Review of Federal Strategy for Nanotechnology-Related Environmental, Health, and Safety Research

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Review of the Federal Strategy for Nanotechnology-Related Environmental, Health, and Safety Research

Committee for Review of the Federal Strategy to Address Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials

Board on Environmental Studies and Toxicology

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Preface

Nanotechnology relies on the ability to engineer, manipulate, and manufacture materials at the nanoscale. Nanotechnology is already enabling the development of an industry that produces and uses engineered nanomaterials in a wide variety of industrial and consumer products. The increasing use of nanomaterials in industrial and consumer products will result in greater exposure of workers and the general public to engineered nanoscale materials.

The U.S. National Nanotechnology Initiative (NNI) is the central locus for the coordination of federal agency investments in nanoscale research and development. In 2007, the National Nanotechnology Coordination Office, which oversees the operation of NNI, asked the National Research Council to review its publication *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research*. The National Research Council's Board on Environmental Studies and Toxicology and National Materials Advisory Board convened the Committee for Review of the Federal Strategy to Address Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials, which produced this report. The committee was composed of members with expertise in nanotechnology, nanomaterials, metrology, toxicology, risk assessment, exposure assessment, ecotoxicology, occupational and public health, and risk management.

The committee was asked to conduct a scientific and technical review of the federal strategy. The committee considered the elements of an effective nanotechnology risk-research strategy, evaluated whether the federal strategy has these elements, and assessed how the research identified in the strategy will support risk-assessment and risk-management needs. To assist its task, the committee held two workshops at which it heard from representatives of NNI agencies, policy experts from the European Commission, and such stakeholders as manufacturing industry, nongovernment organizations, and the insurance sector.

This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that

will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following for their review of this report: David E. Aspnes, North Carolina State University; Chris G. Whipple, ENVIRON International Corporation; Richard A. Denison, Environmental Defense Fund; William H. Farland, Colorado State University; Richard A.L. Jones, University of Sheffield; Gregory V. Lowry, Carnegie Mellon University; David Y. Pui, University of Minnesota; Ronald F. Turco, Purdue University; Mark J. Utell, University of Rochester School of Medicine and Dentistry; David B. Warheit, DuPont Haskell Laboratory.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of the report was overseen by the review coordinator, Richard Schlesinger, Pace University, and the review monitor, Elsa Garmire, Dartmouth College. Appointed by the National Research Council, they were responsible for making certain that an independent examination of the report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of the report rests entirely with the committee and the institution.

The committee gratefully acknowledges the following for their presentations: Pilar Aguar, European Commission; Norris Alderson, U.S. Food and Drug Administration; Carolyn Cairns, Consumers Union; Richard Canady, U.S. Food and Drug Administration; Altaf Carim, U.S. Department of Energy; Thomas Epprecht, Swiss Re; William Gulledge, American Chemistry Council; Michael Holman, Lux Research; William Kojola, AFL-CIO; Philippe Martin, European Commission; Terry Medley, DuPont; Jeffrey Morris, U.S. Environmental Protection Agency; Vladimir Murashov, National Institute for Occupational Safety and Health; Dianne Poster, National Institute of Standards and Technology; William Rees, U.S. Department of Defense; Mihail Roco, National Science Foundation; Jennifer Sass, National Resources Defense Council; Phillip Sayre, U.S. Environmental Protection Agency; Paul Schulte, National Institute for Occupational Safety and Health; Clayton Teague, National Nanotechnology Coordination Office; and Sally Tinkle, National Institute of Environmental Health Sciences.

The committee is also grateful for the assistance of the National Research Council staff in preparing this report. Staff members who contributed to the effort are Eileen Abt, project director; Michael Moloney, senior program officer; James Reisa, director of the Board on Environmental Studies and Toxicology; Heidi Murray-Smith, research associate; Norman Grossblatt, senior editor; Mirsada Karalic-Loncarevic, manager, technical information center; and Panola Golson, senior program assistant.

We would especially like to thank the committee members for their efforts throughout the development of this report.

David L. Eaton, *Chair*
Martin A. Philbert, *Vice Chair*
Committee for Review of the Federal Strategy to
Address Environmental, Health, and Safety Research
Needs for Engineered Nanoscale Materials

Abbreviations

ADME	absorption, distribution, metabolism, elimination
AEC	Atomic Energy Commission
CSREES	Cooperative State Research, Education, and Extension Service
CST	UK Council for Science and Technology
DHS	Department of Homeland Security
DHHS	Department of Health and Human Services
DOC	Department of Commerce
DOD	Department of Defense
DOE	Department of Energy
DOJ	Department of Justice
DOT	Department of Transportation
EC	European Commission
EHS	environmental, health, and safety
EPA	U.S. Environmental Protection Agency
EU	European Union
FDA	Food and Drug Administration
FHWA	Federal Highway Administration
FS	Forest Service
FY	fiscal year
GIN	Global Issues in Nanotechnology Working Group
ICON	International Council on Nanotechnology
IWGN	Interagency Working Group on Nanotechnology
NASA	National Aeronautics and Space Administration
NEHI	Nanotechnology Environmental Health Implications
NIH	National Institutes of Health
NILI	Nanomanufacturing Industry Liaison and Innovation Working Group
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
NNCO	National Nanotechnology Coordination Office
NNI	U.S. National Nanotechnology Initiative
NORA	National Occupational Research Agenda

NPEC	National Public Engagement and Communications Working Group
NRC	National Research Council
NRC	Nuclear Regulatory Commission
NSET	Nanoscale Science, Engineering, and Technology subcommittee
NSF	National Science Foundation
NSTC	National Science and Technology Council
OECD	Organization for Economic Co-operation and Development
OMB	Office of Management and Budget
OSTP	Office of Science and Technology Policy
PART	Program Assessment Rating Tool
PCA	program component area
PCAST	President's Council of Advisors on Science and Technology
QSAR	quantitative structure–activity relationship
R&D	research and development
SCENIHR	Scientific Committee on Emerging and Newly-Identified Health Risks
USDA	U.S. Department of Agriculture
VOI	Value of Information
WPMN	Working Party on Manufactured Nanomaterials

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Summary

The field of nanotechnology relies on the ability to engineer, manipulate, and manufacture materials at the nanoscale.[1] Nanotechnology is already enabling the development of an industry that produces and uses engineered nanomaterials in a wide variety of industrial and consumer products, such as targeted drugs, video displays, remediation of groundwater contaminants, high performance batteries, dirt-repelling coatings on building surfaces and clothing, high-end sporting goods, and skin-care products. Over the next five to ten years, increasingly widespread use of complex engineered nanomaterials is anticipated in such products as medical treatments, super-strong lightweight materials, food additives, and advanced electronics. The increasing use of engineered nanoscale materials in industrial and consumer products will result in greater exposure of workers and the general public to these materials. Responsible development of nanotechnology implies a commitment to develop and to use these materials to meet human and societal needs while making every reasonable effort to anticipate and mitigate adverse effects and unintended consequences.

The U.S. National Nanotechnology Initiative (NNI) is the government's central locus for the coordination of federal agency investments in nanoscale research and development. NNI is responsible for supporting the missions of its member research and regulatory agencies; ensuring U.S. leadership in nanoscale science, engineering, and technology; and contributing to the nation's economic competitiveness. Within NNI, the Nanotechnology Environmental Health Implications (NEHI) Working Group provides a forum for the NNI agencies to coordinate their activities related to understanding the potential risks posed by nanotechnology to protect public health and the environment.[2] The NEHI's co-

[1]Nanoscale refers to materials on the order of one billionth of a meter.

[2]Current members of NEHI consists of officials from the Consumer Product Safety Commission, Cooperative State Research, Education, and Extension Service, Department

ordination efforts have produced a series of documents that identify environmental, health, and safety (EHS) research needs related to nanomaterials (NEHI 2006, 2007, 2008).[3]

In 2007, the National Nanotechnology Coordination Office, which oversees the day-to-day operations of the NNI, asked the National Research Council to review independently its *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* (NEHI 2008). In response, the National Research Council's Board on Environmental Studies and Toxicology and National Materials Advisory Board oversaw the appointment of the Committee for Review of the Federal Strategy to Address Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials, which produced this report. The committee was charged to conduct a scientific and technical review of the federal strategy and to comment in general terms on how the strategy develops information needed to support EHS risk-assessment and risk-management needs with respect to nanomaterials.

Assisted by information-gathering sessions that included representatives from NNI agencies, policy experts from the European Commission, and such stakeholders as manufacturing industry, nongovernment organizations, and the insurance sector, the committee evaluated the federal strategy, asking such questions as the following:

- What are the elements of an effective nanotechnology risk-research strategy?
- Does the federal strategy have those elements?
- With respect to the federal strategy, have the appropriate research needs been identified, are the gap analysis and the selection of priorities among research needs complete, and does the research identified support risk-assessment and risk-management needs?

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of Defense, Department of Energy, Department of State, Department of Transportation, Environmental Protection Agency, Food and Drug Administration, International Trade Commission, National Aeronautics and Space Administration, National Institute for Occupational Safety and Health, National Institutes of Health, National Institute of Standards and Technology, National Science Foundation, Occupational Safety and Health Administration, Office of Science and Technology Policy, Office of Management and Budget, and U.S. Geological Survey.

[3]NEHI (Nanotechnology Environmental Health Implications Working Group). 2006. Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials. Arlington, VA: National Nanotechnology Coordination Office; NEHI (Nanotechnology Environmental Health Implications Working Group). 2007. Prioritization of Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials: An Interim Document for Public Comment. Arlington, VA: National Nanotechnology Coordination Office; NEHI (Nanotechnology Environmental Health Implications Working Group). 2008. Strategy for Nanotechnology-Related Environmental, Health, and Safety Research. Arlington, VA: National Nanotechnology Coordination Office.

WHAT ARE THE ELEMENTS OF AN EFFECTIVE NANOTECHNOLOGY RISK-RESEARCH STRATEGY?

Strategies for conducting scientific research are particularly important when resources are limited and there is a need to ensure that relevant information is being generated as efficiently and cost-effectively as possible. A strategy generally defines a set of goals, often in the context of an overarching vision; a plan of action for achieving the goals; and milestones to indicate when the goals are expected to be achieved. Because scientific research is often open-ended and serendipitous, formulating goals can be difficult.

One specific type of research strategy—a strategy for risk research—addresses challenges of broad societal significance: the reduction or prevention of harm to humans and the environment. Because of their potential influence on public-health and environmental policy and actions, it is critical that risk-research strategies be developed and implemented effectively and in a timely manner. And like any other risk-research strategy, one focused on nanotechnology-related risk research needs to be proactive—identifying possible risks and ways to mitigate risks before the technology has widespread commercial presence. It has to address nanotechnology-based products that are beginning to enter commerce as well as those under development. But it also needs to lay the scientific groundwork for addressing materials and products that potentially will arise out of new research, new tools, and cross-fertilization between distinct fields of science and technology. Therefore, a nanotechnology-related risk-research strategy must rely on both targeted research, which addresses questions that are critical for ensuring the safety of nanomaterials and products that contain them, and exploratory research, which generates new knowledge that will inform future goals and research directions.

In conducting this study, the committee identified nine elements that are integral to any effective risk-research strategy and that informed its evaluation of the 2008 NNI document:

- *Vision, or statement of purpose*. What is the ultimate purpose of conducting research on potential risks associated with nanotechnology?
- *Goals*. What specific research goals need to be achieved to guide the development and implementation of nanotechnologies that are as safe as possible?
- *Evaluation of the state of science*. What is known about the potential for the products of nanotechnology to cause harm and about how possible risks might be managed?
- *Road map*. What is the plan of action to achieve the stated research goals?
- *Evaluation*. How will research progress be measured, and who will be responsible for measuring it? Are there measurable milestones that can be evaluated against a clear timeline?

- *Review*. How will the strategy be revised in light of new findings, to ensure that it remains responsive to the overarching vision and goals?
- *Resources*. Are there sufficient resources to achieve the stated goals? If not, what are the plans to obtain new resources or to leverage other initiatives to achieve the goals?
- *Mechanisms*. What are the most effective approaches to achieving the stated goals?
- *Accountability*. How will stakeholders participate in the process of developing and evaluating a research strategy? Who will be accountable for progress toward stated goals?

DOES THE FEDERAL STRATEGY HAVE THOSE ELEMENTS?

On the basis of the information gathered at its public meetings and the professional expertise and experience of its members, the committee determined that the process of composing the government's 2008 NNI document provided a unique and useful opportunity for coordination, planning, and consensus-building among NEHI-member federal agencies. The strategy demonstrates how the NNI and the agencies have effectively worked together to coordinate their funding and their assessment of EHS aspects of nanotechnology.

However, NNI (NEHI 2008) does not have the essential elements of a research strategy—it does not present a vision, contain a clear set of goals, have a plan of action for how the goals are to be achieved, or describe mechanisms to review and evaluate funded research and assess whether progress has been achieved in the context of what we know about the potential EHS risks posed by nanotechnology.

The NNI document contains various statements of purpose, but it does not provide a clear vision as to where our understanding of the EHS implications of nanotechnology should be in 5 or 10 years. It states that "the NEHI Working Group developed this nanotechnology-related EHS research strategy to accelerate progress in research to protect public health and the environment, and to fill gaps in, and—with the growing level of effort worldwide—to avoid unnecessary duplication of, such research" (NEHI 2008, p. 1). That statement of purpose is adequate for an open-ended research program with no definite objectives, but it falls short of ensuring that the results of strategic research are useful and applicable to decision-making that will reduce the potential environmental and health effects of nanotechnology.

The strategy document does not present goals for research to help ensure that the development and implementation of nanotechnology is as safe as practicable or a road map to ensure that these research goals are achieved. Although the document identifies five "research needs" for each of five research categories—"Instrumentation, Metrology, and Analytical Methods," "Nanomaterials and Human Health," "Nanomaterials and the Environment," "Human and Environmental Exposure Assessment," and "Risk Management Methods"—the needs

are not articulated as clear goals that should be attained. A key element of any strategy is to identify goals and measures of progress or success before assessing what is being done. That allows a clear assessment of the value of current activities. Such an approach enables development of an action plan to leverage other efforts and address research deficiencies in a way that is transparent and measurable. Because the NNI document does not establish goals and a plan of action, there is no element of accountability, and questions are never raised as to what other research activities are needed.

The NNI document does not provide an evaluation of the state of science in each of the five research categories; rather, the research needs are evaluated against research projects that were funded in FY 2006 (see Appendix A of NEHI [2008]) to provide a "snapshot" of research activities. The 2008 NNI document uses the FY 2006 data to assess the extent to which federally funded EHS research related to nanomaterials is supporting selected research priorities and to conduct its gap analysis of the NNI research portfolio. The committee concludes that how the FY 2006 data were used in the analysis is probably the greatest deficiency in the 2008 document, inasmuch as it is the foundation of the document's evaluation of the strengths, weaknesses, and gaps in currently funded federal research. This is problematic because most of the listed FY 2006 research projects were focused on understanding fundamentals of nanoscience that are not explicitly associated with risk or the development of nanotechnology applications.[4] In addition, there is no clear statement of how the FY 2006 research projects would address the identified research needs and inform an understanding of potential human health and environmental risks posed by engineered nanoscale materials.

The 2008 document does provide some information on time frame and sequencing for achieving the research needs (see Figures 3, 5, 7, 9, and 11 of NNI [NEHI 2008]) but with little justification.

The NNI strategy does not identify resources necessary to address questions concerning EHS research needs for nanomaterials. Although the detailed analysis of nanotechnology-related EHS expenditures in FY 2006 provides information about what was spent during that year, there is no assessment of whether the aggregate level of spending was adequate to address EHS research needs or whether the resource expenditures by the agencies were appropriate to address EHS research needs based on their missions. An appropriate research strategy would quantify the resources needed to address research priorities and describe where the resources would come from.

[4]The 246 FY 2006 research projects listed in NNI (NEHI 2008) include additional research on instrumentation and metrology research and on medical-application-oriented research that is not captured in the list of 130 EHS research projects in the annual supplement to the president's budget. The committee's own assessment of the number of FY2006 research projects that are relevant to understanding risk of nanomaterials is discussed in Chapter 4.

Although lead agencies (for example, NIH, NIST, EPA, FDA, and NIOSH) are given roles for overseeing federal nanotechnology research, there is no accountability, that is, there is no single organization or person that will be held accountable for whether the government's overall strategy delivers results. Accountability requires specific quantifiable objectives so that one can determine whether adequate progress is being made. The 2008 NNI document does not adequately incorporate input from other stakeholders, such as industries that produce nanomaterials and end users of nanomaterials; environmental and consumer advocacy groups; foreign interests, including substantial efforts of other countries; and local and state governments. The committee recognizes that the 2006 and 2007 NNI reports have undergone public comment, but public comment is not the same as engaging stakeholders in the process.

Without adequate input from external stakeholders, it is not possible for government agencies to develop an effective research strategy to underpin the emergence of safe nanotechnologies. Federal agencies may have a vested interest in justifying the value of current efforts rather than critically assessing what is being done and how deficiencies might be addressed. For example, when developing their own research strategies, agencies tend to ask, What research can we do within our existing capabilities?, rather than the more appropriate question, What research should we be doing?

REVIEW OF PRIORITY RESEARCH TOPICS, RESEARCH NEEDS, AND GAP ANALYSIS

The committee reviewed the specific research categories and their designated research needs as described in the 2008 NNI document (Section II) and considered the following questions: Were the appropriate research needs identified? Were the gap analysis and priority sequencing of research needs complete? Does the identified research support risk-assessment and risk-management needs?

The NNI's five topical categories each address research that is important for EHS risk assessment and risk management, and collectively they cover the necessary broad research topics. The listed research needs in the five categories are similarly valuable but incomplete, in some cases missing elements crucial for progress in understanding the EHS implications of nanomaterials. For example, the subject of environmental exposure received insufficient emphasis in the exposure-assessment discussion, and characterization of chemical and biologic reactivity of nanoparticles was not included as a research need. That appears to have resulted from an effort to place research needs into one of the five "silo" categories with little discussion of the interrelationships and interconnections among categories.

