterials. The CSN could be used, together with other available structural database systems, to unify the structural modeling community.

Predictive Models and Simulations

The turnaround times for the development and validation of predictive models is measured in years. Pilot websites, applications, and tools should be added to the NCN to speed collaborative code development among relevant modeling and simulation disciplines, including the risk modeling community. The infrastructure should provide for collaborative code development by public and private scientists, code validation exercises, feedback through interested user communities, and the transfer of validated code versions to centers such as NanoHUB (http://www.nanohub.org/). Such facilities would provide the focus for targeting code development resources to the scientific needs of the community while marshalling expertise from different agencies and institutions, which would allow development and validation of code systems for particularly urgent needs, such as relating exposure to dose for different nanomaterial types and routes of exposure. Finally, collaborative efforts could supplement nanomaterial characterization measurements to provide more complete sensitivity information and structure–property relationships.

Build a Collaborative Informatics Infrastructure

The benefits of collaboration are many: the breaking down of data silos; semantic search and sharing of data and models; web-enabled tools for rapid initiation of collaboration across disciplines; and ability to gather information regarding similar and different nanomaterials, structures, environments, mechanisms, and pathways. But the primary advantage is to speed up the rate at which the science can advance by using digital communication to its fullest possible extent.

The larger problems with setting up a better collaborative informatics infrastructure are based on many confounding considerations: the policies and practices of different agencies, funding mechanisms, and funding evaluation schemes for academic research; and intellectual property considerations for industrial research. But initially it is sufficient to allow scientists to interact more effectively scientist-to-scientist, to share appropriate and available data and models, and to begin to gather common requirements and priorities for more efficient systems. Bringing academia and industry together through alternate mechanisms such as through nongovernmental organizations is another possibility, as are consortia for precompetitive partnering.

Rationale for the 2011 Research Need

To delineate the research necessary to accomplish these informatics and modeling goals, the following research need has been established:

Develop computational models of ENM structure–property–activity relationships to support the design and development of ENMs with maximum benefit and minimum risk to humans and the environment

- Validate the predictive capability of *in vitro* and *in vivo* assays and employ that subset of assays in data generation to establish computational models to predict ENM behavior in humans and the environment
- Establish a standard set of physical and chemical characterization parameters, dose metrics, and biological response metrics
- Design and establish structures and ontologies for methods development, data capture, sharing, and analysis
- Evaluate and adapt as necessary existing computational models by beginning with existing models for exposure and dosimetry and using data generated from validated assays
- Use ENM exposure and dosimetry models to develop ENM structure–activity models to predict ENM behavior in humans and the environment
- Establish training sets and beta test sites to refine and validate ENM structure–activity models
- Disseminate ENM structure–activity models through publicly accessible nanotechnology websites

Example of Progress in NanoEHS Research: 3D Structural Information about Nanomaterials

Structural information about nanomaterials, including validated 3D models, would improve scientists' understanding of the EHS implications of these materials. The Collaboratory for Structural Nanobiology was begun in 2007 as a collaboration between researchers at the National Cancer Institute in Frederick, Maryland, and the University of Talca, Chile. Their goal was to prototype a database to construct, validate, and share molecular models of nanomaterials. Their work has resulted in early predictions of the conformation of two nano-engineered constructs in water, DF1 and DF1 mini, representing dendronized carbon fullerene (C_{60}) molecules (see Figure 7-1). These similar constructs have very different physicochemical properties that significantly alter their efficacy and safety in therapeutic medical applications.

Carbon fullerenes have the ability to act as antioxidants and scavenge a large number of hydrogen and oxygen radicals per molecule, making them ideal candidates for the protection of cells sensitive to ionizing irradiation during cancer therapy. To design an effective therapy using C_{60} derivatives, several challenges must be overcome: induction of cell toxicity, insolubility of the nanoscale material, and reduced protection of the fullerene core from ionizing radiation. Synthesis of C_{60} with a single molecular addition was one promising path to solve these problems; however, predictions of C_{60} properties were limited by the availability of only 2D models of the structures.

The top half of Figure 7-1 illustrates the similar 2D structures of DF1 and DF1-mini, which differ in that DF1 has a larger molecular addition than DF1-mini. These 2D models provide no information about the structure of either construct in water. Exploration of several 3D structural models of these nanomaterials (Figure 7-1, bottom) have verified that, despite their chemical similarity, the structures bear little resemblance to one another in water and result in markedly dissimilar properties. The DF1-mini structure is cytotoxic, whereas the dendrons wrapped around the C_{60} core preserve the benefits of the C_{60} core as a radical-scavenger, an effect not readily apparent from the 2D structural analysis. The DF1 simulations exemplify the essential use of 3D structures to organize available data and to guide the design of engineered nanomaterials.

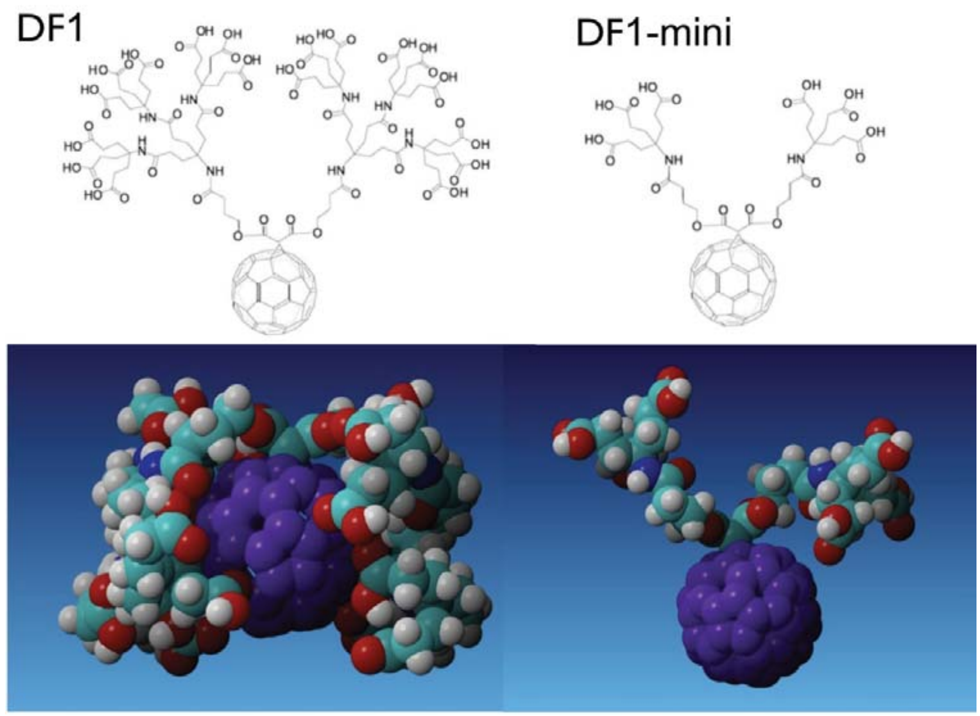

Figure 7-1. DF1 (left) vs. DF1-mini (right) structural models. Top: 2D rendition. Bottom: The most prevalent 3D conformations obtained during simulations.

Source: B. Braden *et al.*, *Proceedings of the National Academy of Sciences USA*, 2000, October 24, 97(22), 12193–12197.

8. The Path Forward

To expeditiously move toward realizing the vision and goals of the NNI EHS Research Strategy, it will be necessary for NNI agencies and programs to be highly focused and to take advantage of the benefits of collaboration and information-sharing among representatives of NNI agencies, academia, industry, NGOs, the general public, and international governance bodies. This chapter notes near-term opportunities to target and accelerate progress in nanoEHS R&D, to maintain close accord with the overall goals and objectives of the National Nanotechnology Initiative, and to effectively coordinate agency research activities and share their results.

Targeting and Accelerating EHS Research

Several issues and challenges span all of the research categories in the NNI EHS Research Strategy and require an integrated approach to advance our understanding of nanomaterial risk. Furthermore, the NNI is committed to a cohesive interagency EHS Research Strategy, with the NSET Subcommittee and its NEHI Working Group serving as a nexus for communication about and facilitation of nanoEHS research through focused interagency collaboration. The NEHI Working Group has identified the following key principles to assist agencies in making strategic decisions about research programs that will efficiently advance the NNI EHS research agenda while meeting their respective missions:

- Prioritize which nanomaterials to research
- Establish standard measurements, terminology, and nomenclature
- Maximize data quality
- Stratify knowledge for risk assessment
- Partner to achieve the NNI EHS research goals
- Engage internationally

It is expected that the application of these principles, discussed in more detail below, will help the individual NNI agencies to more effectively target EHS research, accomplish their individual mandates, and as a group, accelerate the pace and boost the value of their EHS research activities.