The committee notes examples of other research needs that it judged to be insufficiently addressed in the document. For "Nanomaterials and Human Health," a more comprehensive analysis and evaluation of absorption, distribu-

tion, metabolism, elimination, and toxicity of engineered nanomaterials at realistic exposure levels is needed. For "Human and Environmental Exposure," exposures throughout the life cycle of nanomaterials was not sufficiently introduced or adequately integrated into this section, although a discussion was contained within "Risk Management Methods."

The NNI's gap analysis is not accurate in that the relevance of FY 2006 research projects to the research needs is generally overstated. The 2008 document consistently—in every research category—appears to assume that funded projects with only distant links to a research question were meeting that research need. In the "Nanomaterials and Human Health" category, more than 50% of the inventoried projects describe research directly relevant to developing therapeutic strategies aimed at cancer and other ailments rather than any of the research needs listed as relevant to potential EHS risks posed by nanomaterials. The committee acknowledges the value of therapeutic research but believes that it is not directly relevant to understanding potential risks associated with nanomaterials that are important in occupational, environmental, and ecologic exposure scenarios. In the category of risk-management methods, there is no coverage of management of environmental and consumer risks, including specific potential exposure scenarios, such as accidents and spills, environmental discharges, and exposure through consumer products. Uniformly, the committee agreed that many of the 246 research projects listed in Appendix A are of high scientific value, but the vast majority are of little or no direct value in reducing the uncertainty faced by stakeholders making decisions about nanotechnology and its risk-management practices. The 2008 document substantially overestimates the general nanotechnology-related research activity in environmental, health, and safety research.

In many cases, the committee concluded that the sequencing of research needs was generally appropriate but not adequately justified. In a number of cases the committee questioned the rationale for a sequence. For example, in the "Instrumentation, Metrology, and Analytical Methods" category, why put the development of materials to support exposure assessment before materials to support toxicology studies? Why delay research into alternative surface-area measurement methods for 10 years if it is identified as a critical research subject? In the "Nanomaterials and the Environment" category, the committee questioned whether resources could be used more efficiently through the characterization of exposure and transformation processes prior to characterization of organisms as well as higher-level ecosystem effects.

Although many of the NNI's identified research needs support risk-assessment and risk-management needs, the committee concluded that failure to identify important research needs, the lack of rationale for and discussion of research priorities, and the flaws in the gap analysis undermine the ability to ensure that currently funded research adequately supports EHS risk-assessment and risk-management needs and provides critical data for the federal agencies.

CONCLUSIONS AND RECOMMENDATIONS

The NNI's 2008 *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* could be an effective tool for communicating the breadth of federally supported research associated with developing a more complete understanding of the environmental, health, and safety implications of nanotechnology. It is the result of considerable collaboration and coordination among 18 federal agencies and is likely to eliminate unnecessary duplication of their research efforts. However, the document does not describe a strategy for nano-risk research. It lacks input from a diverse stakeholder group, and it lacks essential elements, such as a vision and a clear set of objectives, a comprehensive assessment of the state of the science, a plan or road map that describes how research progress will be measured, and the estimated resources required to conduct such research.

There remains an urgent need for the nation to build on the current research base related to the EHS implications of nanotechnology—including the federally supported research as described in the 2008 NNI document—by developing a national strategic plan for nanotechnology-related environmental, health, and safety research.

A national strategic plan for nanotechnology-related EHS research would identify research needs clearly and estimate the financial and technical resources required to address identified research gaps. It would also provide specific, measurable objectives and a timeline for meeting them. The national strategic plan, unlike the 2008 NNI document, would consider the untapped knowledge of and input from nongovernment researchers and academics, who can contribute to understanding the potential EHS implications of nanotechnology.

Reducing the burden of uncertainty through targeted, effective research that identifies and eliminates potential environmental and health hazards of engineered nanoscale materials should have high priority for the nation. An effective national EHS strategic research plan is essential to the successful development of and public acceptance of nanotechnology-enabled products. This strategy should be informed by value-of-information thinking to determine the research that is needed to reduce the current uncertainties with respect to the potential health and environmental effects of nanomaterials. A national strategic plan would need to address nanotechnology-based products that are entering commerce as well as nanotechnologies that are under development. It would provide a path to developing the scientific knowledge to support nanotechnology-related EHS risk-based decision-making.

The committee concludes that a truly national strategy cannot be developed within the limitations of the scope of research under the umbrella of the NNI. Although the 2008 NNI document potentially represents excellent input into the national strategic plan, the NNI can produce only a strategy that is the

sum of the individual agency strategies and priorities. The structure of the NNI makes the development of a visionary and authoritative research strategy extraordinarily difficult. Because the NNI is not a research funding program but rather a coordination mechanism, comprising the activities of 25 federal agencies, it has no central authority to make budgetary or funding decisions, and it relies on the budgets of its member agencies to gather resources or influence the shape of the overall federal nanotechnology-related EHS research activity. Because the NNI is responsible for ensuring U.S. competitiveness through the rapid development of a robust research and development program in nanotechnology while ensuring the safe and responsible development of nanotechnology, it may be perceived as having a conflict of interest. But the conflict is a false dichotomy. Strategic research on potential risks posed by nanotechnology should be an integral and fundamental part of the sustainable development of nanotechnology. Nonetheless, a clear separation of accountability for development of applications and assessment of potential implications of nanotechnology would help to ensure that the public-health mission has appropriate priority.

The committee is concerned that the actual amount of federal funding specifically addressing the EHS risks posed by nanotechnology is far less than portrayed in the NNI document and may be inadequate. The committee concludes that if no new resources are provided and the current levels of agency funding continue, the research that is generated cannot adequately evaluate the potential health and environmental risks and effects associated with engineered nanomaterials to address the uncertainties in current understanding. Such an evaluation is critical for ensuring that the future of nanotechnology is not burdened by uncertainties and innuendo about potential adverse health and environmental effects. Those concerns have been voiced recently by the nanotechnology industry and various environmental and public-health interest groups.

Having reviewed the 2008 NNI strategy document and discussed what is needed for a path forward, the committee presents the following recommendations:

A robust national strategic plan is needed for nanotechnology-related environmental, health, and safety research that builds on the five categories of research needs identified in the 2008 NNI document. The development of the plan should include input from a broad set of stakeholders across the research community and other interested parties in government, nongovernment, and industrial groups. The strategy should focus on research to support risk assessment and management, should include value-of-information considerations, and should identify

- **Specific research needs for the future in such topics as potential exposures to engineered nanomaterials, toxicity, toxicokinetics, environmental fate, and standardization of testing.**
- **The current state of knowledge in each specific area.**

- **The gap between the knowledge at hand and the knowledge needed.**
- **Research priorities for understanding life-cycle risks to humans and the environment.**
- **The estimated resources that would be needed to address the gap over a specified time frame.**

As part of a broader strategic plan, NNI should continue to foster the successful interagency coordination effort that led to its 2008 document with the aim of ensuring that the federal plan is an integral part of the broader national strategic plan for investments in nanotechnology-related environmental, health, and safety research. In doing so, it will need a more robust gap analysis. The federal plan should identify milestones and mechanisms to ascertain progress and identify investment strategies for each agency. Such a federal plan could feed into a national strategic plan but would not itself be a broad, multistakeholder national strategic plan. Development of a national strategic plan should begin immediately and not await further refinement of the current federal strategy.

CONCLUDING REMARKS

A robust national strategic plan for addressing nanotechnology-related EHS risks will need to focus on promoting research that can assist all stakeholders, including federal agencies, in planning, controlling, and optimizing the use of engineered nanomaterials while minimizing EHS effects of concern to society. Such a plan will ensure the timely development of engineered nanoscale materials that will bring about great improvements in the nation's health, its environmental quality, its economy, and its security.

1

The National Nanotechnology Initiative and the Genesis of the Environmental, Health, and Safety Strategy

Nanotechnology consists of several enabling technologies that take advantage of unique properties of extremely tiny structures in applications ranging from medicine to electronics to material science. Research in nanotechnology is based on understanding the physical and chemical properties of materials at the level of molecules or complexes of molecules, or atomic clusters with the goal to be able to manipulate those properties. Nanotechnology is not simply about small particles, materials, or products and is defined by the federal government as including the following three factors (NSET 2008a):

- Research and technology development at the atomic, molecular, or macromolecular levels on a length scale of about 1-100 nm (a nanometer is one-billionth of a meter—too small to be seen with a conventional optical microscope).
- Creation and use of structures, devices, and systems that have novel properties and functions because they are small or of intermediate size, specifically, at the level of atoms and molecules.
- Ability to control or manipulate materials on an atomic scale.

In the middle 1990s, as better methods for the characterization, processing, and manipulation of matter on the nanoscale were being developed in research programs supported by federal science and technology agencies, the agencies began holding informal discussions on a common vision for nanotechnology. The interagency dialogue culminated in the establishment in 2000 of the National Nanotechnology Initiative (NNI)—Box 1-1 details some of the history of the establishment of the initiative. The NNI serves strictly as a coordination mechanism for government agencies that support nanoscale research, such as the Department of Energy and the National Science Foundation, or that have a stake

BOX 1-1 A Brief History of the National Nanotechnology Initiative

In September 1998, an interagency dialogue on nanotechnology was formalized as the Interagency Working Group on Nanotechnology (IWGN). Established under the National Science and Technology Council (NSTC) of the Office of Science and Technology Policy, the IWGN developed a number of reports on a long-term vision for nanoscale research and development (R&D), on international benchmarking of nanotechnology, and on U.S. government investment in nanotechnology R&D (Siegel et al. 1999; Roco et al. 2001). In March 1999, IWGN representatives proposed a nanotechnology initiative with a budget of a half-billion dollars for FY 2001 (Roco 2004). In November 2000, the National Nanotechnology Initiative (NNI) was formally established, and preparations were begun for a coordinated federal investment in nanoscale R&D.

In August 2000, as the NNI proposal matured, the NSTC established the Nanoscale Science, Engineering and Technology (NSET) Subcommittee to replace the IWGN. The NSET Subcommittee was tasked with implementing the NNI by coordinating with federal agencies and R&D programs. Beginning with eight agencies in 2001, the subcommittee now comprises representatives of over 25 federal departments and agencies and officials of the White House Office of Science and Technology Policy and the White House Office of Management and Budget.

In January 2001, the National Nanotechnology Coordination Office (NNCO) was established to provide daily technical and administrative support to the NSET Subcommittee and to assist in multiagency planning and the preparation of budgets and program-assessment documents. The NNCO was also tasked with assisting the NSET Subcommittee with the collection and dissemination of information on industry, state, and international nanoscale science and technology research, development, and commercialization activities (NRC 2002). The NNCO provides technical guidance and administrative support, organizes monthly NSET Subcommittee meetings, conducts workshops, and prepares information and reports, serving as a point of contact and helping to facilitate communication.

in the outcomes of nanoscale research, such as the Food and Drug Administration (FDA) and the Department of Justice. Under the broad umbrella of the initiative, each participating agency invests in projects and programs in support of its own mission. The NNI consists of individual and cooperative nanotechnology-related activities of 25 federal agencies with a wide array of research and regulatory responsibilities. The NNI itself does not fund research, and its budget is equal to the sum of the amounts at which member agencies fund their individual or joint nanotechnology-related programs and projects. Therefore, the NNI has no authority to make budgetary or funding decisions; it relies on the budgets of its member agencies. The goals of the NNI are as follows (NSET 2008a):

- Advance a world-class nanotechnology research and development program.
- Foster the transfer of new technologies into products for commercial and public benefit.
- Develop and sustain educational resources, a skilled workforce, and the supporting infrastructure and tools to advance nanotechnology.
- Support responsible development of nanotechnology.

The NNI's primary coordination mechanism is the National Science and Technology Council (NSTC) Nanoscale Science, Engineering, and Technology (NSET) Subcommittee (NSET 2008a). Through the operation of the NSET Subcommittee and subordinate structures of the NNI, the initiative addresses the general goals of supporting the missions of the participating agencies; ensuring continuing leadership by the United States in nanoscale science, engineering, and technology; and contributing to the nation's economic competitiveness.

In 2003, the 21st Century Nanotechnology Research and Development Act (Public Law 108-153) was signed into law. The legislation established the NNI's operating structures and required that the president establish or designate an advisory panel with a membership qualified to provide advice and information on nanotechnology research, development, demonstrations, education, technology transfer, commercial applications, and societal and ethical concerns.[1] The President's Council of Advisors on Science and Technology (PCAST) was assigned by the president to play such a role. Figure 1-1 shows the current organizational structure of the NNI.

Thirteen NNI-participating agencies currently report investments in nanotechnology: the Department of Agriculture (USDA) (including the Forest Service [FS] and the Cooperative State Research, Education, and Extension Service [CSREES]), Department of Defense (DOD), Department of Energy (DOE), Department of Homeland Security (DHS), Department of Justice (DOJ), Department of Transportation (DOT), Environmental Protection Agency (EPA), National Aeronautics and Space Administration (NASA), National Institute for Occupational Safety and Health (NIOSH), National Institute of Standards and Technology (NIST), National Institutes of Health (NIH), and National Science Foundation (NSF). In FY 2007, the total investment by those agencies in NNI-related research was about $1.425 billion; DOD, DOE, NIH, NIST, and NSF contributed over 80% of the total NNI budget. The president's research and development (R&D) budget request for the NNI for FY 2009 was $1.527 billion.

Released in December 2007, the updated NNI strategic plan (NSET 2007a) looks 5-10 years ahead to outline a vision of the NNI as working for a "future in which the ability to understand and control matter at the nanoscale

[1]Such a panel had been called for in Small Wonders, Endless Frontiers: A Review of the National Nanotechnology Initiative (NRC 2002).

leads to a revolution in technology and industry that benefits society" (NSET 2007a, p. 3).

The strategic plan outlines program component areas (PCAs)[2] that were developed as a means of categorizing and describing the many investments in nanotechnology R&D by the federal agencies that support research. Table 1-1 shows the FY 2008 estimated agency expenditures for the PCAs among the NNI agencies. The committee notes that there may be additional nanotechnology research being performed by some agencies that is not reported in the table. Figure 1-2 shows shares of NNI funding in FY 2006 among the PCAs.

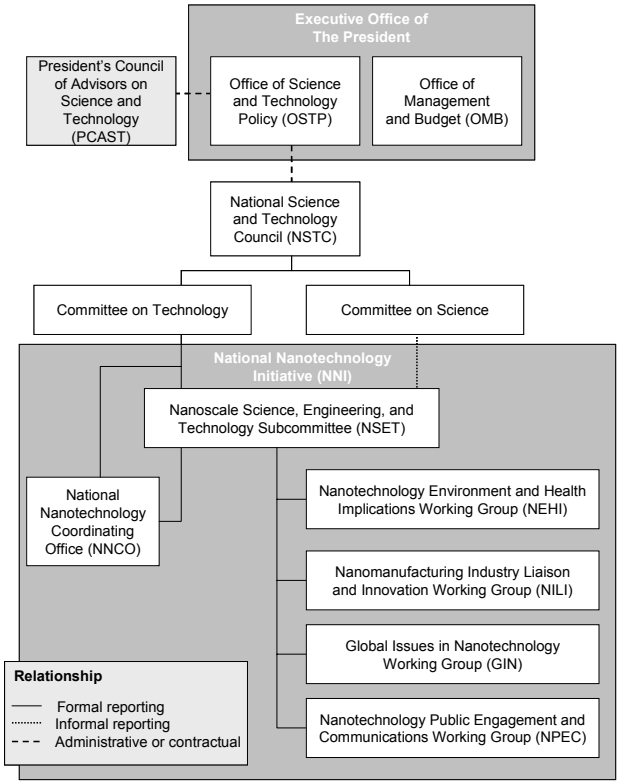

FIGURE 1-1 Organization of NNI. Source: Adapted from Teague 2008.

[2]The PCAs are fundamental nanoscale phenomena and processes; nanomaterials; nanoscale devices and systems; instrumentation research, metrology, and standards for nanotechnology; nanomanufacturing; major research facilities and instrumentation acquisition; environmental, health, and safety; and education and ethical, legal, and other societal dimensions (NSET 2007a).

TABLE 1-1 Estimated FY 2008 Agency NNI-Related Investments by Program Component Area (in $ millions)

	Fundamental Nanoscale Phenomena and Processes	Nanomaterials	Nanoscale Devices and Systems	Instrumentation Research, Metrology, and Standards for Nanotechnology	Nanomanufacturing	Major Research Facilities and Instrumentation Acquisition	Environment, Health and Safety	Societal Dimensions	NNI Total[a]
DOD	258.7	68.9	119.8	8.0	5.4	24.6	2.0		487.4
NSF	138.8	62.1	50.3	16.0	26.9	31.6	29.2	33.8	388.7
DOE	51.4	77.5	13.0	12.0	2.0	92.0	3.0	0.5	251.4
DHHS (NIH)	55.6	25.4	125.8	5.9	0.8		7.7	4.6	225.8
DOC (NIST)	22.5	7.4	21.7	16.1	14.4	5.8	0.8		88.7
NASA	1.5	9.7	6.2			0.4	0.2		18.0
EPA	0.2	0.2	0.2				9.6		10.2
DHHS (NIOSH)							6.0		6.0
USDA (FS)	1.3	1.9	1.2	0.4	0.2				5.0
USDA (CSREES)	0.7	1.6	3.1		0.5		0.1	0.1	6.1
DOJ				2.0					2.0
DHS			1.0						1.0
DOT (FHWA)	0.9								0.9
TOTAL	531.6	254.7	342.3	60.4	50.2	154.4	58.6	39.0	1,491.2

[a]Totals may appear to be incorrect because of rounding.
Source: NSET 2008b, Table 3.