Prioritize Nanomaterials for Research

In order to efficiently and effectively identify plausible human and environmental risks associated with nanomaterials exposure, it is necessary to prioritize nanomaterials and nanotechnology-enabled products for study across their life cycles. NEHI, in response to the PCAST recommendation[20] and in keeping with the more practical guidance provided by the NNI EHS Research Strategy, has chosen to develop research-focused criteria to identify and prioritize ENMs and NEPs that might pose a plausible risk to

20. PCAST, *Report to the President and Congress on the Third Assessment of the National Nanotechnology Initiative* (PCAST, Washington, DC, 2010; http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-nni-report.pdf), p. 13.

human health or the environment. In a research modality, the NEHI members propose dual criteria for prioritizing selection of ENMs for research:

- ***Nanomaterials that may provide a major contribution to the ENM research knowledge base.*** These should be chosen for their ability to contribute systematically to a matrix of structure–property–activity relationships, for example, a matrix that includes examination of physical and chemical characteristics against a defined set of biological responses. This systematic accumulation of data will contribute significantly to identifying the overarching design principles for new nanomaterials that will guide nanomaterials and nanotechnology–enabled product development, maximize benefit, and minimize risk.
- ***Nanomaterials and nanotechnology-enabled products that may pose a safety concern to humans and the environment.*** Prioritizing the ENMs and NEPs that may pose a safety concern to workers, consumers, and the environment requires a different set of selection criteria. Many agencies have established procedures for selecting nanomaterials for safety examination; however, the NEHI Working Group chose five criteria to be considered collectively when determining priority:
  - ***Potential for hazard.*** This would include nanomaterials that have physical or chemical characteristics similar to those of known toxicants, or that activate defense mechanisms and signaling pathways in screening assays. (These criteria might identify, for example, nanotubes with dimensions matching the long-fiber toxicity paradigm and/or nanomaterials containing heavy metals.)
  - ***Likelihood of exposure.*** This would include nanomaterials with a high potential for commercialization or that are already produced in large quantities or incorporated into a larger number of products, or result in exposure of a large number of people or environmental areas, or are produced by industrial manufacturing and processing methods and/or types of applications likely to cause exposure.
  - ***High reactivity.*** This would include nanomaterials with high potential for biotic and abiotic transformation in organisms or the environment, ones that change biokinetics, or ones that have the potential to be manipulated in a biological system by external factors, the result of which confers increased toxicity.
  - ***Biological novelty.*** This would include nanomaterials exhibiting new routes of exposure, sequestration in new biological compartments, biopersistence due to evasion of elimination pathways due to size, new dose metrics such as surface area and solubility, novel biology due to size-dependent properties, novel molecular structure, or self-assembly properties.
  - ***Identified in a health or environmental event.*** This would include nanomaterials that may have produced unanticipated human health effects or environmental impacts, which may require an immediate research effort to evaluate the plausibility of a causal relationship and the degree of risk.

It should be noted that the criteria used to prioritize nanomaterials for EHS research under this dual track are consistent with the value-of-information principle that includes the extent to which information gained will reduce uncertainty about benefits and risks, lead to broad knowledge about properties and behavior, and reduce the potential for adverse human and environmental impact.

Establish Standard Measurements, Terminology, and Nomenclature

Confidence in research results on nanomaterials, essential to science-based risk assessment, is achieved through standardized measurements. Such measurements ensure the accuracy, precision, and reproducibility of research results and thus provide a trustworthy knowledge base for evaluating and understanding exposure and hazards to humans and the environment. Reference materials, protocols, and consensus standards (test methods, specifications, and guides) are required for standardized measurements. Organizations engaged in the research, development, manufacture, and regulation of engineered nanomaterials and nanotechnology-based products should coordinate and cooperate to develop reference materials, protocols, and consensus standards for high-priority nanomaterials.

In addition to the need for standardized measurements, there is a need for standardized terminology and nomenclature to fully characterize and categorize ENMs. NNI agencies should continue active participation in domestic and international terminology and nomenclature activities across government, industry, and academia.

Maximize Data Quality

The NEHI agencies recognize the complexity of experimental design for EHS research and the importance of NNI agency support for several critical issues faced by the research community.

Physico-chemical characterization of nanomaterials is critical to understanding the property–structure–biological activity relationships. The NEHI Working Group strongly recommends that the EHS funding agencies support minimal characterization requirements. Several scientific communities, such as ISO (http://www.iso.org), the MinChar community of practice (http://characterizationmatters.org), and OECD (http://www.oecd.org) have developed lists of physical and chemical properties that are necessary to interpret the toxicological impacts of nanomaterials and to distinguish which characteristics contribute to biological response.

Developing reliable and reproducible EHS data has proven challenging. The NEHI Working Group supports the development of standard methods and techniques with established reliability and reproducibility, and research needs in this strategy reflect this commitment (see also Chapter 7, Informatics and Modeling for EHS Research).

The NNI agencies are critically aware of the importance of alternative test methods to reduce or eliminate the use of animals in research and support the development of alternatives to conventional testing. While the research needs outlined in this strategy primarily employ *in vitro* assays and promote the development of high-throughput screening methods as well as modeling and simulation, animals are currently necessary to extrapolate biological response and potential risk from *in vitro* assays to human response. The NNI agencies promote the reduction of animal use in research by requiring researchers to follow the guidelines established by their Animal Care and Use Committees.

Stratify Knowledge for Risk Assessment

Environmental, health, and safety–related decisions rely on risk assessment tiers ranging from relatively qualitative to relatively quantitative assessments. Each requires different levels of knowledge for the exposure and hazard identification components of risk assessment analysis. Such tiered approaches are known for many applications such as consumer products, pesticides, chemicals, and occupational safety. For example, a more qualitative approach to managing risks in the workplace is known as control banding. In control banding, exposure levels are assessed qualitatively, hazards are assigned into hazard bands, and a limited number of risk mitigating approaches are used. In a more quantitative approach to occupational risk management, personal exposure levels are measured in the workplace, and risk mitigation measures are implemented to bring those levels below occupational exposure limits according to a hierarchy of controls. An understanding of the data and modeling needs for both qualitative and quantitative risk assessments will focus the research to achieve these different knowledge thresholds and to support the development of tiered risk management tools.

Partner to Achieve the NNI EHS Research Goals

The NNI agencies will leverage public–private partnerships with industries, nonprofit foundations, and universities to develop the data for nanoEHS knowledge thresholds. These partnerships should include, where appropriate, joint research solicitations involving nongovernmental organizations and industry. Additionally, NNI member agencies will continue to identify research questions that address the mission and needs of multiple agencies and explore mechanisms to issue interagency joint research solicitations. The NNI Nanotechnology Signature Initiatives (http://www.nano.gov/initiatives/government/signature) are examples of such scientific and investment collaborations.

Engage Internationally

The societal challenges for which nanotechnology may provide solutions are global, and as such, provide opportunities for transparent, inclusive, and international collaboration. Of immediate concern to all countries are the potential implications of exposure to nanomaterials and nanotechnology-enabled products for the environment and human health. International engagement is a priority of the NNI, a critical component of this EHS Research Strategy, and recognized by NNI advisory bodies and external stakeholders as essential to harmonize EHS methods and generate data critical for risk assessment and risk management. NNI member agencies engage internationally by:

- Collaborating on nanotechnology-related EHS research via bilateral and multilateral science and technology agreements, memoranda of understanding, and joint grant solicitations that advance common scientific understanding
- Fostering conditions that favor the responsible transfer of nanotechnologies into products for commercial and public benefit through consensus-based deliberations with other countries, industry, academia, nongovernmental organizations, and treaty-based organizations regarding regulation, trade, and standards development
- Supporting capacity building with our global neighbors, and in particular with developing countries and economies in transition, to ensure that comprehensive information and best practices are available to cultivate awareness of the benefits and risks of nanotechnologies and nanomaterials

Appendix B provides specific examples of NNI agency international activities in each of these three areas.

Linking EHS Research Needs and Goals to the NNI Strategic Plan

As stated in the 2011 NNI Strategic Plan and the introduction to this document, responsible development of nanotechnology (Goal 4) is central to the advancement of the NNI's goals: a world-class R&D program (Goal 1), an educated workforce and public and the supporting infrastructure and tools to advance nanotechnology (Goal 3), and all aspects of nanomanufacturing and product commercialization (Goal 2). The NNI EHS Research Strategy incorporates many concepts outlined in these three NNI goals, but it is most specifically linked to the Goal 4 and its related objectives. Table 8-1 provides an overview of the alignment and integration between the NNI Strategic Plan goals and objectives and those of the NNI EHS Research Strategy.

Table 8-1. Alignment between Goals/Objectives of the NNI Strategic Plan and the NNI EHS Research Strategy

Source: NNI Strategic Plan 2011 (NSTC/NSET, Washington, DC, 2011), pp. 23-32.