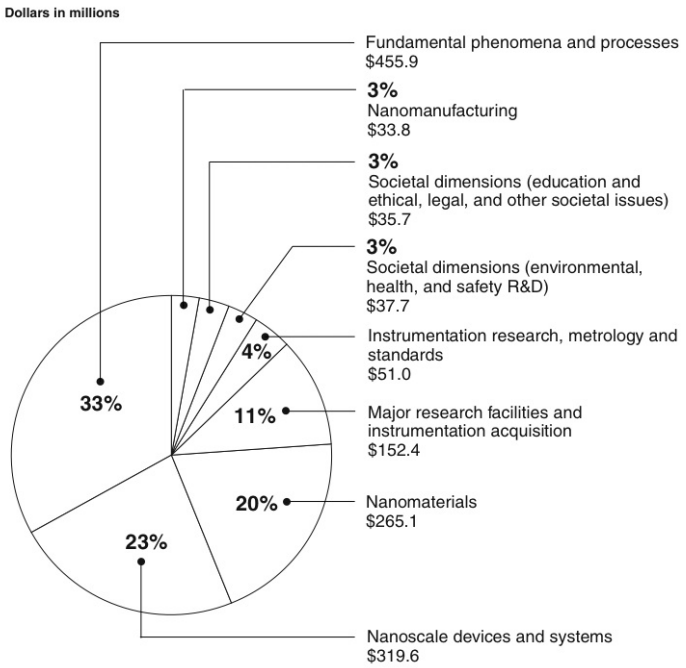

FIGURE 1-2 NNI Research Funding by Program Component Area in FY 2006. Source: GAO 2008.

The PCAs provide a framework that allows the NSET Subcommittee, Office of Science and Technology Policy (OSTP), Office of Management and Budget (OMB), and Congress to be informed of NNI-related activities and that facilitates the management of investments in each PCA and the coordination and direction of nanotechnology-related activities in the participating agencies. The NSET Subcommittee has also established four interagency working groups to address specific cross-agency issues in the context of NNI goals and the PCAs: the Nanotechnology Environment and Health Implications (NEHI) Working Group; the Nanomanufacturing, Industry Liaison, and Innovation Working Group; the Nanotechnology Public Engagement and Communications Working Group; and the Global Issues in Nanotechnology Working Group (see Figure 1-1).

ENVIRONMENT, HEALTH, AND SAFETY

Responsible development of technology can be characterized as the balancing of efforts to maximize the technology's contributions and minimize its adverse consequences. Thus, responsible development of nanotechnology in-

volves an examination of both its applications and its potential implications. It implies a commitment to develop and use technology to meet the most pressing human and societal needs while making every reasonable effort to anticipate and mitigate adverse implications and unintended consequences (NRC 2006).

Nanomaterials have unusual and useful properties. But their unique attributes make them a double-edged sword: although they can be tailored to yield special benefits, they can also have unknown and possibly adverse effects, such as unexpected toxic and environmental effects. The environmental, health, and safety (EHS) implications of nanotechnology are subjects of serious discussion by government agencies and commissions, nongovernment organizations, the research community, industry, insurers, the mass media, and the public. R&D and manufacturing personnel are the ones initially exposed to nanomaterials, so an initial focus of EHS research related to nanomaterials is occupational health and safety risks.

The Growing Importance of Understanding Environmental, Health, and Safety Issues

The Woodrow Wilson Center Project on Emerging Nanotechnologies reported that 609 consumer products involving nanomaterials were on the market as of April 2008.[3] Some 60% of the consumer products reportedly were in the health and fitness category, which includes skin care and other products designed for direct application to the body (PEN 2008). The consulting firm Lux Research predicts that by 2010 the market value of specific nanomaterials will range from $16 million for nanowires to $1.5 billion for ceramic nanoparticles and that there will be a large expansion in all nanomaterial markets from 2005 to 2010 (Holman 2007). As nanomaterials become incorporated into an increasing number and share of consumer products, opportunities for exposure of workers, the general public, and the environment will also increase, so understanding of the potential risks posed by such exposure takes on greater urgency.

In addition to the application of ceramic and other nanoparticles in cosmetics and skin-care products, expanding applications of nanomaterials with relatively high exposure potential include the use of nanosilver in a wide variety of coatings, clothing, and personal-care products for its antimicrobial properties; use of cerium oxide nanoparticles as catalysts in motor-vehicle fuels; and a variety of ceramic and metallic nanoparticles in coatings (Holman 2007). Applications of carbon nanotubes, ceramic nanoparticles, and metal nanoparticles in composite materials, electronic and optical equipment, and other instruments may offer less exposure potential during the use phase of their life cycle but still result in exposure of workers during manufacturing processes and of workers and the general public at the end of the product life cycle. The combination of the heterogeneity of and enormous variations among nanomaterials and their applications; the

[3]These products are identified as nanomaterial-based by the manufacturers or others.

potential for novel forms of toxicity created by their unique size and structural and physical characteristics; and the variations in the frequency, magnitude and duration of releases or exposures, introduces considerable complexity into the design of research programs necessary to understand their potential toxicity.

Researchers, nonprofit organizations, industry, and consumer groups have been calling for an emphasis on EHS research on nanotechnology (Biswas and Wu 2005; Denison 2005; Maynard 2006; Wiesner et al. 2006; Gulledge 2008). In 2004, memorandums from OMB and OSTP to federal-agency heads emphasized the need to give EHS aspects of nanotechnology high priority, noting that "agencies also should support research on the various societal implications of the nascent technology" by placing "a high priority on research on human health and environmental issues…[and] cross-agency approaches" (OMB/OSTP 2004, p.3). The most recent memorandum, for FY 2009, notes that "agencies should strengthen interagency coordination of and support research on potential risks to human health and the environment, consistent with the [NNI (2006)], EHS Research Needs for Engineered Nanoscale Materials" (OMB/OSTP 2007, p. 5).

In 2005, PCAST acknowledged that current knowledge and data for assessing the risks posed by nanotechnology products were incomplete. Furthermore, PCAST said that because exposure to nanomaterials is most likely to occur during manufacturing, research on potential hazards associated with workplace exposure must be given the highest priority (PCAST 2005).[4] In 2005, the NSET Subcommittee formally established the NEHI in a charter that set forth its purpose and objectives (NEHI 2005).[5]

The National Environmental Health Implications Working Group

The NEHI was formed to promote the exchange of information among agencies that support nanotechnology research and those responsible for regulation and guidelines related to nanoproducts; to facilitate identification, priority-setting, and implementation of research needed for the development, use, and oversight of nanotechnology; and to promote communication of information related to research on environmental and health implications of nanotechnology to other government and nongovernment organizations. The NEHI comprises representatives of 18 research and regulatory agencies, OSTP, and OMB and is cochaired by representatives of FDA and the EPA Office of Research and Development.[6]

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[4]The committee recognizes that PCAST has published a second report, *The National Nanotechnology Initiative: Second Assessment and Recommendations of the National Nanotechnology Advisory Panel* (PCAST 2008a). PCAST assessed the NNI draft strategy in a report, PCAST (2008b), that was an addendum to PCAST (2008a).

[5]The committee recognizes that the informal work of NEHI began as early as 2003.

[6]Current members of NEHI consists of officials from the Consumer Product Safety Commission, Cooperative State Research, Education, and Extension Service, Department of Defense, Department of Energy, Department of State, Department of Transportation,

The NEHI, in its charter, was tasked with the following objectives:

- To improve communication of information related to environmental and health aspects of nanotechnology by the National Nanotechnology Coordination Office (NNCO), the NSET Subcommittee, and individual agencies.
- To assist in the development of information and strategies as a basis for the drafting of guidance in the safe handling and use of nanoproducts by researchers, workers, and consumers.
- To support, with input from the NSET Subcommittee and other appropriate interagency groups, the development of tools and methods for identifying and setting priorities among specific research to enable risk analysis of and regulatory decision-making regarding nanoproducts.
- To support development of nanotechnology standards, including nomenclature and terminology, by consensus-based standards organizations.

The structure of the NEHI mirrors that of the NNI, as it serves primarily as a coordinating body across federal research and regulatory agencies. The NEHI, like the NNI, has no authority over the individual agencies and no budget of its own, so it cannot ensure that agencies address or fund specific kinds of EHS research adequately.

The NEHI's formal coordination efforts have resulted in various reports that have identified EHS research priorities for nanomaterials in a series of documents, starting with *Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials* (NEHI 2006), which developed five research categories with a total of 75 research needs. The five research categories were instrumentation, metrology, and analytic methods; nanomaterials and human health; nanomaterials and the environment; health and environmental surveillance; and risk-management methods. In 2007, NNI released *Prioritization of Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials* (NEHI 2007) that reduced the 75 to 25 research needs. In early 2008, *A Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* was released (NEHI 2008).[7] It notes that nanotechnology-related EHS

Environmental Protection Agency, Food and Drug Administration, International Trade Commission, National Aeronautics and Space Administration, National Institute for Occupational Safety and Health, National Institutes of Health, National Institute of Standards and Technology, National Science Foundation, Occupational Safety and Health Administration, Office of Science and Technology Policy, Office of Management and Budget, and U.S. Geological Survey.

[7]In addition to NEHI (2008), many individual agencies have established separate processes to develop their own EHS nanotechnology research strategies. These processes have varied in their structure, their degree of stakeholder involvement, and their complexity. For the most part, the agency personnel engaged in the development of the agency research strategies have been represented on the NEHI, thus allowing for coordination between the NNI research strategy and the individual agency research strategies. The

research and the strategy itself aim to accelerate research to protect public health and the environment and to fill gaps in research, and—in light of the growing level of effort worldwide—to avoid unnecessary duplication of research. The approach, the document notes, is driven by the breadth of issues, from transport in the environment and effects on human health to managing risks and the overarching need to measure and characterize nanomaterials in various environments. Addressing such a variety of issues, the NNI asserts, requires participation by and coordination of the various NNI agencies with their diverse competences and expertise.

STRUCTURE OF THIS REPORT

This National Research Council (NRC) report is an independent assessment of the 2008 NNI document. The NNCO asked the NRC to evaluate the scientific and technical aspects of the draft strategy and to comment in general terms on how the strategy would develop information needed to support the EHS risk-assessment and risk-management needs with respect to nanomaterials.

The committee conducted the evaluation of the NNI draft strategy by asking several questions: What is a research strategy, and more specifically, a risk-research strategy? What are the necessary components of such a strategy (Chapter 2)? Does the strategy have the necessary components (Chapter 3)? For each of the research categories identified in the strategy—including instrumentation, metrology, and analytic methods; human health; environment; exposure assessment; and risk-management methods—are the appropriate research needs identified, is the gap analysis complete and accurate, are priorities among research needs set correctly, and would the research support EHS risk-assessment and risk-management needs (Chapter 4)? Chapter 5 offers the committee's conclusions and recommendations and a look toward future steps in the development of an EHS research strategy for nanomaterials. Society is looking to the scientific community for guidance with respect to nanotechnology, and the committee, in its evaluation, considers nanotechnology to be a field that requires targeted research for understanding the scientific uncertainties surrounding potential EHS risks.

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individual agency research strategies are of course bounded and shaped by the mission, resources, and regulatory obligations of the agencies developing them.

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2

Elements of an Effective Nanotechnology Risk-Research Strategy

OVERVIEW

The term *strategy* is often used to emphasize the importance and relevance of a process, leading to (for example) strategic reports, strategic plans, and strategic research programs. Yet the true meaning of the word has perhaps been lost or diluted through overuse. A possible shift in meaning may be relatively unimportant in many cases. But if there is a need for a well-constructed strategy to address a particular challenge, working from the wrong definition is likely to lead to confusion at best and a poorly conceived plan of action at worst. Therefore, in setting the scene for reviewing the National Nanotechnology Initiative's *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* (NEHI 2008), it is helpful to think through how the term *strategy* might apply to scientific research in general and to risk-focused research in particular.

Our aim in this chapter is to develop a sense of what the elements of an effective risk-focused research strategy might look like. We start by considering how strategic thinking or planning is related to research in general and what some of the key factors are in developing effective research strategies. We then focus on research aimed specifically at risks to people and the environment—whether real or perceived—and consider aspects of research strategies that are effective in avoiding or reducing the risks. Finally, we propose nine "elements" (see Box 2-1) that we believe are important in developing and implementing an effective research strategy aimed at identifying, assessing, and managing risks associated with nanotechnology. These elements are explained in further detail at the end of the chapter. It is against those elements that *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* is assessed later.

DEVELOPING EFFECTIVE RESEARCH STRATEGIES

Strategies generally define a set of goals, often in the context of an over-

arching aim or vision; a plan of action for achieving the goals; and measures for indicating when the goals have been achieved. When that concept is applied to a complex subject, such as scientific research, developing suitable goals, implementable action plans, and measures of success becomes similarly complex. Research is often open-ended and serendipitous, and it can be difficult to formulate goals that will not stifle innovation. Even when the goals are clear—for instance, "to cure cancer" or "to develop renewable energy sources"—the road map for achieving them can be less than obvious. Promising research avenues can lead to dead ends, and seemingly trivial research directions sometimes turn out to be vitally important. Identifying measures of success ahead of time can sometimes seem like staring into a crystal ball. But, as difficult as the process is, strategies are required for science; in which resources are limited and there is a need to justify what is spent on the basis of what is achieved.

Ensuring efficient progress, or "performance," is a key aspect of any research strategy, and selecting useful measures requires a degree of sophistication. In 2002, the Office of Management and Budget designed the Program Assessment Rating Tool (PART) (OMB 2008) in an attempt to evaluate the performance of publicly funded programs, including research and development (R&D) programs. PART does not explicitly address the need for strategies, but it requires agencies to take strategically relevant steps that include defining outcome-based metrics, measuring the efficiency of research programs, and achieving annual efficiency improvements. Applying those steps to scientific research is not easy. The 2008 National Research Council report *Evaluating Research Efficiency in the U.S. Environmental Protection Agency* concluded that "no agency had found a method of evaluating the efficiency of research based on the ultimate outcomes[1] of that research" (p. 10), and indeed the report stated that

BOX 2-1 Elements of a Research Strategy

- Vision, or statement of purpose.
- Goals.
- Evaluation of the existing state of science.
- Roadmap.
- Evaluation.
- Review.
- Resources.
- Mechanisms.
- Accountability.

[1]Ultimate outcomes include such results as lives saved or clean air and cannot be predicted or known in advance, may occur long after research is completed, and usually depend on action taken by others (NRC 2008).

"ultimate-outcome-based metrics cannot be used to evaluate the efficiency of research" (NRC 2008, p. 5). Rather, the report reflected the need for sophisticated and nuanced approaches to setting and evaluating research agendas in concluding that "the primary goal of research is knowledge, and the development of new knowledge depends on so many conditions that its efficiency must be evaluated in the context of quality, relevance, and effectiveness in addressing current priorities and anticipating future R&D questions" (p. 10). Specifically, the report distinguished between investment efficiency—including the need to identify the most promising lines of research for achieving desired outcomes—and process efficiency, which relates input into research (for example, number of labor hours and dollars spent on laboratory equipment) to what is ultimately achieved.

Development of effective research strategies that generate high-quality, relevant, and effective new knowledge will depend on the nature and context of the work to be done and the decisions to be made. There is a loose hierarchy in how science is organized, from laboratory-level studies through interdisciplinary research programs to governmentwide science initiatives; and different strategies to ensure success are used at each level. Overlying the hierarchy are ideas of how to divide and categorize different "types" of science.

In 1945, Vannevar Bush, director of the Office of Scientific Research and Development, wrote in the report *Science: The Endless Frontier* that "basic research is performed without thought of practical ends. It results in general knowledge and an understanding of nature and its laws. This general knowledge provides the means of answering a large number of important practical problems, though it may not give a complete specific answer to any one of them. The function of applied research is to provide such complete answers" (Bush 1945). The dichotomous perception of basic and applied research has dominated science policy in the United States for much of the last 50 years. Yet as Stokes and others have highlighted, a more nuanced and integrated approach to different "types" of science is perhaps more realistic (Stokes 1997). Rather than use the established but conceptually limited terminology, the panel found it helpful to describe research as "exploratory" or "targeted,"[2] with the understanding that in many cases research will demonstrate attributes associated with both descriptions.

In that context, the overarching aim of exploratory research is the expansion of scientific knowledge, whereas targeted research is focused on achieving specific goals, which are usually practical. The success of exploratory research might be measured with such indicators as an increase in knowledge, and the

[2]Similarly, the Environmental Protection Agency uses a nomenclature to describe its research that includes *core research* and *problem-driven research:* problem-driven research is aimed at understanding and solving particular identified environmental problems and reducing associated uncertainties, and core research is aimed at providing broader, more generic information to improve understanding relevant to environmental problems (NRC 1997).

plan of action for a research strategy might include steps to empower the brightest minds to engage in innovative research with as much freedom as possible. In contrast, targeted research has built-in goals, and an implementation plan might consider the best use of multiple mechanisms—contract research, investigator-driven research, or otherwise—to achieve the goals within specific budget and time constraints. In between there is a fruitful crossover regime wherein the ideas underpinning exploratory and targeted research combine, leading to exploratory research that meets real challenges and targeted research that generates knowledge that is not necessarily applied knowledge.

DEVELOPING EFFECTIVE RISK-RESEARCH STRATEGIES

Strategies for risk research—loosely defined as research in support of identifying, assessing, and addressing actual and potential causes of harm to people and the environment—are not typically limited by disciplinary, agency, or philosophic boundaries. They should address challenges of broad societal significance, for example, the reduction or prevention of harm to humans and the environment.

It is the social significance of risk research that perhaps sets it apart from other kinds of research when a research strategy is being developed and implemented. For example, although a poor research strategy for developing new applications might impede progress in a particular field, a poor risk-research strategy has the potential to reverse progress if it results in unanticipated or poorly managed harm to people and the environment. Such a reversal may arise from failure to identify potential risks in a timely manner, failure to understand how to manage new risks effectively, inability to respond to existing risks, or even inability to communicate information on risks effectively. Poor risk-research strategies may also affect perceptions of risk and lead to decision-making in government, business, and society in general that is not necessarily science-based. Ultimately, failure to develop and implement an effective risk-research strategy can potentially lead to economic loss, environmental damage, loss of quality of life, and loss of life itself.

Like any other research strategy, a risk-research strategy will have clearly defined goals, a plan of action for achieving the goals, and measures of success that can inform future modifications of the strategy—all in the context of the existing state of the science. The plan of action for implementing an effective risk-research strategy will rely heavily on targeted research—research that is focused on addressing questions that are critical for ensuring the safety of new materials and products. A long-term risk-research strategy will also encompass exploratory research to generate knowledge that will inform future goals and research directions. With both targeted and exploratory research, useful research will not be limited by conventional disciplines, just as the mechanisms through which materials and products might cause harm do not respect disciplinary boundaries.

Ultimately, the measure of success of a risk-research strategy is the degree to which harm to people and the environment is mitigated or avoided. If the research is in response to an existing problem, success is measured relatively easily as a reduction in the problem (for example, a reduction in lives lost or in the incidence of disease). It is generally acknowledged that risk research ideally is pre-emptive—preventing problems rather than addressing them after the fact—so measures of success are harder to identify. However, it is possible to identify measures that do not rely on prior harm. For instance, in 2006, four research goals to underpin the safety of nanotechnology were identified in a commentary in Maynard et al. (2006)—to develop samplers to detect nanoparticles in air and water, to develop toxicity screening tests, to develop predictive models, and to develop systems for assessing the effects of nanomaterials over their complete life cycle. In each case, it is clear how achieving the goal will help to avoid harmful effects of engineered nanomaterials, and success in achieving the goal is highly measurable.[3] Other approaches to identifying where progress has been made in avoiding harm are possible. And such concepts as "value of information" (which is explored further in Chapter 4) can help to guide limited resources in maximizing the degree to which measurable progress is made (for example, Clemen and Reilly 2004; Yokota and Thompson 2004).

The critical point here is that, hard as it might be to formulate such metrics of success in a risk-research strategy, failure to do so will result in funding of irrelevant research and failure to fund relevant research.

DEVELOPING NANOTECHNOLOGY-SPECIFIC RISK-RESEARCH STRATEGIES

An effective nanotechnology risk-research strategy will be predominantly forward-looking—preparing for potential risks before the technology has a widespread commercial presence. It will address nanotechnology-based products that are beginning to enter commerce and nanotechnologies currently under development. But it will also need to lay the scientific groundwork for addressing future materials and products arising out of new research, new tools, and new cross-fertilization between previously distinct fields of science and technology. The need to be active and forward-looking makes it particularly hard to develop, implement, and evaluate an effective risk-research strategy. In this context, it is helpful to consider briefly how other organizations have approached the challenges of developing such strategies. We aim to highlight some of the approaches taken by others in response to the challenge of developing nanotechnologies safely.

[3]For example, the development, commercialization, and adoption by 2010 of instruments that simultaneously measure personal exposure to airborne nanometer-scale particle number, surface area, and mass concentration, as proposed by Maynard et al. (2006), constitute clear goals whose achievement can be quantified against clear time and performance criteria.

In 2004, the British Royal Society and the Royal Academy of Engineering published what has come to be seen as a seminal report on the development of safe and beneficial nanotechnologies. In *Nanoscience and Nanotechnologies: Opportunities and Uncertainties* (Royal Society 2004), the UK carried out a study to define what is meant by *nanoscience* and *nanotechnology*; to summarize and identify gaps in knowledge; to identify potential health and safety, environmental, ethical, and societal effects; and to look toward the future of the field. This study was executed by a working group of experts of diverse backgrounds assembled by the Royal Society and the Royal Academy of Engineering. The report concluded with 21 recommendations to the UK government and other parties on the responsible development of new and emerging technologies. They addressed industrial applications; possible adverse health, safety, and environmental effects; regulatory issues; social and ethical issues; and stakeholder and public discussion. Although the report was not a strategy in itself, it laid the groundwork for developing strategies that would underpin the responsible development of nanotechnologies—including risk research. Three themes in particular stand out among the recommendations: the need for research into what makes nanotechnologies potentially harmful and how to avoid harm throughout their life cycle, the need for research to inform oversight and regulatory decision-making, and the need for independent review of progress in the responsible development of nanotechnologies.

The UK government responded to the report in 2005 with the document *Characterizing the Potential Risks Posed by Engineered Nanoparticles. A First U.K. Government Research Report* (HM Government 2005). It set out a program of research objectives to address potential risks posed by nanoparticles and funding mechanisms to address these objectives with the aim of developing an appropriate framework and measures for controlling unacceptable risks—engineered nanoparticles being the subset of engineered nanomaterials considered to be of most concern (Royal Society 2004). The result was a nanotechnology risk-research strategy that identified what was needed—19 research objectives were identified—and how the UK government proposed to meet the needs.

In 2007, the UK Council for Science and Technology (CST)—the UK government's top-level advisory body on science and technology policy issues—published a 2-year review of progress toward the government's commitments to developing nanotechnology responsibly (CST 2007). The review praised some aspects of the government's progress and criticized others; the details are not as important here as the process. As a result, later in 2007, the government published a second research report, on characterizing the potential risks posed by engineered nanoparticles (HM Government 2007). The second report described progress in addressing the 19 objectives established in 2005, considered where changes in direction and emphasis were needed, addressed issues raised in the CST review, and planned future steps.

It is beyond our scope to evaluate the substance of the UK nanotechnology risk-research plan, but some aspects of the process align with previous discussions on research strategies. The UK government has identified clear aims and

objectives, established mechanisms for addressing the objectives, and set in place a process of review and revision. There has been a degree of independence in authoritative input into the research strategy, from the original Royal Society and Royal Academy of Engineering report to the inclusion of nongovernment experts and stakeholders in developing and implementing the strategy.

Looking beyond the UK, the European Union (EU) has been active in identifying and supporting research aimed at addressing potential nanotechnology-related risks. In 2004, the European Commission (EC) released the communication *Towards a European Strategy for Nanotechnology* (EC 2004). The document focused on realizing the societal benefits of nanotechnology, but it emphasized addressing potential risks in informed decision-making: "Nanotechnology must be developed in a safe and responsible manner. Ethical principles must be adhered to and potential health, safety or environmental risks scientifically studied, . . . in order to prepare for possible regulation" (p. 3).

After the 2004 communication, the EC published *Nanosciences and Nanotechnologies: An Action Plan for Europe 2005–2009* (EC 2005) as a communication to the Competitiveness Council, the European Parliament, and the Economic and Social Committee. In the action plan, the EC recommended EU and member-state actions to address eight elements of nanotechnology development, including public health, safety, and environmental and consumer protection (action point 6). Key to that action point were commitments and recommendations to identify and address safety concerns, evaluate and minimize exposures, and ensure adequate oversight of nanotechnologies—in essence, to establish a framework for strategic research that led to informed decisions. Like the UK nanotechnology plan, the EC plan provided for regular review, and in 2007 the EC published its first implementation report on the action plan (EC 2007).

Although the European action plan for nanotechnology did not explicitly include a risk-research strategy, it did provide a framework for developing such strategies. In testimony to the committee from representatives of the EU directorate general for science, research, and development and the directorate general for health and consumer affairs (Aguar 2008; Martin 2008), it was clear that the EU response to developing nanotechnologies responsibly involves a complex interplay between EU agencies, member states, and nongovernment stakeholders. There does not appear to be a single overarching strategy governing risk research in Europe, but rather multiple initiatives that together form a cohesive approach to supporting research that will inform policy decisions. Two initiatives in particular highlight the current state of affairs: the European Union Seventh Framework Program for Research and Development and a review of risk-assessment methods for assessing the risks associated with nanomaterials conducted by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). The SCENIHR is an independent scientific committee established to provide the EC with sound scientific advice for preparing policy and proposals related to public health and the environment. It is one of three such committees that address nonfood issues; it complements the Scientific Commit-

tee on Consumer Products and the Scientific Committee on Health and Environmental Risks.

Research at the EU level is funded through framework programs that establish the aims and aspirations of pan-European R&D initiatives. The current program is Framework Program 7 (FP7) and will run from 2007 to 2013 (EC 2006). Over this period, over €3.5 billion will be invested in nanotechnology R&D, some of which will be invested in risk research. Calls for proposals within the framework program range from enabling exploratory research to targeting specific issues and typically require collaboration between disciplines, countries, and public and private organizations. In the 2007 call for proposals, four categories focused specifically on environmental health and safety: portable devices for exposure measurement and analysis, risk assessment of engineered nanoparticles, review of the scientific literature on potential risks, and creation of a critical database on the effects of nanoparticles on the environment, health, and safety. Those topic categories, although forming only a small part of the research needed to address potential adverse effects of nanotechnologies, targeted specific issues identified through consultation with a broad base of experts and stakeholders. This process of consultation is continuing to inform research calls under FP7.

The second initiative of interest here is an "opinion" published by the SCENIHR in 2007 (SCENIHR 2007). The SCENIHR was asked, in light of current scientific knowledge and in relation to the general information on and practices of chemical risk assessment, to assess the appropriateness of risk-assessment methods described in the current chemical-related technical guidance documents for risk assessment of nanomaterials and to suggest improvements in the method. Although it did not result in a risk-research strategy, the assessment was important on three counts: it formed part of the tapestry of independent and expert science-based input into the EU planning and decision-making process, which includes strategic decision-making on research directions; it systematically established the level of information needed on emerging nanomaterials to evaluate—and thus manage—potential risks and in doing so provided a framework for developing research strategies to fill gaps; and it explicitly identified research subjects that need further attention if informed decisions were to be made on responsible development and use of nanomaterials.

Those two examples and others not included here are indicative of an approach to risk research in Europe that engages a broad array of experts and stakeholders, identifies key policy goals, establishes mechanisms for supporting research to address the goals, and periodically reviews progress toward the goals.

The Organisation for Economic Co-operation and Development (OECD) has also begun to address the coordination of nanotechnology risk-research strategies among member countries. In 2006, the Working Party on Manufactured Nanomaterials (WPMN) was established under the OECD Chemicals Committee with the aim of promoting international cooperation in aspects of manufactured nanomaterials related to human health and environmental safety

to assist in the development of rigorous safety evaluation of nanomaterials. The working party is supporting eight projects that collate, coordinate, and disseminate information and activities linking scientific understanding to the effective oversight of engineered nanomaterials; the second project addresses research strategies regarding manufactured nanomaterials.

Although the OECD WPMN is not developing a nanotechnology risk-research strategy, its aim is to exchange information and identify common research needs to address human-health and environmental-safety issues associated with manufactured nanomaterials (or engineered nanomaterials) and to undertake to meet the needs. In many ways, that is a step toward establishing an international framework within which individual countries and economies can develop risk-research strategies that address the needs of decision-makers while being coordinated with other global initiatives. The OECD process predominantly involves government representatives, but there are provisions in the organization's structure for industry and nongovernment environmental organizations to participate in the working party. It is thus likely that when the results of the research-strategies project begin to emerge, they will to some extent represent input from stakeholders beyond government departments and agencies. However, it should be recognized that non-government stakeholder involvement in this process is neither inclusive nor representative.

Apart from national and international government initiatives to develop nanotechnology risk-research strategies, there have been a number of independent initiatives to map out strategic research needs and approaches. Several papers have been published in recent years highlighting specific research needs, including *Principles for Characterizing the Potential Human Health Effects from Exposure to Nanomaterials: Elements of a Screening Strategy* (Oberdörster et al. 2005), *Safe Handling of Nanotechnology* (Maynard et al. 2006), and *Hazard Assessment for Nanoparticles—Report from an Interdisciplinary Workshop* (Balbus et al. 2007).

Recently, the International Council on Nanotechnology released *Towards Predicting Nano-Bio Interactions: An International Assessment of Research Needs for Nanotechnology Environment, Health and Safety* (ICON 2008). It reports on two international multistakeholder workshops that were tasked to identify and set priorities for the research needed to classify nanomaterials by physical and chemical properties and to develop predictive models for their interactions with living systems. The result was 36 recommendations on research needed to understand more fully how nanomaterials interact with biologic systems and on how to use this knowledge to avoid undue harm on near-term, middle-term and long-term time scales.

A comprehensive overview of challenges to and solutions for developing a nanotechnology risk-research strategy was published by the Project on Emerging Nanotechnologies (Maynard 2006). *Nanotechnology: A Research Strategy*

for Addressing Risk draws on nine published reports,[4] including the Royal Society and Royal Academy of Engineering report (Royal Society 2004) and the EC action plan for nanoscience and nanotechnologies published in 2005 (EC 2005), and develops recommendations on the aims, objectives, and implementation of a responsive risk-research strategy. The report differs from others cited here in that it is one person's opinion rather than reflecting the views of multiple stakeholders and experts. However, it draws heavily on opinions and perspectives published elsewhere.

Maynard (2006) identifies "the roll-out of 'safe' nanotechnologies" as the overarching aim of a risk-research strategy and identifies a number of research objectives, including addressing human and environmental health hazards, material characterization and exposure, exposure control, and risk reduction. It considers how the objectives might be best achieved in a timely manner by developing and implementing an effective research strategy. In particular, four components of a government-led strategic research framework are identified and expanded on: linking research to oversight, balancing different approaches to research and research funding (specifically, balancing exploratory and targeted research and using the full spectrum of funding mechanisms appropriately), ensuring authority to direct research, and enabling coordination and partnerships.

Much of the report stresses the importance of targeted research in an effective strategy, which would lead to informed decision-making, but it also stresses the need for exploratory research that will underpin future targeted questions regarding emerging risks. In addition, the report distinguishes between research that addresses nanotechnology risks directly and what it refers to as "indirect research." The latter is identified as research that has the potential to inform an understanding of the effects of nanotechnologies but is not necessarily directed primarily at risks. For example, research into general characterization methods or research into nanotechnology-based drug development might be considered indirect research in the context of risk but lead to risk-relevant information. The report attaches considerable importance to that category of research but warns that "unless this latent potential [is] realized through targeted research, the work will be worthless to understanding and addressing risk."

On the basis of those examples and others not included in this brief overview, it is fair to say that an understanding of what an effective nanotechnology risk-research strategy might look like is still evolving. However, common themes emerge from the above examples and discussions, including the need to link research to decision-making processes, to identify overarching aims and key objectives, to ensure broad expert and multistakeholder input, to ensure access to adequate resources, and to initiate a program of independent review and revision.

[4]Royal Society (2004); Chemical Industry Vision 2020 Technology Partnership and SRC (2005); Dennison (2005); EC (2005); EPA (2005); HM Government (2005); Maynard and Kuempel (2005); NIOSH (2005); and Oberdörster et al. (2005).

ELEMENTS OF A RISK-RESEARCH STRATEGY

On the basis of the preceding discussion of research strategies in general and nanotechnology risk-research strategies in particular, the present committee suggests nine elements as key components of an effective research strategy that addresses environmental, health, and safety effects of emerging nanotechnologies. The importance of those elements will depend on the context of a given research strategy. However, it is hard to imagine a successful risk-research strategy that does not address each one of them to some extent. Consequently, the elements have informed our assessment of the National Nanotechnology Initiative *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* (NEHI 2008).

The nine elements are the following:

- ***Vision, or statement of purpose.*** What is the ultimate purpose of conducting research on potential risks associated with nanotechnology?
- ***Goals.*** What specific research goals need to be achieved to guide the development and implementation of nanotechnologies that are as safe as possible?
- ***Evaluation of the state of science.*** What is known about the potential for the products of nanotechnology to cause harm and about how possible risks might be managed? Could existing knowledge and expertise be mined to provide insight into and solutions to potential nanotechnology-related risks?
- ***Road map.*** What is the plan of action to achieve the stated research goals? What are the specific objectives, and when do they need to be achieved? How will available resources, institutions, and funding mechanisms be used? Are there needs for new mechanisms to ensure that the right research is carried out? How will other efforts and initiatives be leveraged, including industry and international initiatives? How will the road map be adjusted in light of new knowledge? What is the time required for the plan to become effective?
- ***Evaluation.*** How will research progress be measured, and who will be responsible for measuring it? Are there measurable milestones that can be evaluated against a clear timeline?
- ***Review.*** How will the strategy be revised in light of new findings, to ensure that it remains responsive to the overarching vision and goals?
- ***Resources.*** Are there sufficient resources to achieve the stated goals? If not, what are the plans to obtain new resources or to leverage other initiatives to achieve the goals?
- ***Mechanisms.*** What are the most effective approaches to achieving the stated goals? How will exploratory and targeted research be used? What will be the balance between principal-investigator–driven and goal-driven research and between intramural and extramural research programs? How will research efforts be coordinated to ensure a coherent approach to achieving stated goals?

What provisions are there for enabling interdisciplinary research that crosses established funding and agency boundaries?

- ***Accountability.*** How will stakeholders participate in the process of developing and evaluating a research strategy? Who will be accountable for progress toward stated goals? Who will be responsible for disseminating information generated within the research strategy and ensuring its use in raising awareness and making decisions?

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3

Evaluation of the Federal Strategy

In Chapter 2, the committee identified the key elements of a nano-risk research strategy: an evaluation of the existing state of science, an overarching vision or statement of purpose, goals to ensure safe development of nanotechnologies, a road map for ensuring achievement of stated goals, evaluation for assessing progress in achieving the goals, a process of review to ensure the strategy remains responsive to the overarching vision and goals, identification of resources, mechanisms to achieve goals, and accountability. The committee evaluated *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* (NEHI 2008) by considering whether it contained those elements. In its evaluation, the committee considered input from public sessions held at the National Academies (March 31 and May 5, 2008) at which representatives of the Nanotechnology Environmental and Health Implications Working Group (NEHI) and of the stakeholder community—including industry, nongovernment organizations, and the insurance sector—provided comments on the federal strategy. Many of the stakeholders' comments echoed sentiments of the committee and are provided here as support for the committee's views on NNI (NEHI 2008). (See Appendix C for an agenda of the public sessions.)

The committee concluded that the development of the NNI (NEHI 2008) has provided a unique opportunity for coordination, planning, and consensus-building among 18 agencies within NEHI. However, the committee determined that the NNI document does not have the essential elements of a nano-risk research strategy, inasmuch as it does not evaluate the state of science, does not contain a clear set of goals, and does not have a plan of action for achieving the goals or mechanisms to review and evaluate funded research and assess whether progress has been achieved. There is no attempt to show how existing research will lead to answers to critical questions that the federal government, the research community, and other stakeholders are grappling with.

IS THERE AN EVALUATION OF THE EXISTING STATE OF SCIENCE?

The research categories and needs presented in the strategy are based on

priorities reviewed and evaluated in the previous NNI reports, *Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials* (NEHI 2006) and *Prioritization of Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials: An Interim Document for Public Comment* (NEHI 2007), both of which received public comment. The first of those reports developed five research categories with a total of 75 research priorities. The priorities were reduced to 25 in the second report. The new strategy (NEHI 2008) attempts to develop timelines and sequence the research needs and uses an accounting of research projects of FY 2006 to determine the strengths, limitations, and data gaps of the research portfolio.