NNI Strategic Plan Objective 4.1.1.1:	NNI EHS Research Strategy Goals:	Explanation of the Relationship:
Incorporate safety evaluation of nanomaterials into the product life cycle, foster responsible development, and, where appropriate, sustainability across the nanotechnology innovation pipeline, by developing and applying measurement and screening tools (defined as protocols, standards, models, data, and instruments) to assess the physico-chemical properties of nanomaterials and their biological effects in the environment and on human health and to quantify exposure across the nanotechnology product life cycle.	• NMI: Develop measurement tools to detect engineered nanoscale materials in relevant media and in products and relevant matrices and determine their physico-chemical properties throughout all stages of their life cycles. • NMI: Develop measurement tools for determination of biological response, and to enable assessment of hazards and exposure for humans and the environment from engineered nanomaterials and nanotechnology-based products throughout all stages of their life cycles • Human Health: Understand the relationship of physico-chemical properties of engineered nanoscale materials to *in vivo* physico-chemical properties and biological response. • Human Exposure: Identify potential sources, characterize the exposure scenarios, and quantify actual exposures of workers, the general public and consumers to nanomaterials. • Environment: Understand the environmental fate, exposure, and ecological effects of engineered nanomaterials.	*The NNI EHS Research Strategy goals and research needs map directly onto NNI Strategic Plan (SP) objective 4.1.1.1. The Nanomaterial Measurement Infrastructure (NMI) goals direct development of measurement tools to determine the physico-chemical properties of ENMs in relevant media and in NEP and for the biological response across the ENM and NEP life cycles. The NMI research needs specify the types of assays and measurement tools necessary to achieve the NMI goals, and the resulting tools are applied in the human exposure assessment, human health, and environment categories to make the quantitative measurements of exposure and biological effect. Quantitative measures of exposure are also consistent with the human exposure assessment goal to identify, characterize, and quantify exposures of workers, the general public, and consumers to nanomaterials.*

NNI Strategic Plan Objective 4.1.1.2:	EHS Research Strategy Goals:	Explanation:
Incorporate safety evaluation of nanomaterials into the product life cycle, foster responsible development, and, where appropriate, sustainability across the nanotechnology innovation pipeline, by developing and applying models, including risk assessment models, to assess safety of nanomaterials throughout the life cycle of the material or product.	• Human Health: Develop high-confidence predictive models of *in vivo* biological responses and causal physico-chemical properties of ENMs. • Human Health: Understand the relationship of physico-chemical properties of engineered nanoscale materials to *in vivo* physico-chemical properties and biological response. • Human Exposure: Characterize and identify the health outcomes among exposed populations to determine benchmark levels of exposures • Risk Assessment & Risk Management Methods: Increase available information for better decision-making in assessing and managing risks from nanomaterials, including using comparative risk assessment and decision analysis, life cycle considerations and additional perspectives such as ELSI considerations, stakeholders' values, additional decision makers' considerations, among others	*This SP objective integrates research derived from several of the EHS research needs. Models that predict biological response will require precise data that describe the relationship of physico-chemical properties of ENMs to biological response in a property/structure-activity relationship. Models of exposure by port-of-entry tissue will derive from Human Exposure Assessment exposure measurement scenarios and Human Health research on uptake by port-of-entry tissues. These activity and exposure models also support the objectives outlined in SP Goals 1 and 2 as property/structure-activity relationships will inform nanomaterials R&D as well as technology transfer and product development. Risk assessment models will incorporate life cycle considerations and relevant risk characterization information, hazard identification, exposure science, and risk modeling and methods into the development and evaluation of risk assessment models and management methods. Resulting data will meet the Risk Assessment and Risk Management Methods goal to increase available information for better decision-making and risk management, as well as the SP objective to develop risk assessment models.*

NNI Strategic Plan Objective 4.1.1.3:	NNI EHS Research Strategy Goal:	Explanation:
Incorporate safety evaluation of nanomaterials into the product life cycle, foster responsible development, and, where appropriate, sustainability across the nanotechnology innovation pipeline, by developing and applying health surveillance models as appropriate for the nanotechnology workforce, consumers, susceptible populations, and the environment.	• Human Exposure: Characterize and identify the health outcomes among exposed populations to determine benchmark levels of exposures **NNI EHS Research Strategy Needs:** • Human Exposure #1: Understand processes and factors that determine exposures to NMs • Human Exposure #2: Identify population groups exposed to ENMs • Human Exposure #3: Characterize individual exposures to ENMs • Human Exposure #4: Conduct health surveillance of exposed populations • Human Health #4: Understand relationship between ENM physico-chemical properties and uptake • Human Health #6: Determine the extent to which life stage and/or susceptibility factors modulate health effects from exposure to ENMs, NEPs, and their applications.	*The Human Exposure Assessment goal and research needs to support characterization and identification of health outcomes among exposed populations will provide data to determine benchmark levels for human exposure. The Human Health research needs investigating mechanisms of uptake and biological response also contribute to the understanding of the human health outcomes that might be measured.*

NNI Strategic Plan Objective 4.1.2:	**NNI EHS Research Strategy Components and Concepts:**	**Explanation:** *The SP objective will create mechanisms for appropriate and timely research data information sharing and dissemination among stakeholders. A robust nanotechnology knowledge infrastructure will improve research outcomes, reduce costs, increase the availability of resources, and promote broader collaboration among a wider range of practitioners and stakeholders. This will be achieved, in part, through the organization and collation of available information on nanomaterial properties, hazards, and exposures, and the dissemination of data and ENM property/structure-activity models through publicly accessible nanotechnology websites. This knowledge infrastructure will also support the NNI Strategic Plan goals to advance a world-class R&D program and to foster the transfer of new technologies into products for commercial and public benefit. Additionally, the NNI EHS Research Strategy includes discussion of knowledge thresholds to understand data and modeling needs for qualitative and quantitative risk assessments and dissemination of knowledge through traditional and newer electronic media. It should be noted that dissemination of knowledge in this document includes sharing of safety and hazard information with industry and the general public as well as the scientific community.*
Incorporate safety evaluation of nanomaterials into the product life cycle, foster responsible development, and, where appropriate, sustainability across the nanotechnology innovation pipeline, by creating mechanisms for appropriate and timely information sharing and dissemination among stakeholders, including academia, industry, legal entities, Federal agencies, regulatory communities, governments, the general public, and other relevant stakeholders.	• Informatics Needs for EHS Research • The Path Forward: Stratifying Knowledge for Risk Assessment • The Path Forward: Dissemination of Knowledge	

NNI Strategic Plan Objective 4.2: Develop tools and procedures for domestic and international outreach and engagement to assist stakeholders in developing best practices for communicating and managing risk.	**NNI EHS Research Strategy Goal:** • Risk Assessment & Risk Management Methods: Increase available information for better decision-making in assessing and managing risks from nanomaterials including using comparative risk assessment and decision analysis, life cycle considerations and additional perspectives such as ELSI considerations, stakeholders' values, additional decision makers' considerations, among others. **NNI EHS Research Strategy Need:** • Risk Assessment & Risk Management Methods #3: Integrate and standardize risk communication within the risk management framework **NNI EHS Research Strategy Concept:** • International Engagement	**Explanation:** *SP objective 4.2 continues the theme of public engagement. This theme falls within the scope of the NNI EHS Research Strategy and aligns with the risk communication goal as expressed in the Risk Assessment and Risk Management Methods research needs. Specifically, this goal will increase and integrate available information for assessing and managing risks. The addition of life cycle and ELSI considerations, stakeholders' values, and additional decision makers' perspectives will ground the risk communication in the needs of the stakeholders. The Risk Assessment and Risk Management Methods research needs direct the development of processes and information to achieve this objective.*
NNI Strategic Plan Objective 4.3.1: Identify and manage the ethical, legal, and social implications (ELSI) of research leading to nanotechnology-enabled products and processes, by increasing the capacity of Federal agencies to identify and address ELSI issues specific to nanotechnology by fostering the development of a community of expertise on ELSI issues related to nanotechnology and by providing a current resource list of experts that is accessible to a broad range of users.	**NNI EHS Research Strategy Goal:** • Risk Assessment & Risk Management Methods: Increase available information for better decision-making in assessing and managing risks from nanomaterials including using comparative risk assessment and decision analysis, life cycle considerations and additional perspectives such as ELSI, stakeholders' values, additional decision makers' considerations, among others.	**Explanation:** *The Risk Assessment and Risk Management Methods goal—to increase available information for assessing and managing risk—again provides the bridge between the SP objective and the EHS research needs. ELSI considerations, as described previously in this document, provide a perspective that guides decisions about types of research needed and risk analysis and management decisions. ELSI is presented in this strategy as an overarching theme and ties directly to research in the Human Exposure Assessment, Human Health, and Environment chapters and this SP objective.*

Implementation and Coordination of the NNI EHS Research Strategy

This interagency strategy document will guide programs and investment decisions by the individual agencies as well as in coordinated interagency activities in the coming years. It should be noted that the agencies have varied missions, and their individual priorities may differ in scope and focus from those outlined in this report. For these reasons, continuous coordination is essential, and agencies will work through the NSET Subcommittee, its NEHI Working Group, and the NNCO Coordinator for EHS (described below), to ensure the integration of agency implementation plans.