There is no evaluation of the existing state of science or of federally funded research in each of the five categories identified in the strategy—instrumentation, metrology, and analytic methods; nanomaterials and human health; nanomaterials and the environment; human and environmental exposure assessment; and risk-management methods. Rather, the research categories and identified research needs (see Box 3-1) are analyzed solely in the context of FY 2006 research projects. The committee questions the NNI's use of FY 2006 data to assess the extent to which federally funded environmental, health, and safety (EHS) research for nanomaterials is supporting the selected research needs. The majority of the research projects listed for FY 2006 focused on fundamentals of nanoscience that are not explicitly associated with risk, or on developing nanotechnology applications.[1] There also is no clear connection between the research projects and how they will inform an understanding of risk. Without a clear articulation of how the research projects will inform that understanding, the report's assessment is highly misleading and inappropriately used to identify whether research needs are being addressed.

NNI (NEHI 2008) contains conflicting statements about the use of FY 2006 research projects to evaluate research needs. The document states that "this analysis of strengths, weaknesses, and gaps will inform agency decisions about the magnitude and balance of future EHS research investments" (NEHI 2008, p. 9). But the document continues, "data gathered for FY 2006 represent a one-time-only 'snapshot' of the NNI agencies' EHS research portfolios in one year. However, these are likely to be indicative of the overall trends in agency investments in more recent years" (NEHI 2008, p. 9). The strategy goes on to acknowledge limits of the gap analysis, including statements that the data represent only projects funded in FY 2006; that the data represent planned research, not research results; and that only federally funded research is accounted for—there is no mention of research funded by industry, nonprofit organizations, or other countries. Those statements in the strategy were echoed by Altaf Carim,

[1]The 246 FY 2006 research projects listed include research on instrumentation and metrology and on medical applications that is not captured in the list of 130 environmental, health, and safety research projects included in the annual supplement to the president's budget (Teague, unpublished material, 2008).

program manager in the Office of Science, Department of Energy, who acknowledged in his written testimony to the committee "that data was one of the *inputs* to the planning process—a snapshot of Federal activity that in fact was analyzed in order to determine where there were gaps and to identify the priority areas for future investment" (Carim 2008, p.1).

BOX 3-1 Priority Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials, as Identified in the 2008 National Nanotechnology Initiative Research Strategy

Instrumentation, Metrology, and Analytical Methods

1. Develop methods to detect nanomaterials in biological matrices, environment, and workplace.
2. Understand how chemical and physical modifications affect the properties of nanomaterials.
3. Develop methods for standardizing assessment of particle size, size distribution, shape, structure, and surface area.
4. Develop certified reference materials for chemical and physical characterization of nanomaterials.
5. Develop methods to characterize a nanomaterial's spatio-chemical composition, purity, and heterogeneity.

Nanomaterials and Human Health

Overarching Research Priority: Understand generalizable characteristics of nanomaterials in relation to toxicity in biological systems.

Broad Research Needs:

- Understand the absorption and transport of nanomaterials throughout the human body.
- Develop methods to quantify and characterize exposure to nanomaterials and characterize nanomaterials in biological matrices.
- Identify or develop appropriate *in vitro* and *in vivo* assays/models to predict *in vivo* human responses to nanomaterials exposure.
- Understand the relationship between the properties of nanomaterials and uptake via the respiratory or digestive tracts or through the eyes or skin, and assess body burden.
- Determine the mechanisms of interaction between nanomaterials and the body at the molecular, cellular, and tissular levels.

Nanomaterials and the Environment

1. Understand the effects of engineered nanomaterials in individuals of a species and the applicability of testing schemes to measure effects.

(Continued)

BOX 3-1 Continued

2. Understand environmental exposures through identification of principle sources of exposure and exposure routes.
3. Evaluate abiotic and ecosystem-wide effects.
4. Determine factors affecting the environmental transport of nanomaterials.
5. Understand the transformation of nanomaterials under different environmental conditions.

Human and Environmental Exposure Assessment

1. Characterize exposures among workers.
2. Identify population groups and environments exposed to engineered nanoscale materials.
3. Characterize exposure to the general population from industrial processes and industrial and consumer products containing nanomaterials.
4. Characterize health of exposed populations and environments.
5. Understand workplace processes and factors that determine exposure to nanomaterials.

Risk Management Methods

Overarching Research Priority: Evaluate risk management approaches for identifying and addressing risks from nanomaterials.

1. Understand and develop best workplace practices, processes, and environmental exposure controls.
2. Examine product or material life cycle to inform risk reduction decisions.
3. Develop risk characterization information to determine and classify nanomaterials based on physical or chemical properties.
4. Develop nanomaterial-use and safety-incident trend information to help focus risk management efforts.
5. Develop specific two-way risk communication approaches and materials.

Source: NEHI 2008.

The committee's concerns about the limitations of the assessment of the state of science were reflected by Carolyn Cairns, program leader of product safety for Consumer's Union, at the May 5, 2008 workshop: "The document resembles a laundry list of ad hoc projects that some agencies have shoe-horned into relevance for environmental health and safety. It is not a strategy that will accelerate the research needed to prevent our toxic past from repeating itself in

nano-form. The document fails to articulate how the disparate projects outlined will be pulled together to glean meaningful conclusions that participating agencies can use to protect the public from dangers inherent in commercializing nanomaterials" (Cairns 2008, p.1).

DOES THE STRATEGY HAVE A VISION OR STATED PURPOSE?

The strategy document has various statements of purpose, but none provides a clear vision of where understanding of the environmental, health, and safety implications of nanotechnology should be in 5 or 10 years, including ensuring that the results of research are useful and applicable to decision-making for reducing potential environmental, health, and safety effects of nanomaterials. Relevant research is also needed for policy decisions on government oversight, in industry, and in a broader societal context.

The statement that stands out most as the purpose of the strategy document is that "the NEHI Working Group developed this nanotechnology-related EHS research strategy to accelerate progress in research to protect public health and the environment, and to fill gaps in, and—with the growing level of effort worldwide—to avoid unnecessary duplication of, such research" (NEHI 2008, p. 1). That statement is adequate for an open-ended research program with no definite objectives, but it stops short of ensuring that the results of strategic research are useful and applicable to decision-making that will reduce the potential environmental and health effects of nanotechnologies.

The committee notes that in some cases the strategy document reads as though it has two stated objectives: continuing to support nanotechnology and understanding risks. As the strategy states, "this effort has entailed identifying and prioritizing EHS research for nanomaterials; analyzing the current research portfolio in detail; performing a gap analysis to determine areas requiring emphasis; and developing a strategy to address these areas and *to sustain the diverse program aimed at advancing knowledge and supporting risk decision making*" (NEHI 2008, p.1; emphasis added). Those two objectives are emphasized again: "the NNI aims to maximize the benefits of this new technology at the same time it is developing an understanding of any potential risks and means to manage such risks" (NEHI 2008, p. 1). Stakeholders at the committee's May 5, 2008 public session expressed concerns, similar to those of the committee, that the strategy document seemed to be divided between protecting public health from potential risks of nanomaterials and developing nanotechnology products.

A clear and distinct vision may be difficult for the coordinating agencies to articulate and agree to inasmuch as they reflect different backgrounds, goals, and legislative mandates (see discussion on limitations of the NNI and the NEHI at the end of this chapter).

DOES THE STRATEGY HAVE GOALS TO ENSURE THE SAFE DEVELOPMENT OF NANOTECHNOLOGIES, AND IS THERE A ROAD MAP FOR ACHIEVING STATED GOALS?

NNI (NEHI 2008) does not present goals or a plan of action for achieving them. Although it identifies five "research needs" for each of the five general categories (see Box 3-1), the needs are not articulated as clear goals. There also are no measures of progress to evaluate how and to what extent the goals are being attained. As William Kojola, AFL-CIO industrial hygienist, commented, "a comprehensive set of goals and objectives should first be identified and then a strategy needs to be developed to accomplish these goals and objectives. . . . The current NNI strategy appears to essentially consist of a listing of agency projects cobbled together to look like a strategy" (Kojola 2008, p. 2).

The committee recognizes that the "emphasis diagrams" (NEHI 2008, Figures 3, 5, 7, 9, and 11) for the research needs in the five categories provide some element of timeframe and sequencing. As the strategy states, "priority. . . was considered both in terms of the kind of information developed (some information is of greater relevance than others to supporting risk management) and the appropriate sequencing of research (some research should be timed to occur following other research in order to gain the greatest benefit to decision making with respect to product use, regulations, and conduct of research)" (NEHI 2008, p. 10). Some research needs (for example, in the category of instrumentation, metrology, and analytic methods) could be translated into measureable objectives, but for many others there are insufficient details to determine the measurable objectives.

A key element of any strategy is to identify goals and measures of progress or success *before* assessing what is being done. That allows a clear assessment of the value of current activities, whether in the organization—the government in this case—or outside it (such as research supported by industry, nonprofits, or other countries). Such an approach enables development of an action plan to leverage other efforts and to address and measure research deficiencies in a way that is transparent.

Because NNI (NEHI 2008) does not establish goals and a plan of action, there is no roadmap; the document never raises such questions as, What other research activities should be leveraged? and What additional research activities are needed? Rather, it asserts that current activities are addressing research needs. Terry Medley, global director of corporate regulatory affairs at DuPont, highlighted in his May 5, 2008 presentation to the committee the need for metrics for evaluation as a critical component of successful implementation of the NNI strategy (Medley 2008).

The committee notes that the role of goals and milestones in a complex and emerging research field is not to predict and hold research organizations to the predictions but to map out a systematic plan with chartable actions, which

will of necessity change. The committee recognizes that useful goals and a plan of action in this context are not easy to formulate, but they are urgently needed.

DOES THE STRATEGY PROVIDE FOR EVALUATION OF RESEARCH PRIORITIES AND AN ASSESSMENT OF RESEARCH PROGRESS?

NNI (NEHI 2008) states that "the task forces analyzed the portfolio of projects in each category to determine the balance of effort. . . . In addition to tabulating the number of projects and total funding . . . the task forces considered the breadth of research, such as variety of nanomaterials or routes of exposure" (NEHI 2008, p. 7). Although there is some justification in the document for the research priorities selected, it is marginal. The research priorities were developed in NNI (NEHI 2006) and NNI (NEHI 2007), but it is not clear from those documents how they were ultimately selected.[2] It is also not possible to discern relative priorities among the various research needs shown in each of the five categories or even among the five categories. Although the strategy clearly states that no effort was made to set priorities among the categories, because the category of instrumentation, metrology, and analytic methods is cross-cutting—supporting research in every other category—it has high priority itself (NEHI 2008, p. 9).

In general, the process behind the selection of the research priorities and the later priority weightings in the emphasis diagrams is not transparent. There also is little discussion of the itemized research needs in the emphasis diagrams. Many of the research needs make sense, but a few are questionable. For instance, why put the development of materials to support exposure assessment before the development of materials to support toxicology studies (NEHI 2008, p. 18)? Why delay research into alternative surface-area measurement methods for 10 years in light of its being identified as a critical research subject (NEHI 2008, p. 18)? Why delay the development of high-throughput screening methods by 5 years (NEHI 2008, p. 24)? There are many other examples. Further discussion of research priority-setting in each of the research categories is discussed in Chapter 4.

Without clear goals, as discussed above, effective priority-setting is nearly impossible. Without effective priority-setting among research needs, measurement of research progress makes little sense.

[2]NNI (NEHI 2006) and NNI (NEHI 2007) identify principles for identifying and setting priorities for EHS research, including value of information, leveraging research by other governments and the private sector, and adaptive management of nanomaterial EHS research; but it is not clear how these principles were used in selecting the research priorities.

DOES THE STRATEGY IDENTIFY THE RESOURCES NEEDED TO ACHIEVE STATED GOALS?

The strategy does not identify resources necessary to address questions concerning EHS research needs for understanding nanomaterials and does not identify the projected resources needed to execute the strategy, including funding, education, and training of personnel. This absence of a discussion of resources constitutes a major deficiency. Although the detailed analysis of nanotechnology EHS expenditures in FY 2006 provides information about what was spent during that particular year, there is no assessment of whether the spending was adequate to address EHS research needs voiced by individuals, organizations, and governments worldwide (Denison 2005; Maynard 2007; Ziegler 2007), whether the expenditures by the agencies were appropriate to address EHS research needs based on their missions, or how much additional resources would be required.

From the FY 2006 expenditures, it is difficult even to assess the balance of research among objectives, because in many cases the monetary value of a research project is a function of an agency's budget rather than of scientific needs. However, with respect to the overall funding level, the strategy document suggests that sufficient funding is already being dedicated to EHS research by the NNI and that funds should not be redirected to this research from other kinds of nanotechnology research. The strategy states, surprisingly, that "the current balance of research funding addresses such basic investigations and supports regulatory decision making. Gaps identified in the research that supports regulatory decision making should not be addressed at the cost of broad-based fundamental research—to do so would ultimately undercut the U.S. nanotechnology initiative as a whole" (NEHI 2008, p. 46). An appropriate research strategy should quantify the resources needed to address research priorities, identify where the resources might come from, and ensure that there is adequate training of personnel.

DOES THE STRATEGY PROVIDE ACCOUNTABILITY FOR ACHIEVING STATED GOALS?

Although lead agencies are identified for each of the five research categories, there is no accountability—no organization or person will be held accountable for the success or failure of the strategy to deliver results. The strategy states that "the success of the strategy . . . depends on the collective efforts of the NNI agencies through their individual and joint activities coordinated by the NEHI Working Group and the NSET Subcommittee. Progress will also depend on the agency priorities and resources" (NEHI 2008, p. 7). That is, accountability is divided among agencies, a working group, and the NSET Subcommittee, and progress depends on individual agency priorities and resources.

In comments to the committee, Terry Medley, of DuPont, stated (Medley 2008, p. 4):

> The executive summary of the document raises two critical questions. 1) Who will implement the strategy? 2) How will the strategy be implemented? With regard to who will implement the strategy, it identifies agencies that will serve as coordinators for the five research areas, it does not explicitly address the coordinating agencies ability to make final decisions regarding the activities in their specific research areas. With regard to how the strategy will be implemented it states that as nanotechnology EHS research and knowledge continue to grow, needs and priorities will evolve. Accordingly, this plan will be reviewed and updated as research progresses. Again, the strategy calls for a coordinated approach as the research progresses, but does not specifically address who has the authority to make changes or revisions needed.

Because of the absence of clearly stated goals and measurable objectives, it is difficult to imagine how the strategy could be used objectively to measure the success of future research efforts. Accountability may require specific quantifiable objectives so that one can determine whether progress is being made.

The strategy does demonstrate how the NNI and other federal agencies have worked together effectively to coordinate their funding and assessment of EHS aspects of nanotechnology and thus avoided, to some extent, unnecessary duplication of research. That is indicative of the function of the NNI, which has been described as a "coordinating platform" (Murashov 2008). However, there is essentially no stakeholder input outside these federal agencies, and in essence the strategy has been constructed in a federal vacuum.

The strategy does not adequately incorporate input from other stakeholders, such as industries that produce nanomaterials and end users of nanomaterials; environmental and consumer advocacy groups; foreign interests, including substantial efforts of other countries; and local and state governments. The committee recognizes that the 2006 and 2007 NNI documents have undergone public comment, but public comment is not the same as actively engaging other stakeholders in the process. In light of the extensive contributions and interests of other nations, in particular the European Union and Japan, it is particularly surprising that the federal strategy appears largely to ignore what other nations are doing. International coordination would help to ensure that there is not unnecessary duplication of research efforts and that data quality is maintained.

To have effective stakeholder engagement requires that the strategy be developed through a process of stakeholder input and consultation. There are many models of this, including tripartite input from government, industry, and civil society representatives, which would ensure that the strategy developed served the needs of regulators, industry, and citizens without being unduly biased by any particular group. Another model is the National Institute for Occupational Safety and Health's National Occupational Research Agenda, in which research

needs and directions are developed through a well-established system of stakeholder input (NORA 2008).

Without input from and accountability to external stakeholders, it is not possible for government agencies to develop an effective research strategy to underpin the emergence of safe nanotechnologies. The reason is that federal agencies have a vested interest in justifying the applicability of current efforts rather than critically assessing what is not being done and how deficiencies might be addressed. For example, when agencies are developing their own research strategies, they tend to ask, what research can we do within our existing capabilities?, rather than the more appropriate, What research should we be doing? Other relevant questions need to be addressed, such as, Are resources adequate? Are adequate mechanisms and organizational structures in place to achieve the desired goals? As a result, the federal strategy becomes a justification for current activities based on a retrospective examination that demonstrates success rather than the development of a prospective strategy that questions current practices with an eye to future research needs. That is reflected in remarks by William Gulledge, senior director of the Chemical Products and Technology Division of the American Chemistry Council, an industry trade association, who emphasized the need for a more broadly defined strategy, noting that the NNI plan "'represents a bottom-up approach where agencies identify their priorities. . .We still need a top-down, broad, overall look' at nanomaterials" (Risk Policy Report 2008, p.2).

CONCLUSIONS

The committee concludes that *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* should not be considered a nano-risk research strategy, because it is missing the necessary elements. Nevertheless, it is important to recognize what the document is and what it has achieved. The NNI strategy represents an impressive collaboration and coordination effort involving 18 federal agencies whose nanotechnology research interests span the gamut from exploratory research (for example, research funded by the National Science Foundation to characterize materials on the surface of nanostructures or nanoparticles) to targeted research (for example, research funded by the Environmental Protection Agency to examine the bioaccumulation of nanomaterials in the food chain). The increased collaboration will probably eliminate unnecessary duplication of research efforts. As the document states, "agencies whose missions support nanomaterial research may use this document to better understand where their activities fit into the overall strategy. Moreover, agencies can use it to identify opportunities for collaboration and cooperation, and manage their relationships with other agencies and their research" (NEHI 2008, p. 6).

The development of the strategy has led to extensive discussion and consensus-building among program managers in the various agencies that participate in the NEHI Working Group and in the NSET Subcommittee; in many

cases, these are the same program managers who set priorities and make funding decisions on research proposals (Carim 2008). The strategy is also referenced in requests for research solicitations and has stimulated proposal submissions by individual researchers (Carim 2008). In addition, it has spawned the development of EHS strategies by federal agencies.

The limitations of the document may be due to the NNI-NEHI structure, in that perhaps only a bottoms-up approach could be developed. The NEHI is primarily a coordinating body rather than a visionary one (see Chapter 1). It sees its role as ensuring coordination of activities of otherwise independent agencies that have their own distinct missions. That limits the ability of the NEHI and the NNI to create a vision and an overall plan for federal research to understand potential EHS risks posed by nanomaterials most efficiently. Without an explicit vision or clearly stated purpose, the result of the effort is what is reflected in the document: a compilation of studies rather than a more difficult priority-setting and development of milestones and evaluation measures for determining progress toward a vision. As the strategy states, "development of specific EHS research programs—by NNI agencies singly or jointly—is informed largely, but not exclusively, by the research and information needs of agencies with regulatory and oversight responsibilities" (NEHI 2008, p. 3).

The structure of the NNI and the NEHI, comprising the activities of a large number of diverse agencies with differing missions, makes the development of a visionary and authoritative research strategy extraordinarily difficult. Because the NEHI has essentially no authority over the individual agencies—and so no one agency has authority to shape a research agenda within a second agency—this means that the product of the NEHI can be little more than a compilation of individual agency agendas. Because the NNI has no authority to make budgetary or funding decisions (see Chapter 1) and simply relies on the budgets of its member agencies, it has no resources or influence to shape the overall federal EHS research activity. The NEHI must devise a research strategy that is responsive to individual agency budgetary priorities rather than developing a much-needed vision and strategy that include assurances that adequate resources go to the appropriate agencies to realize the vision. Finally, the NNI has no central figure who is not affiliated with any of the member agencies but is charged with oversight of EHS research and has the budgetary authority to make the necessary research and resource decisions.

Because the NNI is responsible for ensuring U.S. competitiveness through the development of a robust research and development program and ensuring the safe development of nanotechnology, it may be perceived as having a conflict of interest. That may be implied in the previously cited statement in the NNI document that addressing EHS research gaps must not detract from fundamental research to develop the technology. The committee concludes that the conflict constitutes a false dichotomy and that strategic research on potential risks posed by nanotechnology can be an integral and fundamental part of the sustainable development of nanotechnology. Nevertheless, a clear separation of accountability for development of applications and assessment of potential implications of

nanotechnology would help to ensure that the public-health mission receives appropriate priority. The nation has addressed concerns about separation of technology development and regulatory oversight authorities for a new and potentially hazardous technology in the past. When both supporters and critics of nuclear energy raised strong concerns about both development and regulatory oversight being housed in the Atomic Energy Commission (AEC), Congress responded in 1974 by creating the Nuclear Regulatory Commission (NRC) to house the oversight function and moved the technology development research into the Department of Energy (U.S. NRC 2008). Congress and the executive branch should consider this model in assuring the safe development of nanotechnology. As an interim step, the NNI Amendments Act of 2008 [H.R.5940.RFS] establishes a separate authority within the NNI with accountability for EHS research.

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4

Review of High-Priority Research Topics, Research Needs, and Gap Analysis

In this chapter, the committee examines the analysis and conclusions presented in Section II (pp. 9-44), "Summary of NNI EHS Research: Portfolio Review and Gap Analysis," of the National Nanotechnology Initiative document *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* (NEHI 2008). That section discusses research categories, research needs, knowledge gaps, and inventories, and it presents the most specific and detailed technical discussion of topics relevant to decision-making for understanding and assessing the environmental, health, and safety (EHS) implications of nanotechnology. Although the committee perceived the NNI document as falling short of its aim of defining a research strategy, elements of Section II would be important for future development of a federal research strategy.

The committee approached the evaluation of Section II of the NNI document by asking four questions (see Box 4-1) that were directly responsive to the charge to the committee, which was to review the scientific and technical aspects of the draft strategy and comment in general terms on how the strategy would develop information needed to support the EHS risk-assessment and risk-management needs with respect to nanomaterials. The discussion that follows is framed by the preceding materials in Chapters 2 and 3, on the elements of a research strategy, and the committee's own collective assessment of federally funded research in FY2006, which allowed the committee to identify and evaluate the strengths and weaknesses of the NNI document.

As indicated in Chapter 2, an important challenge in developing a risk-research strategy is defining its focus—in effect, the rationale for project selection. Resources are limited, and they must be deployed to create relevant information as efficiently as possible. Embedded in any strategy document are underlying principles that determine the allocation of resources, mechanisms by which research is funded, and how research is evaluated. In connection with the four questions in Box 4-1, those principles determine what is "appropriate" or "correct." The committee believes that the value-of-information (VOI) paradigm

BOX 4-1 Questions that Structured the Committee's Analysis

- Is the list of research needs appropriate?
- Is the gap analysis complete and accurate?
- Was the priority-setting of needs correct?
- Does the research support environmental, health, and safety risk assessment and risk management?

might have been an excellent approach to informing the development of a research strategy from the outset. The committee recognizes that the 2006 NNI report identified VOI as one of the principles for identifying and setting priorities for EHS research.

A VOI approach would help assess what information would be most valuable in improving understanding of the EHS risks of engineered nanomaterials. Its application relies on assessment of both the quality and the relevance of information, and it necessarily weights efforts in favor of the most pressing research needs.

One fundamental rule of thumb emerging from this approach is that information that cannot change one's (or one's agency's) decision *has no additional value* for decision-making. New knowledge could have other favorable social effects and advance our understanding of the natural world and still not have a place in a nanotechnology EHS research strategy. Application of quantitative VOI approaches clearly is premature, but qualitative concepts could be used in the development of an effective EHS research strategy.

In the review of Section II of the 2008 NNI document, it was apparent that a number of issues cut across most or all of the research priority topics. They are highlighted in the next section of this chapter and are followed by an in-depth technical evaluation of each of the high-priority research topics in Section II that reflects issues specific to the five research categories (Box 4-2). The last section of the chapter discusses the committee's assessment of the current distribution of federal investment in nanotechnology-related EHS research; it became clear to the committee when it evaluated the NNI document that its perception of the balance of relevant research among the five research categories differed substantially from the NNI's perception (see p. 44, NEHI 2008).

CROSS-CUTTING CONCLUSIONS ON ANALYSIS OF SPECIFIC RESEARCH CATEGORIES

The NNI strategy document organizes EHS research into five overarching topical categories (see Box 4-2), with five research needs in each category. Each category addresses research important to EHS risk assessment. The committee

BOX 4-2 Environmental, Health, and Safety Research Categories Identified by the National Nanotechnology Initiative

- Instrumentation, metrology, and analytic methods.
- Nanomaterials and human health.
- Nanomaterials and the environment.
- Human and environmental exposure assessment.
- Risk-management methods.

generally agreed that the five categories are logical, complete, and appropriately weighted in scope. The five categories align with the missions and research programs established within and across the regulatory and research agencies that participate in the NEHI Working Group. They provide an excellent organizational framework for describing research activities. Some committee members questioned the position of risk assessment in the document—whether it should be elevated into a separate category or left as an integrating research theme—and this was the subject of some debate. Otherwise, the committee concluded that the basic topics spanned the diverse and complex space of this problem and provided a good organization for the listing of research needs.

The committee found that, with some exceptions, the specific research needs within each category were appropriate for nanotechnology EHS research. The research needs identified substantial aims important for the given research category. However, the committee believed that the lists were incomplete, in some cases missing elements crucial for progress in understanding the EHS implications of nanomaterials or not recognizing common research threads across research categories. For example, the issue of environmental exposure received insufficient emphasis in the exposure-assessment discussion although it was addressed in the nanomaterials in the environment section. The potential for nanomaterials to undergo change within biologic matrices is a common research theme that should be addressed in discussions of nanomaterials and the environment; nanomaterials and human health; and instrumentation, metrology, and analytical methods. Characterization of chemical and biologic reactivity of nanoparticles was not included as a research need in the report. Often, as will become clear, the missing research pieces would have been at an interface between categories, and their absence could have resulted from confusion about where to place them. For example, is environmental exposure a problem best tackled by researchers focused on environmental impact or by those looking at exposure assessment? Missing research needs are detailed in the appropriate sections of the topical reviews that follow.

The gap analysis is neither accurate nor complete in laying a foundation for a research strategy. As discussed in Chapter 3, the NNI strategy document defines a "gap analysis" as a major input in the development of its research strategy (pp. 6-7). The approach of evaluating the status of a specific technical field at a given time (for example, the snapshot) and comparing it with expected or desired goals is a useful exercise. However, the gap analysis by the NNI embodies perhaps the most important flaw that the committee identified in the document. Issues arising from the ineffective gap analysis led to serious deficiencies in all topical categories described in Section II.

The gap analysis was inaccurate because the relevance of existing research projects to the listed research needs was generally overstated. In addition, equating the focus of research projects with research results that address a specific risk-research need is misleading. The document consistently—in every part—assumed that funded projects with only distant links to a research question were indeed meeting that research need. For example, in the measurement and characterization discussion, the development of a subangstrom-resolution microscope was said to fulfill the need "to detect nanomaterials in biological matrices." In another category, human health, it was the committee's expert judgment that more than 50% of the inventoried projects[1] describe research directly relevant to therapeutics rather than to any of the research needs listed as relevant to potential EHS risks related to nanomaterials. The discussion of risk management, for example, considered economists who were collating the anticipated size of the markets for nanotechnology as addressing needs in risk management. The committee considered that many of the 246 research projects listed in Appendix A were of high scientific value but that they were of little or no direct value in reducing the uncertainty faced by stakeholders making decisions about nanotechnology and its EHS risk-management practices. Thus, NNI (NEHI 2008) significantly overestimates the currently funded general research activity focused on EHS research, and this contributes to the inaccuracy of the gap analysis.

The second issue related to the gap analysis is that the approach taken limits the analysis to 1 year (FY 2006) of federally funded research and does not consider EHS research supported by the private sector and elsewhere in the world. Relying solely on U.S. government research has led to a document that lacks the necessary breadth to position our nation's research on the international scene wisely. A recognition of the large-scale effort in Japan (Thomas et al. 2006), for example, to complete exposure and hazard assessments of aerosols might alter the priorities for nanotechnology EHS funding in this country. A more complete gap analysis would cast a far wider net across the technical peer-reviewed literature and related disciplines.

[1]The president's 2006 budget considered that there were 43 projects in this category; NNI (NEHI 2008) considered that there were 100 projects, the additional 57 projects being ones that are not "primarily aimed at understanding risks posed by nanomaterials" but also include research on medical-application-oriented research (NEHI 2008; Teague, unpublished material, 2008).

The criteria for priority-setting of research is not clearly stated. Information on priority-setting is only implicit in the graphical timelines (Figures 3, 5, 7, 9, and 11), and rarely explicit in the text. In evaluating each high-priority research need in Section II, the committee consistently observed that there was no clear rationale as to how research priorities were determined. Furthermore, the only representation of research priorities was that implied by the graphical timelines; and the priorities were not discussed at length in the text of NNI (NEHI 2008).

The committee assumes that the criteria for priority-setting stem from NNI (NEHI 2007), *Prioritization of Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials: An Interim Document for Public Comment,* but that document is cited only once in NNI (NEHI 2008), and then only in the context of establishing the five research categories and 25 research needs. Even if those criteria were the basis of the graphical timelines, the lack of explanation in the text makes it nearly impossible to assess the rationale behind the decisions made by the NNI in constructing the figures. As a consequence, it was generally believed that the absence of more explicit information on priority-setting limits the value and impact of the list of research needs.

In addition, there were a few cases in which the committee questioned the validity of priorities of research needs represented in the graphical timelines. For instance, under research need 2 of the instrumentation, metrology, and analytic methods category ("Understand how chemical and physical modifications affect the properties of nanomaterials," p. 14), it is unclear why "Understanding the effect of surface function on mobility and transformations in water" is considered to have medium-term priority when, given the current production and use of unbound nanoparticles, it must be assumed that nanomaterials are already entering waterways.

The document suffers universally from a lack of coherent and consistent criteria for determining the value of information provided by various research activities and for establishing priorities among the research needs. Criteria and a framework for priority-setting of research would ideally be based on an understanding of the value of each of the research needs and the relationships between them. The committee observed that little or no attempt was made to assess how the information that would be generated by addressing the research needs would be used beneficially. Consequently, there is neither a systematic framework within which research needs can be prioritized, funded, and evaluated nor a mechanism for differentiating between high-cost low-value research and lower-cost higher-value research. Both types of research need to be considered in making pragmatic decisions on directing limited resources to address a specific set of challenges.

For example, many of the research needs and topics listed in the instrumentation, metrology, and analytic methods category are relevant to EHS risk assessment and management, but without a means of distinguishing research with high and low value in addressing potential risks, projects of questionable

value are cited as addressing EHS needs. Research listed as relevant to risk in this category includes the National High Magnetic Field Laboratory (National Science Foundation [NSF], project a1-30), Bioabsorbable Membranes for Prevention of Adhesion (National Institutes of Health [NIH], project b2-2), and Using Viral Particles to Detect Cancer (NIH, project b5-6). It is hard to see how such projects will lead directly to information that reduces uncertainty and informs decision-making related to assessing and managing potential risks posed by nanomaterials. If such research is undertaken at the expense of studies of higher value in relation to EHS, it will be indicative of a broken or absent strategy.

A similar situation is found in the Nanomaterials and Human Health research category. In the NNI assessment of relevant FY 2006 research projects, a large portion of the research targets human health through therapeutics. Its primary focus is to develop novel strategies for treating cancer and other ailments that deserve the attention of scientists and clinicians. That may accelerate progress in cancer research and will undoubtedly advance knowledge of nanomaterial-biologic interactions that are relevant to potential risks posed by specific nanomaterials, but it will not contribute directly to the body of knowledge needed to ensure protection of public health and the environment from potential risks posed by nanotechnology and its products. In the detailed assessment of the NNI document that follows, the committee concluded that the current research portfolio does not address the most rudimentary problems in environmental, health, and safety.

ANALYSIS OF SPECIFIC RESEARCH CATEGORIES

The subsections below address the five research categories (see Box 4-2), considering the questions presented in Box 4-1. Each subsection is divided into three parts; the introduction that explains the committee's approach, the evaluation and assessment, and the conclusions.

Instrumentation, Metrology, and Analytic Methods

Introduction

Because the behavior of nanomaterials depends on their structure at the nanoscale (such as physical shape and size and the location and distribution of chemical components), sophisticated characterization and measurement methods are essential for understanding and addressing potential risks.

The potential association between scale-related physicochemical characteristics and biologic effects of nanomaterials challenges conventional approaches to risk. In the past, risk decision-making was typically driven by the chemical constituents of a material, not by physical structure—although there are a few notable exceptions, such as asbestos and the distinctions between in-

halable and respirable airborne particles. That approach has generally enabled risks associated with materials to be managed reasonably effectively. But the likelihood that some nanomaterials can cause harm by virtue of their nanoscale structure places a much greater emphasis on aspects of nanomaterials not previously considered important.

The challenges in instrumentation, metrology, and analytic methods for identifying, assessing, and managing nanotechnology EHS effects are threefold: establishing the usefulness of methods currently used to assess risk, translating existing methods to address risk (a process of method bridging), and developing new methods. Those challenges (once risk parameters are clarified) raise three overarching issues: grouping nanomaterials that have similar risk-relevant characteristics, ascertaining the appropriate tolerances of risk-related measurements, and determining the context of risk-related characterization and measurement.

An ability to group nanomaterials according to their biologically relevant behavior is essential if material variants are to be rationalized into a finite number of material classes. Developing methods to assess and to monitor the potential effects of every combination of size, form, chemistry, and other properties of engineered nanomaterials clearly is not feasible. But if materials with similar biologically relevant properties could be grouped, it might be possible to reduce the challenge of characterization to a much smaller set of nanomaterial groups.

Tolerance, the accuracy and precision that measurements need to support risk-based decisions, is likely to vary from nanomaterial to nanomaterial and also over time as new information on the importance (or lack thereof) of specific physicochemical characteristics is developed. Without some idea of the tolerance to which measurements should be made, it is not possible to establish a clear research strategy. For instance, if particles of a nanomaterial have similar biologic behavior whether they are 20 nm or 40 nm in diameter (Jiang et al. 2008b), investing tens of millions of dollars on instrumentation with a resolution of 0.05 nm will not advance their risk assessment and management to any important degree.[2] Understanding appropriate tolerances will be an iterative process that emerges from a well thought-out and integrated research strategy. If resources are to be assigned appropriately, some initial estimates of what is important are needed.

That leads to the third overarching issue: context. Risk-related nanomaterial metrology will depend on the type of material under investigation, the context in which the material is being used (or exposure occurs), and the current level of knowledge on which material characteristics are likely to be important. Metrology requirements for exploratory research on biologic interactions will differ from those for evaluating material toxicity, which in turn will bear only a passing resemblance to measurement and characterization requirements for exposure monitoring and material-dispersion evaluation. Likewise, analytic methods will need to be tied, where possible, to important physicochemical charac-

[2]This is a hypothetical example that is loosely based on the Transmission Electron Aberration-Corrected Microscope (TEAM) project discussed in NEHI (2006).

teristics that may differ between nanomaterials. For example, understanding the interactions between gold nanoparticles and DNA will require a detailed understanding of particle shape, size, and surface chemistry; but in monitoring exposure to the same material in the workplace, it may be sufficient to measure mass concentration or surface area concentration for all particles and aggregates that are smaller than a few micrometers in diameter.

In summary, components of an effective research strategy to address nanomaterial instrumentation, metrology, and analytic methods in the context of risk should include

- An assessment of the current state of the art of nanomaterial analysis.
- Classification and grouping of nanomaterials that convey the physical and chemical properties relevant to biologic effects.
- Definition and evaluation of appropriate accuracy and precision (tolerance) for measuring those properties.
- Identification and clarification of the analytic needs of researchers working with nanomaterials in toxicology, exposure assessment, environmental science, and medicine.
- Standardization of methods and metrics used in nanotoxicology studies, including standardized approaches for route of administration and dose metrics.
- Cross-disciplinary translation of established methods to the needs of the nanotechnology-related EHS researchers.
- Development of new methods that meet the specialized demands of nanotechnology-related EHS research.