The NNI, as a program, does not fund research; rather, its funding is the sum of nanotechnology-related funding allocated by each of the participating agencies. Through its member agencies, the NNI informs and influences the Federal budget and planning processes. Annual funding by each agency for research in the EHS program component area since FY 2006 is identified in Table 8-2.

Table 8-2. Agency Investments for NanoEHS Research
(in millions of dollars; totals may not add due to rounding*)

Chartered NEHI Agencies	Actual					
	FY 2006	**FY 2007**	**FY 2008**	**FY 2009**	**FY 2009 ARRA**	**FY 2010**
NSF	21.0	26.9	29.2	26.8	3.4	27.1
DOD	1.0		3.8	4.1		0.0
DOE	0.5		2.6	3.1	0.2	2.6
DHHS (NIH)	5.2	7.7	11.9	12.0	8.4	20.0
DOC (NIST)	2.4	0.9	1.3	3.5		3.4
EPA	3.7	7.1	11.6	11.1		17.1
USDA (CSREES/NIFA)	0.1	0.1	0.6	0.5		3.7
USDA (FS)	0.0	0.0	0.0	0.0		0.0
DHHS (NIOSH)	3.8	5.6	6.9	6.7		8.5
DHHS (FDA)				6.5		7.3
CPSC				0.2		0.5
TOTAL	**37.7**	**48.3**	**67.9**	**74.5**	**12.0**	**90.2**

* USDA (FS) did not allocate funding for EHS during FY 2006-FY 2010; DHHS (FDA) and CPSC began allocating EHS funding in FY 2009.

The framework for implementation of the NNI EHS Research Strategy outlined below describes the various activities and coordination that are needed to address the full spectrum of NNI EHS research. It also provides for participation, interaction, and partnership with non-Federal stakeholders to leverage efforts and to expedite progress. A tabulation of domestic and international interagency activities that pertain to this framework is found in Appendix B.

- **Increase agency participation in NNI EHS research.** Two NNI/NEHI agencies have developed research programs and now contribute to the NNI budget crosscut.

  - CPSC is meeting identified data needs by supporting interagency collaborations that develop testing methods to adequately address product safety.
  - FDA is supporting agency priorities, including laboratory and product testing capacity, scientific staff training and development, and collaborative and interdisciplinary research to address product characterization and safety.

- **Name NNCO EHS Coordinator.** Consistent with the PCAST recommendation, OSTP has named an NNCO Coordinator for EHS to assist agencies in integrating research across the nanoEHS continuum to achieve the objectives presented in the NNI 2011 Strategic Plan. The new NNCO EHS Coordinator serves on the NSET/NEHI leadership team; leads the NNCO and NSET Subcommittee's efforts in identifying and leveraging research collaborations domestically and internationally; serves as the NNI point of contact for stakeholders with nanoEHS concerns; and spearheads the NNI EHS Research Strategy's implementation, coordination, and evaluation.
- **Refocus NEHI.** Through consultation with agency representatives, the leadership of the NEHI Working Group adapted its meeting format to ensure better coordination of research to achieve the goals of the NNI EHS Research Strategy. Four priority areas were identified: ongoing updates on agency nanoEHS activities; new opportunities for collaboration; research strategy implementation, coordination, and evaluation; and planning and outreach.
- **Expand media and networking opportunities.** NEHI is exploring new social media opportunities to improve interagency communication and stakeholder interactions by:
  - Establishing (Spring 2011) an internal collaborative workspace for NEHI to improve interagency communication and information sharing.
  - Exploiting the new nano.gov website to provide NEHI with opportunities to engage in direct dialogue with academia, industry, nongovernmental organizations, state and regional entities, and other stakeholders through the use of new social media tools (e.g., blogs, tweets, and webinars).
  - Exploring opportunities to host webinars 2–3 times a year, to engage stakeholders in discussions on the status of nanotechnology and nanoEHS research, to address stakeholder concerns, and to exchange information and ideas.
- **Enable a broad base of nanoEHS research to support regulatory decision making.** The NNI EHS Research Strategy fundamentally depends on sustaining the broad spectrum of basic and applied research, with support from agencies that investigate the fundamental properties of nanomaterials and directly apply research for responsible development (including NSF, DOE, NIST, NIH, and NIOSH). This research effort will support regulatory decision making based on the best available science. For example, the NIH/NIEHS Centers for Nanotechnology Health Implications Research are designed to more precisely link the physical and chemical properties of nanomaterials to the human biological response and to translate the methods used for this analysis into an expanded, nanomaterials-specific risk assessment paradigm.

- **Coordinate existing, and foster expanded, agency efforts to address priority EHS research needs and identified gaps.** The NEHI Working Group will continue to facilitate coordination and increased collaboration among the NNI agencies' research programs by:
  - Clarifying priorities and areas of focus to pursue, through collaboration, monthly NEHI Working Group meetings, and workshops.
  - Identifying synergistic opportunities through annual webinars, workshops, and other mechanisms for information exchange to assess the state of science and current research, and to reassess areas of weakness and gaps.
  - Facilitating development of joint programs among NNI member agencies to fund nanoEHS research of mutual interest and avoid unproductive redundancy. The Nanotechnology Signature Initiatives offer NEHI a new mechanism through which to organize and leverage interagency efforts (http://www.nano.gov/initiatives/government/signature).
- **Facilitate partnerships with industry.** The NEHI Working Group will continue to utilize existing Federal Small Business Innovation Research (SBIR)/Small Business Technology Transfer Research (STTR) programs and explore and develop new mechanisms for NNI agencies to partner with industry. The SBIR/STTR programs support translational research by assisting researchers and small businessmen to move research ideas from the laboratory to prototype to commercialization of nanomaterials and nanotechnology enabled products. New programs could support industry–public partners–agency collaborations on EHS research.
- **Coordinate efforts internationally.** Several NNI agencies participate in international efforts related to EHS research. The OECD Working Party on Manufactured Nanomaterials (WPMN) is a program to develop internationally accepted nanoEHS research priorities, testing protocols, and predictive tools. ISO and ASTM International are actively developing international standards, nomenclature, and terminology. Additionally, the NEHI Working Group is coordinating a European Union–United States workshop to bring together EHS scientists, risk assessors, regulators, policy experts, and stakeholders to assess EHS data needs and identify points of contact, shared research interests, and mechanisms for collaboration. The working group anticipates an annual meeting with international partners.
- **Adaptively manage the NNI EHS Research Strategy.** The NEHI Working Group will continue the adaptive management process that was utilized in the production of this EHS Research Strategy by conducting periodic progress reviews of Federally funded and international research, the status of the science, and stakeholder concerns. These reviews will, in turn, provide the information necessary to update the research needs and priorities to maintain a dynamic and current NNI EHS Research Strategy.

Dissemination of Knowledge

Nanotechnology is a multidisciplinary field, requiring the engagement of scientists in disciplines as diverse as materials science, physics, biology, chemistry, engineering, toxicology, clinical practice, social science, and risk assessment, as well as leaders in industry, public health advocacy, healthcare, and the general public. To share information among these diverse groups, it is necessary to develop and maintain data communication infrastructures and organizations. Essential steps include identifying what information is required, who needs the information, how the information should be furnished, and when and where. Therefore, the NNI agencies engage in:

- Scientific meetings, workshops, and summits at the local, state, national, and international levels
- Direct communication with stakeholders and research communities
- Participation in international standards organizations
- New media outreach through websites, webcasts, blogs, etc.
- Creation of data repositories for scientific results

As part of its 2011 revision of the NNI EHS Research Strategy, NNI proposes:

- Continuing engagement in traditional scientific forums
- Building on new-media efforts to engage more stakeholders, for example, in developing prevention strategies, good handling practices, and regulatory standards
- Expanding work in data storage and management (see Section 7, Informatics and Modeling for NanoEHS Research)
- Creating public engagement events to share information on safety research and efforts to maximize societal benefits from nanotechnology while minimizing risks. This includes outreach to the general public. Such outreach may be particularly important in considering ethical, legal, and societal implications of nanotechnology and for risk management and risk mitigation issues.

Conclusion

The vision of this 2011 National Nanotechnology Initiative EHS Research Strategy—a future in which nanotechnology provides maximum benefit to the environment and to human social and economic well-being—is a national priority with intense and sustained Federal effort. It complements the NNI Strategic Plan and is critical to achieving many of its objectives. The multicomponent risk management research framework that forms the foundation of this strategy will require focused and sustained coordination by the NNI agencies and regular review by the agencies and by stakeholders. The Federal agencies have an essential role to play in defining and coordinating these activities because of the broad economic, national security, and public health and environmental impacts of nanotechnology and because of the diverse science and engineering fields that are needed for its success. The NNI agencies have a proven track record of working together and will continue to refine mechanisms of collaboration. Stakeholders have an essential role to play as the researchers, workers, and consumers directly involved in the development, manufacture, use, and recycling of ENMs and NEPs. As we move forward to achieve the NNI EHS research goals, agencies, in partnership with stakeholders, accept this responsibility to develop ENMs and NEPs that maximize benefit and minimize risk to public health and the environment.

Appendix A. Selected Readings

1. *NNI Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials* (NSTC/NSET, Washington, DC, 2006; http://nano.gov/NNI_EHS_research_needs.pdf).
2. *NNI Prioritization of Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials* (NSTC/NSET, Washington, DC, 2007; http://nano.gov/Prioritization_EHS_Research_Needs_Engineered_Nanoscale_Materials.pdf).
3. *NNI Strategy for Nanotechnology-Related Environmental, Safety, and Health Research* (NSTC/NSET, Washington, DC, 2008; http://nano.gov/NNI_EHS_Research_Strategy.pdf).
4. *Review of the Federal Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* (National Academies Press, Washington, DC, 2009; http://download.nap.edu/cart/deliver.cgi?record_id=12559).
5. *Report to the President and Congress on the Third Assessment of the National Nanotechnology Initiative* (PCAST, Washington, DC, 2010; http://whitehouse.gov/sites/default/files/microsites/ostp/pcast-nni-report.pdf).

Appendix B. International and Domestic Cooperative Activities

International Cooperative Activities

Coordination: The Global Issues in Nanotechnology (GIN) Working Group under the NSET Subcommittee, with leadership from the U.S. State Department and White House Office of Science & Technology Policy, coordinates the National Nanotechnology Initiative (NNI) international activities in nanotechnology, monitors foreign nanotechnology programs, promotes the trade and commercial interests of the United States, and seeks to broaden international cooperation and communications regarding nanotechnology R&D. The working group includes representatives from Federal agencies that have active nanotechnology R&D programs, as well as from numerous agencies that have oversight roles in international affairs. In keeping with the NNI goal of establishing a framework for the safe, secure, and responsible development of nanotechnology worldwide, international cooperation is important to ensuring that environmental, health, and safety concerns are appropriately addressed by the global scientific community and relevant regulatory agencies.

Activities: Because of their cross-cutting nature, nanotechnology-related efforts within the Organisation for Economic Cooperation and Development (OECD) are especially significant when evaluating international nanotechnology activities. The United States has played critical leadership roles in both the OECD Working Party on Manufactured Nanomaterials (WPMN) and the OECD Working Party on Nanotechnology (WPN), as noted in Box 1.

Box 1. Nanotechnology Activities within the Organisation for Economic Cooperation and Development

OECD Working Party on Nanotechnology (WPN): The WPN is a forum to advise on emerging policy issues in science, technology, and innovation related to the responsible development and use of nanotechnology. It is the premiere multilateral forum that brings governments together to discuss and create policy perspectives relating to nanotechnology. The U.S. Department of State was the founding chair of the WPN, and continues to play a critical leadership role on the WPN Bureau. In the current work program, the U.S. FDA is leading an effort to inventory regulatory frameworks for nanotechnology in food and medical products. Additional efforts are planned in areas such as business environments and green growth (http://www.oecd.org/sti/nano).

OECD Working Party on Manufactured Nanomaterials (WPMN): The WPMN is leading an international effort by the OECD member nations and other nonmember nations and organizations to coordinate and collaborate on approaches for better understanding the environmental, health, and safety impacts and the benefits of nanotechnology. In 2008, the WPMN embarked on a cooperative international program to conduct testing on 14 nanomaterials types across 59 environmental endpoints. EPA is leading the U.S. effort to sponsor the testing of many of these materials. NIOSH continues its leadership role in the OECD WPMN steering group on Cooperation on Exposure Measurement and Exposure Mitigation (http://www.oecd.org/env/nanosafety).

Activities by NNI member agencies in support of international engagement are summarized in the following three sections: (1) International collaboration in science, technology, and innovation; (2) Fostering conditions that favor the responsible transfer of nanotechnologies into products for commercial and public benefit; and (3) Capacity building with our global neighbors. Tables B1-B3 highlight examples of supporting activities in each of these areas, with an emphasis on efforts drawn from multiple NNI member agencies. Coordinated activities between NNI agencies and other institutions are reported on an annual basis in the NNI Supplement to the President's Budget (available at http://www.nano.gov).

International Collaboration in Science, Technology, and Innovation

The U.S. values robust, rewarding partnerships with other nations that advance our common interest in nanotechnology science, technology, and innovation as well as the responsible development of nanotechnology. Cooperation under the auspices of bilateral and multilateral science & technology agreements and memoranda of understanding is an effective mechanism to achieve these goals and should continue to be pursued. The Federal Government also encourages collaborative research across the international community, for example, by issuing joint grant solicitations between U.S. agencies and other nations.

International Collaboration on nanoEHS Research

Table B-1. Examples of Activities Supporting International Collaboration in Nanotechnology

Federal Agency(ies)	Partner(s)	Activity Description	Type of Activity
EPA	United Kingdom	Joint funding of research "e-consortia" teams each at $2 million for 4 years.	Joint research funding opportunity
EPA, NSF, NIH/NIEHS, NIOSH, USDA/NIFA	European Commission	An interagency solicitation with EPA (lead), NSF, NIH/NIEHS, NIOSH, and USDA/NIFA in coordination with the EC, focuses on exposure and safety research data for engineered nanomaterials.	Joint research funding opportunity
EPA, NSF, USDA/NIFA	European Commission	Joint solicitation with EC: "Increasing Scientific Data on the Fate, Transport, and Behavior of Engineered Nanomaterials in Selected Environmental and Biological Matrices"; total U.S. award est. $4.2 million.	Joint research funding opportunity
NIH/NCI, NIH/NIEHS	Chinese Academy of Sciences	First Joint U.S. - China Symposium on Nanobiology and Nanomedicine in Beijing, October 20-22, 2008; followed up in Washington, DC in September 16-18, 2010. Exchanged research experiences, considered possible collaborations.	Symposium; information sharing
NIH/NCI, NIH/NIEHS	India	1st Indo-U.S. Cancer Nanotechnology Symposium in New Delhi, Feb 4-6, 2009 brought together NCI researchers with Indian cancer researchers.	Symposium; information sharing

DOE, NIH, NIOSH, State Dept., Exec Office of the President, NSF	Russia	U.S. - Russia Bilateral Presidential Commission (http://www.state.gov/p/eur/rls/fs/130616.htm); Nanotechnology sub working group under the Science & Technology Working Group is covering Energy and Environmental, Health, and Safety R&D.	Research & Development; information sharing
NIH	Russia	U.S.-Russia Biomedical Forum, August 20-21, 2009 held at NIH on the topic of: "New Directions in Prostate Cancer Chemotherapy: Natural Products, Synthetic Compounds, Nanomedicinal Chemistry"	Symposium; information sharing
NIOSH, NIST, CDC, NIH/NCI	International Alliance for NanoEHS Harmonization (IANH)	IANH coordinates round robin testing of nanomaterials. It is a peer-group of scientists from around the world that voluntarily collaborate on the questions of reproducibility and standards in the arena of nanobiology and nanosafety.	Research & Development; testing protocols Nanomaterial Measurement Infrastructure
NNI agencies (State Dept. lead)	EU	U.S.-EU Joint Committee Meeting, May 11-12, 2010 brought together the NNCO director and agency representatives to discuss opportunities and barriers to collaboration. As a result of discussions that took place in this venue, both parties proceeded to plan a joint research meeting slated for March 2011.	Research & Development; Policy Coordination
USDA/NIFA, DOE	Canada	Following the successful joint grantees' meeting with Canada's Advanced Food and Materials Network (AFMNet) held in conjunction with the DOE CINT nanotechnology user conference in September 2009, USDA/NIFA is planning for a nanotechnology grantee's meeting with AFMNet and Canada's National Institute for Nanotechnology.	Symposium

Foster conditions that favor the responsible transfer of nanotechnologies into products for commercial and public benefit

There is a fundamental shared desire among the U.S. Government agencies for regulation that ensures safety but does not unjustifiably inhibit innovation, stigmatize new nanotechnologies, or create trade barriers. The U.S. approach to nanotechnology-related regulation, trade, and standards development is developed and disseminated through regulatory discussions across the Federal Government with existing groups and with key international trading partners. Another important component to achieving favorable nanotechnology transfer is a sustained commitment to voluntary consensus-based standards development such as globally harmonized data collection, data reporting, and voluntary risk management schemes.