Evaluation and Assessment

Each of the five identified research needs in this category (NEHI 2008, Figure 3, p. 18) is important for nanoscience and nanotechnology generally (see Box 4-3). However, the breadth of many of the research needs is so great that it is difficult to understand how they will be useful in practice for guiding a nanotechnology-related EHS research strategy.

There is poor balance between near-term needs for research targeted to immediate issues faced by the EHS community (including characterization of nanomaterials in toxicology studies and monitoring of occupational exposures and environmental releases) and evaluation of the efficacy of control and containment measures.

There also appears to be a gap between the identified research needs and the examples of funded research provided in the text that is not clearly resolved (pp. 12-17 and 57-67). Many of the FY 2006 research projects listed in Appendix A as relevant to this research category—although important for the advancement of nanoscience and nanotechnology—have little obvious relevance to EHS issues. There is little effort to address the gap between what is needed and what has been funded.

BOX 4-3 Research Needs for Instrumentation, Metrology, and Analytical Methods

1. Develop methods to detect nanomaterials in biological matrices, the environment, and the workplace.
2. Understand how chemical and physical modifications affect the properties of nanomaterials.
3. Develop methods for standardizing assessment of particle size, size distribution, shape, structure, and surface area.
4. Develop certified reference materials for chemical and physical characterization of nanomaterials.
5. Develop methods to characterize a nanomaterial's spatio-chemical composition, purity, and heterogeneity.

Source: NEHI 2008.

Research need 1, "Develop methods to detect nanomaterials in biological matrices, the environment, and the workplace," is important but broad and would benefit from being split into three research needs that address biologic matrices, the environment, and the workplace separately. Detecting exogenous nanomaterials in biologic matrices is essential for understanding their movement in the body and doses at the organ, cellular, and subcellular levels. Likewise, detecting nanomaterials in the environment will be essential for both monitoring ecologic exposures and containing possible releases. Workplace exposure is an immediate issue for all of nanotechnology, and methods to address it are necessary. Those three topics underpin much of the research and action needed to understand and address potential environmental and health implications of engineered nanomaterials, and their discussion should be tightly linked to research needs described elsewhere in the document.

All the specific aims listed under this research need are useful, but they constitute a collection of research interests that lacks coherence. Creating three new research needs would enable more attention to be given to sequencing relevant measurement and characterization research in the context of what is needed to address potential risks.

In common with other research needs, this section is filled with examples of funded projects that bear little relationship to the overall stated goals. For example, several projects mentioned on p. 13 of the NNI document focus on single-molecule fluorescence. Molecular-level interaction of nanomaterials with cells is interesting, but it does not directly concern detection of nanomaterials in biologic matrices and has little relevance to the practical needs for nanotechnology-related EHS research. Likewise, research aimed at developing nanoparticles as contrast enhancers has limited relevance to the general problem of detecting

exogenous nanoparticles within biologic matrices, given that the aim of such research is specifically to develop nanoparticles that are easy to detect. Similar issues arise in the case of cited research on sensors: the projects described are of a general nature, and their specific value to EHS issues is not clear. Without clearer explanation, it is hard to see how, for example, the following projects are justified as addressing nanotechnology-related EHS research needs: National High Magnetic Field Laboratory (NSF, project A1-30), Bioabsorbable Membranes for Prevention of Adhesion (NIH, project B2-3), Using Plasmon Peaks in Electron Energy-Loss Spectroscopy to Determine the Physical and Mechanical Properties of Nanoscale Materials (Department of Energy, project A2-5), and Using Viral Particles to Detect Cancer (NIH, project B5-6).

Research need 2, "Understand how chemical and physical modifications affect the properties of nanomaterals" sits uneasily in this section of the document, as in this area measurement needs cannot be divorced from biological and environmental behavior. It would have been far more effective if research need 2 was directed specifically to issues relevant to biologic and ecologic effects, perhaps by restating it as "biologic" properties. More important, this suggested research need, the correlation of the fundamental structure of a nanomaterial with its biologic properties, does not belong in this research category. Rather, because it is driven primarily by the study of biologic interactions, it should be addressed as a cross-cutting research need between the nanomaterials and human health and the nanomaterials and the environment categories. What does belong in this high-priority group is a discussion of how to characterize the molecular properties of the nanomaterial-biologic and nanomaterial-environmental interface. Information on a nanomaterial's physical and chemical properties is critical for enabling a general understanding of structure-function relationships that will guide future nanotechnology-related EHS research. It is a long-range and exploratory research need, but it is highly relevant to the potential safety or harmfulness of increasingly sophisticated engineered nanomaterials and should form a key component of a strategic research program.

Although the overall need is too broad to be of much use in addressing nanotechnology-related EHS issues, the two specific research subjects identified—"Evaluate solubility in hydrophobic and hydrophilic media as a function of modifications to further modeling of biological uptake" and "Understand the effect of surface function on mobility and transformation in water"—are by contrast too narrowly defined to support strategically relevant progress. These two research areas on their own do not adequately address the studies needed to develop a clearer understanding of how physical and chemical modifications affect the properties of nanomaterials.

Research need 3, "Develop methods for standardizing assessment of particle size, size distribution, shape, structure, and surface area," is based on the fact that such methods are vital for developing a clear understanding of how engineered nanomaterials might affect human health and the environment—and how

to avoid the effects. Many of the specific aims listed here are relevant to and important for addressing nanotechnology-related EHS issues. This should remain a high priority research need and receive sufficient attention and support to ensure timely and relevant progress.

What is missing from the strategy document is an assessment of relative importance: What standardization and metrics are suitable for risk assessment and management? Without that context, the research aims become a vehicle to justify broad metrology research across nanotechnology to the detriment of more targeted risk-relevant research. That is especially the case where the precision and accuracy needed for exposure monitoring or toxicity testing are not as high as those needed for quality control or exploratory research.

One emphasis that is essential to this research need but is missing is the importance of community-building activities. Only the broad research community can define and standardize biologically relevant, effective protocols for nanomaterial characterization. The free availability and wide dissemination of methods should be as important an outcome of community-building activities that include round-robin evaluations as the measurement of the accuracy and precision of the methods.

Research need 4, "Develop certified reference materials for chemical and physical characterization of nanomaterials," is important but complex. Standard materials are required to validate the characterization protocols described in research need 3. It is also important to identify metrics with which the standards would be characterized and made available, for example, surface area, size, or chemical activity per unit surface area, such as reactive oxygen species per surface area (Jiang et al. 2008b). Substantial community-building activities (for example, workshops and multistakeholder input) are required to create a pool of useful materials that are relevant to nanotechnology-related EHS research. Efforts to train users to handle and work with the nanomaterials in biologic and environmental testing should also be addressed.

In common with other research needs in the category, the question, How much is enough? is important for assessing and managing risk and is not addressed. Without such understanding of the limitations of reference materials, there are no safeguards to prevent inappropriate levels of investment on irrelevant materials.

Research need 5, "Develop methods to characterize a nanomaterial's spatio-chemical composition, purity, and heterogeneity," is broad, and tolerance and relevance are not addressed in the subtopics. As discussed previously, this research need involves the characterization of nanoscience generally and is ill-suited to the goals of addressing potential EHS effects of nanomaterials. It may be that the intent of this research need was to characterize the nanomaterial-biologic interface. It would be more compelling if it included specific discussion of the critical needs for characterizing this interface and of the tools that could be applied to the needs. Metrology is required that goes beyond nanomaterial detection (research need 1) and nanomaterial gross physical properties (research

need 3) because it is important in connection with the molecular-level detail of the nanomaterial-biologic interface. However, to conduct this research requires specific quantitative analysis with the necessary spatial resolution and strategies for handling the challenges of such analysis in relevant biologic matrices.

Some discussion of research in the text (NEHI 2008, p. 16) is not connected to the subtopics in Figure 3. These are important research topics, but their linkages to the identified research needs are not apparent. The descriptions of research projects in the text are generally current exploratory and application-based research projects that in some cases happen to have some relevance to risk. Although the identified research needs and topics intersect to a degree with the needs of the nanotechnology-EHS community (NEHI 2008, Figure 3), the funded programs are often disconnected.

Overall, this section of the report could be improved if it presented a clear strategic route to addressing characterization-related EHS issues. The priorities presented, although reasonable in parts, do not provide such a route.

A notable absence from the instrumentation, metrology, and analytic methods category is research related to the chemical properties of nanomaterials. That would involve adding a topic to research need 5 to address adsorption, compatibility, and reactivity of nanomaterials. For example, the nonspecific fouling of nanomaterial surfaces has important consequences for the absorption, fate, and distribution of the material. Methods to evaluate the corona, the molecules and macromolecules that interact with nanomaterial surfaces, accurately and rapidly are thus of immediate importance. In addition, acellular assays that can monitor reactivity of nanomaterials, such as their participation in the generation and cycling of reactive oxygen species, are important and should be addressed. Another important topic is the change in physical and chemical characteristics of the nanomaterials in biologic systems. For example, nanomaterials of some size may agglomerate to different degrees in a biologic fluid and have different effects (Maynard 2002; Oberdörster et al. 2005; Jiang et al. 2008a).

The 2006 funded projects described in the document do support EHS risk assessment to some extent, but the degree of support is not commensurate with the investment, and the mechanisms to apply many of these research projects to nanotechnology EHS seem to be lacking. The funded projects are important, and they represent a large research investment that broadly advances nanoscience and nanotechnology; but they do not necessarily increase our ability to identify, assess, and manage the potential EHS effects of engineered nanomaterials.

Largely missing are projects that directly advance both immediate applied research and long-range fundamental knowledge specifically directed towards addressing nanotechnology-related risk research.

More effective identification, assessment, and management of nanotechnology-related risk is a challenging goal that will require many resources and focused effort; the current document's description of 2006 research suggests that this investment is not being made.

Conclusions

A strength of this section is that the importance of metrology and analysis is highlighted and recognized. The identification of standard reference materials and methods is notable, and represents some of the research topics (for example, production of commercial samples for workplace monitoring) that need to be present in a federal research strategy. The "Summary of Balance-Assessment for Instrumentation, Metrology, and Analytical Methods Category" (p. 17) is critical for seeing how all the programs fit together; its expansion and a clearer analysis would go a long way toward conveying the big picture.

There is no analysis of the state of the art to justify existing and future research investments. No consideration is given to the relevance of current abilities and methods and the extent to which they negate the need for future research in some fields. For instance, methods already exist to characterize airborne particles by size, mass, surface area, and number concentration that extend down to a few nanometers. Analytic techniques exist that are capable of measuring trace quantities of specific chemicals; and electron and atomic-force microscopy with a resolution of tenths of a nanometer are mature technologies. To what extent are they already being used to address potential nanomaterial effects?

There is no attempt to translate established methods to nanotechnology-related EHS research needs. No consideration is given to how existing and emerging analytic methods might be applied to EHS effects. There is little evidence that characterization techniques in fields outside risk research can be applied to potential effects without substantial investment in translating the technology to a new kind of application or developing risk-specific technologies. Justifying general metrology research as relevant to risk research without appropriate "bridging" is deceptive.

Funded projects are disconnected from research needs. The list of projects funded in FY 2006 and identified as relevant to these research needs seems to be a list of convenience in that it represents current exploratory and application-based research that may have some relevance to addressing risk. Assessing the projects does not provide a strategic route to addressing characterization-related EHS issues. The text is littered with subjective qualifiers: research "can be applied," "could be useful," "will likely benefit." It is the language of wishful thinking, not critical analysis.

Research is not relevant to immediate nanotechnology-related EHS needs. No consideration is given to the accuracy and precision required for risk-relevant nanomaterial characterization. As a result, the research is open-ended and apt to consume considerable resources in addressing questions that are not relevant to protecting public health and the environment. No consideration is

given to the different contexts within which risk-related measurements are needed; consequently, there is a danger of substantial research investment in projects and programs that do not address critical issues.

Finally, it is important to keep research on instrumentation, metrology, and analytic methods a primary focus in the federal strategy. Progress in nanotechnology-related EHS research requires advances not just in hazard identification, exposure assessment, standard development, and risk management but in the measurement and characterization of the materials. The current strategy falls short of supporting the necessary research. More effort is needed to ensure that existing and future research efforts address nanotechnology-related EHS needs in a way that provides stakeholders with the knowledge and tools they need to identify, assess, and manage potential risks associated with nanomaterials across their life cycle.

Nanomaterials and Human Health

Introduction

The rapidly expanding development, marketing, and application of nanomaterials with little information on their ability to interact with or disrupt biologic systems raise concerns about their safety in occupational and environmental settings. The safety of nanomaterials is of concern to multiple stakeholders, including government bodies with human or environmental health missions (for example, the Food and Drug Administration, the Environmental Protection Agency [EPA], and the National Institute for Occupational Safety and Health), commercial producers, and nongovernment organizations (for example, the Natural Resources Defense Council, the Environmental Defense Fund, and the American Federation of Labor and Congress of Industrial Organizations). Each of those stakeholder organizations focuses on EHS-related concerns regarding nanomaterials, including medical and therapeutic applications and safety, occupational exposure and worker health, and environmental and consumer exposure and health. The committee reviewed the adequacy of the nanomaterials and human health research section in the context of its completeness, accuracy, and ability to address important EHS issues for each of the stakeholders by addressing the questions posed in Box 4-1.

Evaluation and Assessment

The NNI document identifies five broad, inclusive high-priority research needs related to nanomaterials and human health (NEHI 2008, see Figure 5, p. 24) and specifies a total of 29 focused research topics in connection with them. Each topic is essential for addressing EHS risk assessment and management needs. The emphasis on biologic responses and on exposure routes and measurements is logical and noteworthy. Overall, the list of research needs on nano-

materials and human health is reasonably complete (see Box 4-4). However, some important clarifications and additions need to be incorporated.

The combined list of research in the two needs "Understand the absorption and transport of nanomaterials throughout the human body" and "Understand the relationship between the properties of nanomaterials and uptake via the respiratory or digestive tracts or through the eyes or skin, and assess body burden" is complete except for the absence of an emphasis on quantitative kinetics and application of kinetic models. It should include, where appropriate, quantitative models, such as physiologically based pharmacokinetic models, that account for the influence of physiologic, biologic, and other processes that influence nanomaterial kinetics. Such models would facilitate assessment of interindividual, interspecies, and life-stage-dependent differences in kinetics and dosimetry and other susceptibility factors. The models would constitute a first step in developing more inclusive, integrative computational models for predicting biologic effects.

Moreover, those two research needs describe a single research topic that comprises the human body's absorption, distribution, metabolism and transformation, and elimination (ADME) of nanomaterials. Therefore, they should be integrated into a single research activity focused on understanding the absorption and transport of nanomaterials through the human body and the influence of their physicochemical properties on ADME and toxicity. An important element in understanding the ADME aspects of nanomaterials is to determine whether biologic processes modify the physico-chemical characteristics of the nanomaterial, including changes in surface properties, size, and oxidation state of the components.

The research need "Identify or develop appropriate *in vitro* and *in vivo* assays/models to predict *in vivo* human responses to nanomaterials exposure" emphasizes *in vivo* and *in vitro* hazard-screening tools and offers prediction of biologic response (for example, toxicity) as a goal. The committee notes that prediction of biologic response requires the development of quantitative dose-response data and in some cases mechanistic or mode-of-action data from highly coordinated studies, the articulation of a quantitative representation of the biologic and physical processes, and ultimately the development and use of integrative, quantitative computational (*in silico*) models (ICON 2008). The NNI document should articulate the research required to address each of those steps. For example, both quantitative structure-property-activity relationships and development of biologically based dose-response models should be specifically included as research needs to assist in the integration of data and prediction of toxicity.

The topics identified in the two remaining research needs, "Develop methods to quantify and characterize exposure to nanomaterials and characterize nanomaterials in biological matrices" and "Determine the mechanisms of interaction between nanomaterials and the body at the molecular, cellular, and tissue levels," were deemed complete. However, the committee did consider that,

BOX 4-4 Research Needs for Nanomaterials and Human Health

Understand the absorption and transport of nanomaterials throughout the human body.

Develop methods to quantify and characterize exposure to nanomaterials and characterize nanomaterials in biological matrices.

Identify or develop appropriate *in vitro* and *in vivo* assays/models to predict *in vivo* human responses to nanomaterials exposure.

Understand the relationship between the properties of nanomaterials and uptake via the respiratory or digestive tracts or though the eyes or skin, and assess body burden.

Determine the mechanisms of interaction between nanomaterials and the body at the molecular, cellular, and tissular levels.

Source: NEHI 2008.

where feasible, it would be prudent to identify activities in each category that complement and influence those in other categories in an effort to promote research coordination. For example, studies addressing research needs in nanomaterials and human health would benefit from a focus on occupationally or environmentally relevant materials, exposure levels, and exposure routes on the basis of well-characterized nanomaterials (research that is addressed in the instrumentation, metrology, and analytic methods category and the human and environmental exposure assessment category). The more integrated approach would increase the value and relevance of the research.

Although the rationale for selecting priorities of the research topics (NEHI 2008, Figure 5) was not clear to the committee, it considered that the sequence of implementation was for the most part logical. An initial focus on development of methods to quantify nanomaterials *in situ* is reasonable because these methods are required for the success of the other research, all of which involves exposure, dose measures, or tracking of nanomaterials in biologic matrices. Initial efforts to identify which portals of entry have high rates of absorption and which organ systems preferentially accumulate nanomaterials were also viewed as appropriate. However, consideration of the diversity of nanomaterials and their applications is critical. Such knowledge should guide selection of appropriate *in vitro* and *in vivo* systems for hazard screening and mechanistic work.

The NNI implied, in Figure 5, that all mechanistic work was of value and should be conducted in the near term. The committee considers that some clarification is needed. Targeted mechanistic research on the interaction of nanomaterials with known biologic or toxicologic pathways and mechanisms (for exam-

ple, oxidative stress, mutagenesis, or inflammation) addresses important questions about hazard and classification of materials by response in the near term. Although hypothesis-driven, exploratory mechanistic research could address important questions in the near term, purely exploratory mechanistic work might be most valuable if guided by knowledge about relevant exposures routes, end points, and tissues and cell types and may be more useful once some initial research questions are addressed.