Table B-2. Examples of Activities Supporting the Responsible Transfer of Nanotechnology into Products

Federal Agency(ies)	Partner(s)	Activity Description	Type of Activity	EHS Research Category
NNI agencies and other USG agencies (State Dept., DOC, and EOP leads)	EU	Transatlantic Economic Council (TEC) was established in April 2007 under the Framework for Advancing Transatlantic Economic Integration between the U.S. and the European Union. Activities under the TEC include: (1) Innovation Action Partnership (http://www.state.gov/p/eur/rt/eu/tec/c34871.htm); (2) High Level Regulatory Cooperation Forum.	Standards / Regulatory / Trade	Risk Assessment & Risk Management Methods
DOD, DOE, EPA, NIOSH, NIH/NCI, NIST, USDA/FS, USDA/FAS, State Dept., DOC, FDA, EOP	International Organisation for Standardization (ISO) TC 229	ISO Technical Committee 229 (TC229, Nanotechnologies) is working to develop standards in nanotechnology through the U.S. Technical Advisory Group, which is coordinated by the American National Standards Institute. ISO has 159 member nations.	Standards development	Nanomaterial Measurement Infrastructure
NIST, EPA, NIH/NCI, DOD, NIOSH, FDA	ASTM International	ASTM International Technical Committee E56 (Nanotechnology) develops standards in nanotechnology.	Standards development	Nanomaterial Measurement Infrastructure
NIST	International Electrotech-nical Commission (IEC)	IEC Technical Committee 113 (Nanotechnology Standardization for Electrical and Electronics Products and Systems) develops standards in nanotechnology.	Standards development	Nanomaterial Measurement Infrastructure
NIST	Versailles Project on Advanced Materials and Standards (VAMAS)	VAMAS Technical Working Area 34 (Nanoparticle Populations Working Group) develops international consensus measurement methods.	Standards development	Nanomaterial Measurement Infrastructure
NIST, NIH/NCI	Institute of Electrical and Electronics Engineers (IEEE)	IEEE develops standards in nanotechnology.	Standards development	Nanomaterial Measurement Infrastructure
DHS, DOC, DOD, DOE, DOT, EOP, EPA, FDA, OSHA, USDA, and other agencies	n/a	Emerging Technologies Interagency Policy Coordination Committee (est. 3/2010) is a high-level policy group that is anticipated to make decisions that create and coordinate U.S. Government - wide policies relating to the safe use of nanotechnology.	Standards/ Regulatory (Policy coordination)	Risk Assessment & Risk Management Methods
CPSC, DHHS, DHS, DOEd, DOE, DOJ, State Dept., DOT, DoTreas, EPA, EOP, ITA, ITC, NASA, NIST, NSF, USPTO, and other agencies	n/a	NSTC Subcommittee on Standards (est. 4/2010), co-chaired by NIST and DOJ. This Federal group focuses on standards used in support of regula-tions, procurement, or grant guidance.	Standards-related policy guidance	Targeting and Accelerating Research

Engage in Capacity Building with our Global Neighbors

The U.S. continues to engage internationally, and with developing countries and economies in transition in particular, to ensure a balance of the potential benefits and risks of nanotechnologies and nanomaterials. These countries may encounter issues such as inequity, disparate access to safe workplace environments, and an overall dearth of comprehensive information to inform decisions. U.S. participation in international organizations that focus on these issues can facilitate this capacity building. Best practices in environmental, health, and safety protocols and approaches (i.e., workplace safety, exposure assessment, toxicity testing, public engagement, risk assessment, etc.) continue to be identified and disseminated.

Table B-3. Example Activities Supporting Capacity Building

Federal Agency(ies)	Partner(s)	Activity Description	Type of Activity
NIOSH	International Council on Nanotechnology (ICON)	ICON's "Nano Good Practices Wiki": NIOSH continues to participate in the Wiki at http://www.goodnanoguide.org, a collaboration platform designed to enhance the ability of experts to exchange ideas on how best to handle nanomaterials in an occupational setting. Beta sponsors include a number of Canadian organizations along with ICON and NIOSH.	Capacity Building; Information sharing
NIOSH	World Health Organization (WHO)	WHO collaborating centers: NIOSH continues developing and disseminating best practices globally for working with nanomaterials.	Policy coordination, risk management
DOS, EPA	UNEP / Strategic Approach to International Chemicals Management (SAICM)	SAICM supports the achievement of the goal agreed to at the 2002 Johannesburg World Summit on Sustainable Development of ensuring that, by the year 2020, chemicals are produced and used in ways that minimize significant adverse impacts on the environment and human health.	Risk Assessment & Risk Management Methods; Ethical, Legal, and Societal Implications
USDA, FDA	Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO)	FAO/WHO Expert meeting on "the application of nanotechnologies in the food and agriculture sectors: potential food safety implications," June 2009 (see report, published in 2010, (http://www.who.int/foodsafety/fs_management/meetings/nano_june09/en/)). U.S. agencies participated as experts at the meeting, which was intended to provide information about applications of nanotechnology and potential food safety implications, formulate a plan of work for risk assessment, and analyze ongoing communication efforts for constructive dialogue.	Risk Assessment & Risk Management Methods; Ethical, Legal, and Societal Implications

Domestic Cooperative Activities

Table B-4. Cooperative Activities Among NEHI Agencies

Federal Agency(ies)	Partner(s)	Activity Description	Type of Activity	EHS Research Categories
CPSC, NIOSH, EPA		CPSC to establish interagency agreements with NIOSH and EPA to complete a literature search and develop experimental procedures to quantify releases of and consumer exposures to nanosilver in treated consumer products.	Risk Management; Ethical, Legal and Societal Implications	Risk Assessment & Risk Management Methods
EPA, NSF, NIH/NIEHS, NIOSH, DOE		Since 2004 EPA's Science to Achieve Results (STAR) grants program has coordinated interagency requests for applications; agencies involved have included NSF, NIEHS, NIOSH, and DOE. The fourth joint research solicitation by EPA's STAR program was issued in 2007. The solicitation was a collaboration between EPA, NSF, and DOE; over 130 research proposals were received. EPA awarded 15 grants, NSF awarded 6, and DOE awarded one and made several awards to DOE laboratories. Individual grant awards totaled approx. $9 million. In addition, EPA recently awarded $2 million to study fate and transport in biological systems as part of an NIEHS-led request for applications.	Grants	Environment
FDA, other agencies	Universities	There are many classes of products where the FDA is currently the only agency to conduct research for science-based safety and/or risk assessments. While the agency can undertake some self-initiated research, the scale and range of issues and expertise involved necessitates collaborations with academic and government labs.	Research	Nanomaterial Measurement Infrastructure Human Health Risk Assessment & Risk Management Methods
NIH/NIEHS, NIST, NIH/NCI, FDA, NIOSH	Oregon Nanoscience and Microtechnologies Institute and ASTM International	Workshop on Enabling Standards for Nanomaterial Characterization to address the urgent need to accelerate standards development at the pre-standards stage.	Standards development	Nanomaterial Measurement Infrastructure
NIH/NCI, NIH/NIEHS, NIH/NIBIB, NIST		NIH/NCI and NIST held a one-day workshop to establish an International Collaboration for NanoEHS Informatics aimed at development a federated database system.	Informatics	Informatics

NIH/NIEHS, EPA	University of Massachusetts	International Conference on the Environmental Implications and Applications of Nanotechnology, the aim of which was to provide a valuable forum for scientists, regulators, and policymakers from academia, government, and industry to interact and share new knowledge on the health and environmental impacts of nanotechnology, green nanotechnology, and new environmental applications, and to help direct future research and regulatory needs.	Conference	Human Health Environment Risk Assessment & Risk Management Methods
NIOSH, NIST, EPA, NIEHS, FDA and all other NEHI agencies		NNI 2009-2011 NanoEHS series of four workshops to provide an open forum to identify progress, gaps, and barriers to environmental, health, and safety research program laid forth in the 2008 NNI EHS Research Strategy.	Workshops	All research needs
NIOSH, CPSC		Under an interagency agreement between CPSC and NIOSH, NIOSH will conduct testing to determine the exposure impact of bathroom spray that contains engineered nanomaterials .	Research	Risk Assessment & Risk Management Methods
NIST, DOD		NIST and the U.S. Army Corps of Engineers co-organized a nanosilver workshop to identify the most pressing measurements and standards needs, including the selection of potential forms of nanosilver for international laboratory studies on nanosilver properties and stability.	Standards development	Nanomaterial Measurement Infrastructure
NIST, CPSC		NIST is leading a coordinated research program with CPSC to determine the release of nanoparticle flame retardants from fabrics and foams.	Research	Nanomaterial Measurement Infrastructure Risk Assessment & Risk Management Methods
NIST, FDA, and EPA		These agencies are coordinating the development of benchmark data, measurement methods, and prototype reference materials for nanosilver for biomedical applications, including EHS assessments.	Standards Development, Research	

NSF, EPA		To ensure that nanotechnology is developed in a responsible manner, NSF and EPA continue to fund two Centers for the Environmental Implications of Nanotechnology (CEIN). Led by UCLA and Duke U., the CEINs will study how nano-materials interact with the environment and human health, resulting in better risk assessment and risk mitigation strategies.	Grants	All research needs

Appendix C. Definitions

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,* February 2011.

ISO TC 229 Core Terms

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

Nanoscale is the size range from approximately 1 nm to 100 nm.

Nano-object is a material with one, two, or three external dimensions in the ***nanoscale***.

Nanoparticle or ***nanoscale particle*** is a ***nano-object*** with all three external dimensions in the ***nanoscale***.

Nanostructured material is a material having internal nanostructure or surface nanostructure.

Nanomaterial or ***nanoscale material*** is a material with any external dimension in the nanoscale or having an internal structure or surface structure in the nanoscale. This generic term is inclusive of ***nano-object*** or ***nanostructured material***.

Engineered nanomaterials are designed for a specific purpose or function.

Manufactured nanomaterial is intentionally produced for commercial purposes to have specific properties or specific composition.

Nanomanufacturing is the intentional synthesis, generation, or control of ***nanomaterials*** or fabrication steps in the ***nanoscale*** for commercial purposes.

(ISO/TS 27687:2008, available at http://cdb.iso.org/)

Agglomerate is a collection of weakly bound particles or aggregates or mixtures of the two where the resulting external surface area is similar to the sum of the surface areas of the individual components.

Aggregate is a particle composed of strongly bonded or fused particles where the resulting external surface area may be significantly smaller than the sum of calculated surface areas of the individual components.

Appendix D. Comprehensive Chart of 2011 EHS Research Strategy Needs

Table D-1. The Core EHS Research Categories and their Highest-Priority Research Needs (RNs)

Key Research Needs	Subordinate Research Needs
1. Nanomaterial Measurement Infrastructure Research Needs Develop measurement tools to detect and identify engineered nanoscale materials in products and relevant matrices and determine their physico-chemical properties throughout all stages of their life cycles. Develop measurement tools for determination of biological response and to enable assessment of hazards and exposure for humans and the environment from engineered nanomaterials and nanotechnology-based products throughout all stages of their life cycles.	
RN#1. Develop measurement tools for determination of physico-chemical properties of ENMs in relevant media and during the life cycles of ENMs and NEPs	• Physical dimensions and morphology: size, size distribution, characteristic dimensions, shape • Internal structure: atomic-molecular, core-shell • Surface and interfacial properties: surface charge, zeta potential, surface structure, elemental composition, surface-bound molecular coatings and conjugates, reactivity • Bulk composition: elemental or molecular composition, crystalline phase(s) • Dispersion properties: degree and state of dispersion • Mobility and other transport properties: diffusivity, transport in biological and environmental matrices
RN#2. Develop measurement tools for detection and monitoring of ENMs in realistic exposure media and conditions during the life cycles of ENMs and NEPs	• Sampling and collection of ENMs • Detecting the presence of ENMs • Quantity of ENMs—concentration based on surface area, mass, and number concentrations • Size and size distribution of ENMs • Spatial distribution of ENMs • Discriminating ENMs from ambient NMs such as combustion products and welding fumes • Discriminating multiple types of ENMs such as metals and metal oxides
RN#3. Develop measurement tools for evaluation of transformations of ENMs in relevant media and during the life cycles of ENMs and NEPs	• Agglomeration and de-agglomeration • Dissolution and solubility • Adsorption of natural organic matter and bioconstituents • Oxidation and reduction • Deposition of ENMs on surfaces

Key Research Needs	Subordinate Research Needs
RN#4. Develop measurement tools for evaluation of biological responses to ENMs and NEPs in relevant media and during the life cycles of ENMs and NEPs	• Adequacy of existing assays • New assays or high-throughput, high content assays • Correlation of biological responses with physico-chemical properties • Surface reactivity at the interfaces between ENMs and biological receptors • Biomarkers of toxicological response
RN#5: Develop measurement tools for evaluation of release mechanisms of ENMs from NEPs in relevant media and during the life cycles of NEPs	• Release by fire, combustion, and incineration • Release by mechanical degradation, such as abrasion, deformation, and impact • Release by dissolution of matrix material • Release by chemical reactions of the matrix material • Release by photo-induced degradation of the matrix material • Release by consumer interactions, such as spraying, mouthing, and swallowing • Release by interactions with biological organisms in the environment
2. Human Exposure Assessment Research Needs Identify potential sources, characterize the exposure scenarios, and quantify actual exposures of workers, the general public, and consumers to nanomaterials. Characterize and identify the health outcomes among exposed populations in conjunction with information about the control strategies used and exposures to determine practices that result in safe levels of exposures.	
RN#1. Understand processes and factors that determine exposures to nanomaterials	• Conduct studies to understand processes and factors that determine exposure to engineered nanomaterials • Develop exposure classifications of nanomaterials and processes • Develop internationally harmonized and validated protocols for exposure surveys, sample collection and analysis, and reporting through existing and newly created international frameworks • Develop comprehensive predictive models for exposures to a broad range of engineered nanomaterials and processes • Characterize process- and task-specific exposure scenarios in the workplace
RN#2. Identify population groups exposed to engineered nanomaterials	• Systematically collect and analyze information about nanomaterial manufacture, processing, and direct use in commercial and consumer products over time to discern geographic areas where engineered nanomaterials may be emitted into the environment, consumed in the form of ingredients of products, and/or disposed of in solid waste, wastewater, etc. • Conduct population-based surveys to obtain information on use patterns for consumer products • Identify potential subpopulations that are more susceptible to exposure to engineered nanomaterials than others • Develop quantitative assessment methods appropriate for target population groups and conduct assessments of those population groups most likely to be exposed to engineered nanomaterials

Key Research Needs	Subordinate Research Needs
RN#3. Characterize individual exposures to nanomaterials	• Expand currently available exposure assessment techniques to facilitate more accurate exposure assessment for engineered nanomaterials at benchmark concentration levels using feasible methods • Develop new tools through national and international surveys to support effective exposure characterization of individuals • Characterize and detect nanomaterials in biological matrices and conduct studies to understand transformations of nanomaterials during transport in the environment and in human bodies • Conduct studies to examine emissions and human contact during normal use and after wear and tear have degraded a product, as well as during repeated exposures • Develop engineered nanomaterials exposure assessment models based on identified critical exposure descriptors • Develop databases to contain the collected data and information
RN#4. Conduct health surveillance of exposed populations	• Establish a program for the epidemiological investigation of physician case reports and reports of suspicious patterns of adverse events • Establish exposure registry and medical surveillance programs for workers • Analyze injury and illness reporting in existing programs
3. Human Health Research Needs Understand the relationship of physico-chemical properties of engineered nanoscale materials to *in vivo* physico-chemical properties and biological response. Develop high-confidence predictive models of *in vivo* biological responses and causal physico-chemical properties of ENMs.	
RN#1. Identify or develop appropriate, reliable, and reproducible *in vitro* and *in vivo* assays and models to predict *in vivo* human responses to ENMs	• Establish a system to develop and apply reliable and reproducible *in vitro* and *in vivo* test methods • Evaluate the degree to which an *in vitro* response correlates with an *in vivo* response • Evaluate the degree to which *in vitro* and *in vivo* models predict human response • Translate structure-activity relationship and other research data into computational models to predict toxicity *in silico*
RN#2. Quantify and characterize ENMs in exposure matrices and biological matrices	• Determine critical ENM measurands in biological and environmental matrices and ensure the development of tools to measure ENMs in appropriate matrices as needed • Determine matrix and/or weathering effects that may alter the physico-chemical characteristics of the ENM measurands • Identify key factors that may influence the detection of each measurand in a particular matrix (e.g., sample preparation, detection method, storage, temperature, solvents/solutions) • Characterize and quantify exposure for all exposure routes using *in vivo* models to identify the most likely routes of human exposure • Identify biomarkers of exposure and analytical methods for their determination

Key Research Needs	Subordinate Research Needs
RN#3. Understand the relationship between the physico-chemical properties of ENMs and their transport, distribution, metabolism, excretion, and body burden in the human body	• Characterize ENM physico-chemical properties and link to mechanisms of transport and distribution in the human body • Understand the relationship of the physico-chemical properties of ENMs to the mechanisms of sequestration in and translocation of ENMs out of the exposure organ and secondary organs, and to routes of excretion from the human body • Determine the metabolism or biological transformation of ENMs in the human body
RN#4. Understand the relationship between the physico-chemical properties of ENMs and uptake through the human port-of-entry tissues	• Characterize ENMs at and in port-of-entry tissues, including nontraditional routes of entry such as the ear and eye, and identify mechanisms of ENM uptake into tissues • Determine the relationship of ENM physico-chemical properties to deposition and uptake under acute exposure conditions and under chronic exposure conditions • Translate data on ENM properties and uptake to knowledge that may be used to intentionally redesign ENMs for optimum human and environmental safety and product efficacy
RN#5. Determine the modes of action underlying the human biological response to ENMs at the molecular, cellular, tissue, organ, and whole body levels	• Determine the dose response and time course of biological responses at the primary site of exposure and at distal organs following ENM exposure • Understand the mechanisms and molecular pathway(s) associated with ENM biology within cellular, organ, and whole organism systems • Link mechanisms of response with ENM physico-chemical properties and employ this information in the design and development of future ENMs • Develop translational alternative *in vitro* testing methods for the rapid screening of future ENMs based on mechanism(s) of response that are predictive of *in vivo* biological responses
RN#6. Determine the extent to which life stage and/or susceptibility factors modulate health effects associated with exposure to ENMs and nanotechnology-enabled products and applications	• Determine the effect of life stage and/or gender on biological response to ENMs • Establish the role of genetic and epigenetic susceptibility on the biological response to ENMs in the context of life stage and/or susceptibility factors • Understand mechanistically the influence of preexisting disease on the biological response to ENMs in the context of life stage and other susceptibility factors • Identify exposure conditions that make susceptible individuals more vulnerable to the health effects associated with ENMs and nanotechnology-enabled applications • Establish a database that contains published, peer-reviewed literature, occupational and consumer reports, and toxicological profiles that describe altered responses to ENMs and nanotechnology-enabled applications in susceptible animal models or individuals following exposure

Key Research Needs	Subordinate Research Needs
4. Environment Research Needs Understand the environmental fate, exposure, and ecological effects of engineered nanomaterials, with priority placed on materials with highest potential for release, exposure, and/or hazard to the environment.	
RN#1. Understand environmental exposures through the identification of principal sources of exposure and exposure routes	• Manufacturing processes and product incorporation • Life cycle of technology and exposures subsequent to product manufacturing • Analytical approaches to measure temporal changes in nanoparticle properties throughout the life cycle • Models to estimate releases • Environmental receptors for exposure assessment
RN#2. Determine factors affecting the environmental transport of nanomaterials	• Determine key physico-chemical properties affecting transport • Determine key transport and fate processes relevant to environmental media • Develop new tools and adaptation of current predictive tools to accommodate unique properties of nanomaterials
RN#3. Understand the transformation of nanomaterials under different environmental conditions	• Identify and evaluate nanomaterial properties and transformation processes that will reduce environmental persistence, toxicity, and production of toxic products • Determine the rate of aggregation and long-term stability of agglomeration/aggregation and the long-term stability of these aggregates and agglomerates. • Develop tools to predict the transformations or degradability of nanomaterials
RN#4. Understand the effects of engineered nanomaterials on individuals of a species and the applicability of testing schemes to measure effects	• Test protocols • Dose-response characterization • Uptake/elimination kinetics, tissue / organ distribution • Mode/mechanism of action, predictive tools • Tiered testing schemes / environmental realism
RN#5. Evaluate the effects of engineered nanomaterials at the population, community, and ecosystem levels	• Population • Community • Other ecosystem-level effects • Predictive tools for population-, community-, and ecosystem-level effects

Key Research Needs	Subordinate Research Needs
5. Risk Assessment and Risk Management Methods Research Needs Increase available information for better decision making in assessing and managing risks from nanomaterials, including using comparative risk assessment and decision analysis; life cycle considerations; and additional perspectives such as ELSI considerations, stakeholders' values, and additional decision makers' considerations.	
RN#1. Incorporate relevant risk characterization information, hazard identification, exposure science, and risk modeling and methods into the safety evaluation of nanomaterials	• Characterization, fate, and release of nanoparticles throughout the life cycles of nanotechnology-enabled products • Development of predictive models on accumulation, migration, and release of nanoparticles throughout the life cycles of nanotechnology-enabled products • Safety of nanoparticles throughout the life cycles of the nanotechnology-enabled products • Comprehensive and predictive models to assess the potential risks of nanoparticles during the manufacturing and life cycle of nanoproducts, with inputs from human and environment exposures and on nanomaterial properties
RN#2. Understand, characterize, and control workplace exposures to nanomaterials	• Dissemination and implementation of effective techniques and protocols to measure exposures in the workplace • Identification and demonstration of effective containment and control technologies including for accidents and spills • Development of an effective industry surveillance system • Design and deployment of a prospective epidemiological framework relevant to exposure science • Systematic approaches for occupational risk modeling
RN#3. Integrate life cycle considerations into risk assessment	• Establishment of nanotechnology-specific taxonomy for life cycle stages • Integration of risk assessment, life cycle analyses, and decision-making approaches into regulatory decision making processes • Application of adaptive management tools based on monitoring/implementation to evaluate life cycle analysis implementation • Development of case studies, e.g., green chemistry, nanomaterials selection, nanomaterials acquisition process, illustrating application of these risk management methods
RN#4. Integrate risk assessment into decision-making frameworks for risk management	• Development of comparative risk assessment and formal decision-analytical methods as opposed to "absolute" risk assessment strategies • Application of formal decision-analytical methods to prioritize risk management alternatives • Use of gap analyses and value of information analysis to identify research needs • Integration of stakeholder values and risk perceptions into risk management processes • Application of integrated decision framework through case studies in risk management decision making

Key Research Needs	Subordinate Research Needs
RN#5. Integrate and standardize risk communication within the risk management framework	• Development and use of standardized terminology in risk communications • Early information-sharing on hazards and risk among Federal agencies • Development of appropriate risk communication approaches for agency-specific needs
Informatics and Modeling Research Need	
RN#1. Develop computational models of ENM structure-property-activity relationships to support the design and development of ENM with maximum benefit and minimum risk to humans and the environment	• Validate the predictive capability of *in vitro* and *in vivo* assays and employ that subset of assays in data generation to establish computational models to predict ENM behavior in humans and the environment • Establish a standard set of physical and chemical characterization parameters, dose metrics, and biological response metrics • Design and establish structures and ontologies for methods development, data capture, sharing, and analysis • Evaluate and adapt as necessary existing computational models by beginning with existing models for exposure and dosimetry and using data generated from validated assays • Use ENM exposure and dosimetry models to develop ENM structure-activity models to predict ENM behavior in humans and the environment • Establish training sets and beta test sites to refine and validate ENM structure–activity models • Disseminate ENM structure-activity models through publicly accessible nano-technology websites

Appendix E. Glossary

ADME	absorption, distribution, metabolism, and excretion (toxicity parameters)
ARRA	American Recovery and Reinvestment Act
CEIN	Center for the Environmental Implications of Nanotechnology at UCLA
CEINT	Center for the Environmental Implications of Nanotechnology at Duke University
CINT	Center for Integrated Nanotechnologies at Sandia and Los Alamos National Laboratories
CNST	Center for Nanoscale Science and Technology (NIST)
CPSC	Consumer Product Safety Commission
CSN	Collaboratory for Structural Nanobiology
DHS	Department of Homeland Security
DHHS	Department of Health and Human Services
DNI	Director of National Intelligence
DOC	Department of Commerce
DOD	Department of Defense
DOE	Department of Energy
DOEd	Department of Education
DOJ	Department of Justice
DOL	Department of Labor
DOS	Department of State
DOT	Department of Transportation
EC	European Commission
EHS	environment(al), health, and safety (aspects of nanotechnology)
ELSI	ethical, legal, and social implications (of nanotechnology)
ENM	engineered nanomaterial
EOP	Executive Office of the President
EPA	Environmental Protection Agency
FAS	Foreign Agricultural Service (USDA)
FDA	Food and Drug Administration (DHHS)

FHWA	Federal Highway Administration (DOT)
FS	Forest Service (USDA)
GAO	Government Accountability Office
ILS	interlaboratory studies
IMA	Instrumentation, Metrology, and Analytical Methods (2008 research category)
ISO	International Standards Organization
nanoEHS	environment(al), health, and safety aspects of nanotechnology
NA	National Academies
NASA	National Aeronautics and Space Administration
NCI	National Cancer Institute (DHHS/NIH)
NCN	Network for Computational Nanotechnology
NEHI	Nanotechnology Environmental and Health Implications Working Group (NSET)
NEP	nanotechnology-enabled product
NIEHS	National Institute of Environmental Health Sciences (DHHS/NIH)
NIBIB	National Institute of Biomedical Imaging and Bioengineering (NIH)
NIFA	National Institute of Food and Agriculture (USDA)
NIH	National Institutes of Health (DHHS)
NIOSH	National Institute for Occupational Safety and Health (DHHS/CDC)
NIST	National Institute of Standards and Technology (DOC)
NM	nanomaterial
NMI	Nanomaterial Measurement Infrastructure (2011 Research Need category)
NNAP	National Nanotechnology Advisory Panel (designated as PCAST)
NNCO	National Nanotechnology Coordination Office
NNI	National Nanotechnology Initiative
NSE	nanoscale science and engineering
NSET	Nanoscale Science, Engineering, and Technology Subcommittee of the NSTC Committee on Technology
NSF	National Science Foundation
NSTC	National Science and Technology Council
OECD	Organisation for Economic Co-operation and Development

OMB	Office of Management and Budget (Executive Office of the President)
OSHA	Occupational Safety and Health Administration (DOL)
OSTP	Office of Science and Technology Policy (Executive Office of the President)
PBZ	personal breathing-zone
PCAST	President's Council of Advisors on Science and Technology
ppb	parts per billion
R&D	research and development
RA	risk assessment
RAMM	Risk Assessment and Management Methods (2011 Research Need Category)
RM	reference material (see also SRM)
RMM	risk management methods
SRM	standard reference material
TEM	transmission electron microscope/y
UNEP	United Nations Environment Programme
USPTO	U.S. Patent and Trademark Office (DOC)
USDA	U.S. Department of Agriculture

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

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