The NNI conducted its gap analysis without substantive consideration of the relevance of the research to the two distinct communities that use the information (research focused on clinical uses and patient populations and research focused on occupational and environmental health risks). More than 50% of the projects listed for human health target research directly relevant to therapeutics rather than assessing the potential EHS risks posed by nanomaterials. The committee felt that the relevance of the therapeutic studies was overstated. Three examples of the imbalance in the funded research projects are presented below.

The NNI identified 30 grants as addressing the research need "Understand the absorption and transport of nanomaterials throughout the human body" (which contained seven specific objectives). The sole conclusion regarding gaps identified was that "further research on gastrointestinal and intraocular uptake is needed." However, on closer examination of the 30 grants identified as relevant, only two were focused on issues that directly addressed ADME data that might be useful for environmental and occupational risk evaluation: "Effect of nanoscale materials on biological systems: Relationship between physicochemical properties and toxicological properties" and "Impact of physicochemical properties on skin absorption of manufactured nanomaterials." The remaining 28 funded projects were focused on medical applications of nanotechnology, such as the design of drug-delivery systems or other aspects of therapeutics. Those research projects will undoubtedly generate information that is conceptually useful in understanding the behavior of specific types of nanomaterials, but it is unlikely that they will generate data that would be directly applicable to risk assessment of environmental and occupational health hazards. The NNI document states, with little justification or documentation, that 17 projects directly addressed that research need; this implies that 13 projects have no particular relevance, so it is not clear why the entire budgets of those projects would be included in the tally of funding in this topic. Thus, if one were to carefully examine the FY 2006 funding committed to understanding each of the seven subtopics identified in the research need "Understand the absorption and transport of nanomaterials throughout the human body," there would be at most two grants that might provide useful information in them. It is hard to imagine that the only "gaps" identified by the NNI are in gastrointestinal and ocular uptake, inasmuch as no exposure assessments have been conducted to understand the extent to which gastrointestinal uptake and intraocular uptake are important routes of exposure .

Another example of the flawed gap analysis is in the research need "Identify or develop appropriate *in vitro* and *in vivo* assays/models to predict *in vivo*

human responses to nanomaterials exposure." Eight appropriate subcategories were identified (Figure 5). In connection with this research need, only six FY 2006 projects were identified. Although the NNI states that all six directly address the need, examination of their content suggests that only three directly address one or more of the subtopics (B3-1, B3-5, and B3-6 in Appendix A). The other three projects (B3-2, B3-3, and B3-4) may generate relevant information but do not explicitly address any of the subtopics in a way that would be useful for environmental or occupational risk assessment. The NNI acknowledges that the gap analysis is flawed, but it offers no recommendations on how to address this critical limitation. "While there is a low number of projects in this priority research need, this assessment does not capture applicable research in other areas nor many additional research efforts on testing schemes that were not captured by the gap analysis, so a determination of future priorities based on this analysis may be misleading" (p. 22). Indeed, the "Summary of Balance-Assessment" for the section does not mention the paucity of research addressing predictive toxicology for nanomaterials (development and validation of *in vitro* assays that predict *in vivo* toxicity). It is difficult to fathom how two federally funded projects in FY 2006 (B3-1 and B3-5) that directly address the development of *in vitro* and *in vivo* assays and models to predict human response to nanomaterials would be considered a sufficient research effort.

The focus of the research on therapeutics means that the data needs for risk assessment are not being supported. The gap analysis does not accurately or adequately represent research gaps related to nanomaterials that might pose health and safety risks to consumers, researchers, and workers. The committee considers the apparent lack of a sizable number of research projects that directly address the immediate research needs related to potential occupational and consumer risks posed by nanomaterials to be a substantial data gap. Revision of the table (NEHI 2008, p. 20) to separate studies focused on therapeutics from studies that emphasize materials important to these other communities (workers, consumers, and the public) would facilitate a transparent and unbiased assessment of data gaps that will help to spur the needed research.

The small number of projects addressing the research needs in the nanomaterials and human health section and their bias toward therapeutic applications rather than materials relevant to the environmental, occupational, and consumer exposure settings constituted sufficient evidence that the funded research will not support risk-assessment and risk-management needs for these classes of nanomaterials, generate the information needed to support EHS risk assessment and risk management, or provide critical data for regulatory agencies.

Conclusions

There is a need for broad coordination in the parallel pursuit of research needs in the nanomaterial and human health category and across research categories. Research projects in nanomaterials and human health would

benefit from research on occupationally or environmentally relevant materials, exposure levels, and exposure routes—work that is carried out in other research categories. A more integrated approach would increase the value and relevance of the research.

The list of high-priority research on nanomaterials and human health is, with few notable exceptions, complete. Additional emphasis of research on the analysis and evaluation of ADME and toxicity of engineered and other nanoscale materials that are related to likely exposures is needed. In particular, there is a need for the collection of quantitative kinetic data and the development of quantitative kinetic models, including, where appropriate, physiologically based models and structure-property-activity models.

The gap analysis was neither accurate nor complete. The gap analysis resulted in the NNI's overstating the relevance of therapeutic studies to the identified research needs and not fairly representing the paucity of projects that truly address the potential EHS risks posed by nanomaterials. Although most of the therapeutic studies are focused on developing novel strategies for treating cancer and other ailments that deserve the attention of scientists and clinicians, they will not directly contribute to the body of knowledge needed to ensure protection of public health and the environment from potential risks posed by nanotechnology and its products.

Nanomaterials and the Environment

Introduction

Nanomaterial exposures and their effects on organisms and ecosystems are influenced by the nature of the material and its applications and will probably depend on the physical and chemical characteristics of the particles, including size, shape, surface chemistry; the frequency, magnitude, and duration of releases or exposures; and countless modifications in material structure and properties mediated by environmental processes. A research strategy that addresses environmental end points must address the breadth of possible variables that may define nanomaterial transport, transformation, bioavailability, bioaccumulation, and trophic transfer and mechanisms that may control toxicity on cellular and organismal scales.

Classically, environmental research has focused on the relationship between chemical composition of contaminants and their environmental behavior and effects. The recognition that nanoscale structure may be more predictive of environmental parameters has forced researchers to rethink concentration-response approaches and place more emphasis on more robust particle characterization in environmental matrices. Broadening exposure characterization will inevitably lead to better predictions of effects.

Several challenges face environmental scientists who are conducting research on nanomaterials: developing reproducible testing methods that provide insight into environmental characteristics, quantifying appropriate effect end points that reflect both physical and chemical stress, developing quantitative structure-activity relationships, and incorporating this information into ecologic risk assessment. Addressing those challenges will require multidisciplinary approaches that include material scientists and physicists in the more traditional environmental collaborations of engineers, chemists, biologists, and toxicologists.

Test methods designed to characterize environmental soluble contaminants may not be appropriate for use with nanoparticles. Quantifying the behavior of a solute in environmental matrices is already challenging; understanding the behavior of nanoparticles may require restructuring assay systems that facilitate particle detection and characterization. That is critical because research has suggested that nanoparticle behavior depends heavily on the characteristics of the environmental matrix. Therefore, it is not sufficient to characterize the test material only before conducting the assay. Particles must also be characterized during the assay, and how their characteristics change must be evaluated (Maynard 2002; Oberdörster et al. 2005; Jiang et al. 2008a). For example, nanoparticle suspensions in freshwater may have aggregation rates that result in substantial changes in aquatic organisms' exposure to them. The response of aquatic organisms may therefore depend on aggregation rate and on exposure duration (for example, continuous vs episodic).

Most ecotoxicologists are not accustomed to quantifying responses of organisms to particles. Although some approaches and insights can be garnered from existing mammal-particle toxicologic research, they will not be useful or predictive for all trophic levels. Research has suggested that aquatic organisms discriminate among colloids of different sizes, but there are no data that support extrapolation of these relationships to nanoparticles (Christaki et al. 1998).

Quantitative structure-activity relationships (QSARs) have been developed for myriad contaminants and used successfully in ecologic risk assessment. Quantifying the influence of nanoscale structure and suspension characteristics (for example, particle size, shape, surface chemistry, and aggregation rate) on environmental characteristics might lead to development of QSAR-like predictive tools. However before such tools can be developed, the appropriate measures of the nanomaterial properties that may affect end points must first be identified, through extensive testing of many different well-characterized nanomaterials for these endpoints.

Current ecologic risk-assessment methods may be a useful starting point, but methods for quantifying nanoparticle-related risk may need to evolve as research on behavior and effects unfolds. It is not apparent that classic metrics for predicting exposure and effects are applicable to nanoparticles. For example, nanoparticle suspensions may have both physical effects associated with their size and shape and chemical effects associated with their surface chemistry and

particle composition. The applicability of such measures as volatility or octanol-water partitioning is doubtful.

Elements of an effective research strategy to address the environmental behavior, fate, bioavailability, and effects of nanomaterials and their associated ecologic risk should include

- The development of reproducible testing methods that provide insight into environmental characteristics.
- An assessment of the most important nanostructural characteristics that influence environmental characteristics.
- Determining the appropriate ranges of environmental concentrations to inform effects research.
- Development of mathematical tools that link environmental characteristics to appropriate environmental effects or end points.
- Identification of the appropriate end points.
- Incorporation of nanomaterial research results into ecologic risk assessment and modification of risk-assessment methods to accommodate effects and exposure phenomena peculiar to nanoparticles.

Evaluation and Assessment

The committee reviewed the adequacy of the nanomaterials and the environment section of the 2008 NNI document to assess its ability to encourage research and facilitate quantitative ecologic risk assessment. The strategy was reviewed for its completeness, research priority-setting, and ability to support risk-assessment and risk-management needs.

The NNI document identified five research needs in the category of Nanomaterials and the Environment (NEHI 2008, Figure 7, p. 31). Each of the needs is critical for advancing knowledge and supporting ecologic risk assessment and management (see Box 4-5). The research needs appear to have been derived by extrapolating from the inventory of current research activities rather than as a high-level assessment of near-term to long-term needs. Some discussion of research needs that moves beyond such extrapolation is found in the background paragraphs that describe the need for improved measurement of toxicity, determination of mechanisms of toxicity, development of structure-activity relationships, and consideration of environmental modifications of nanomaterials. Strategic planning for research is also reflected in Figure 7 (NEHI 2008, p. 31). Trophic transfer, including bioaccumulation and bioconcentration, is one possible ecologic end point that, although meriting research, appears to be absent from the proposed strategy. Similarly, it is not clear how weak links in ecosystem-level responses—for example, those related to such ecosystem services as nutrient cycling—will be identified.

BOX 4-5 Research Needs for Nanomaterials and the Environment

1. Understand the effects of engineered nanomaterials in individuals of a species, and applicability of testing schemes to measure effects.
2. Understand environmental exposures through identification of principal sources of exposure and exposure routes.
3. Determine factors affecting the environmental transport of nanomaterials.
4. Understand the transformation of nanomaterials under different environmental conditions.
5. Evaluate abiotic, and ecosystem-wide, effects.

Source: NEHI 2008.

The report sorts 38 projects into the five research needs. The research needs are important for accomplishing the goals laid out for this section. While the goals are presented and described as a priority list, most of the current projects (22 of 38) address research need 3, "Determine factors affecting the environmental transport of nanomaterials." One concern is NNI's priority-setting of research needs. Exposure scenarios should precede toxicity testing for ecosystem risk assessments. Similarly, understanding of environmental fate and transport would be necessary before assessment of organisms at risk. For example, if the behavior of a particular nanomaterial results in sediment deposition, testing effects on sediment-dwelling rather than pelagic organisms might be a priority. While some bioavailability and mechanistic toxicity testing should be a high priority, the committee cautions against extensive toxicity testing without fully understanding environmental fate and transport processes necessary to quantify exposure. Effects characterization without an adequate understanding of environmental exposure may result in resources being expended on research that does not contribute to ecologic risk assessment or facilitate extension to higher-level ecosystem effects. The committee agrees that toxicity bioassay method development must be a high priority.

The first research need concerns the effects of engineered nanomaterials on organisms and the development of methods for measuring the effects at the genomic, molecular, cellular, organismal, and population levels. Determining whether nanomaterials have an effect as defined by a widely accepted, measurable end point is critical for determining whether they should be considered further for the purposes of risk assessment. However, these end points have been developed and refined largely in response to soluble contaminants, not particles. Therefore, the committee supports the priority of research investigations that focus on nontraditional ecotoxicologic end points that are more appropriate for particles, such as nanoparticle effects on protein configuration or phagocytotic responses. Information about testable hypotheses can be gleaned from the scien-

tific literature on the human health effects of exposure to particulate contaminants such as silica, asbestos, and carbon black which have been extensively studied. In addition to different end points, toxicity assessments must include exposure characterizations. The committee supports the priority of understanding the influence of particle characteristics on ecotoxicologic bioassays. Currently these bioassays are always accompanied by quantitative assessments of contaminant exposure (concentration); bioassays of nanoparticles need to include contaminant characterization beyond a mass exposure number. Particle size, shape, surface area, and surface chemistry are all potential determinants in the outcome of biota-nanoparticle interactions. The most important part of this research is the development of sensitive, reproducible ecotoxicologic bioassays for the assessment of the effects of particles.

The second-ranked priority research need is to understand exposure by identifying principal sources and exposure routes. Only one project was identified as addressing that topic during FY 2006. This work should have high priority and should be done quickly because it will inform the array of relevant concentrations to be studied and because it is impossible to predict which organisms will be exposed without adequate exposure characterization. However, the research void introduces considerable uncertainty into the range of concentrations that should be used and even the systems that should be studied. The research void is substantiated by the fact that a search of the EPA Web site yields only one research project focusing on nanoparticle exposure funded in FY 2007 and only three focusing on fate and transport (EPA 2008).

Similarly, in the 2006 inventory, one project was identified as addressing ecosystemwide effects, that is, effects that go beyond those of individual species ("Nanoscale Size Effects on the Biogeochemical Reactivity of Iron Oxides in Active Environmental Nanosystems"). That is not surprising inasmuch as the entire ecotoxicologic literature is slanted to individuals, and few studies focus on higher orders of organization (for example, populations, communities, and ecosystems). The need to cover a wider array of nanomaterials than those of natural origin identified for study in the inventoried 2006 projects is cited in NNI (NEHI 2008). This is a critical need. To apply current knowledge on materials of natural origin to an understanding of risks posed by engineered nanomaterials, more research is needed to understand how the physicochemical properties and toxicity of natural and engineered nanomaterials differ (see discussion of research gaps below).

The largest fraction of research projects on nanomaterials and the environment identified in the FY 2006 inventory investigates factors that affect environmental transport of nanomaterials. The NNI document identifies a lack of emphasis on "more applied" research and little evaluation of existing transport models (NEHI 2008, p. 28). One research need identified here is the determination of physicochemical processes that control the fate and transport of different nanomaterials. Surface modification of nanoparticles in the environment is important because of its potential influence on particle behavior, including agglomeration, aggregation, and sedimentation which may affect bioavailability

and possibly nanoparticle reactivity. A more mechanistic approach might provide the foundation of the development of predictive models, provide insights into exposure pathways, and identify organisms at risk. Results of this research may provide insights into exposure pathways and organisms at particular risk, so substantial effort is warranted.

Research need 4 is "Understand the transformation of nanomaterials under different environmental conditions." Physical, chemical, and biologic transformations are all identified as meriting research.

There were 10 projects that were not sorted into the five research needs. Their importance was noted in that they could also lead to nanotechnology applications that contribute to lessening current environmental contamination.

In summary, all the research needs identified as having priority in the NNI document are appropriate and even critical for providing information needed for informed risk assessment. The committee reinforces the need for characterization methods to identify nanomaterials in biologic and environmental matrices and the products of nanomaterial-environment interactions. As stated by the NNI, this must be an overarching consideration. The call to focus on "as-manufactured" nanomaterials may misdirect interim risk assessments by creating large gaps in the understanding of how "manufactured" nanomaterials and those found in natural systems may differ.

With the caveats described above, the priorities in this category are appropriate in that a consideration of hazard below the level of ecosystems often precedes ecosystem-level evaluation. However, estimates of transport and transformation are required to assess environmental exposure and should therefore have higher priority than evaluation of ecosystemwide effects because the latter cannot be usefully studied without knowing what the likely environmental concentrations will be and what organisms might be exposed. Therefore, the committee recommends that the research needs be rearranged as (2), (4), (1), (3), (5). Exposure and transport processes would be characterized before effects. That would provide a rationale for the selection of bioassay species. Transformation processes would be characterized before higher-level ecosystem effects. At present, the distribution of projects among the research needs does not appear to be consistent with the proposed priorities or with our recommended sequence. Attention should be given to making resource allocation consistent with the prioritized research needs.

Although the research strategy appears to reflect an important collection of existing federally funded research, there are several gaps in the identified research needs:

- The strategy document does not specifically identify the need for studying naturally occurring or incidental nanoparticles that have similar structures or that may be identical with manufactured nanomaterials.
- The document does not identify development of protocols to evaluate nanomaterial loss from products as a research need despite an apparent trend

toward using nanomaterials predominantly as composites in more complex matrices of resins, fabrics, and coatings.

- The document does not consider characterization of bioavailability and toxicity of nanoparticles in complex media, such as effluents. It is important because many nanoparticles will enter the environment in effluents and discharges.
- The document does not mention the need to characterize interactions among nanoparticles and other environmental contaminants. Such interactions could alter environmental behavior, bioavailability, and toxicity of nanomaterials.
- Characterization of nanoparticle transport through food webs is critical for ecosystem health, including potential human exposure.
- Methods for identifying nanomaterial sources, such as isotopic "fingerprinting" techniques, and modeling techniques to track movement of nanoparticles in the environment are needed.
- Research to assess the potential environmental "collateral damage" associated with nanomaterial fabrication needs to be clearly linked to life-cycle analysis mentioned in the NNI document.

The latter topic goes far beyond using off-the-shelf technologies for risk management in material production. It requires an assessment of the quantities and qualities of wastes generated in manufacturing specific nanomaterials and of the risks associated with handling and disposing of the wastes and of the feedstocks used in the manufacture of nanomaterials.

Although the document notes the need to develop methods for characterizing nanomaterials in complex matrices, it does not describe a mechanism for ensuring translation of method developments that may occur in the biomedical sciences, fundamental nanochemistry, or elsewhere in the EHS community. The disconnect between ecologic risk-assessment and risk-management methods for particles vs solutes has not been addressed, and environmental scientists are left to borrow from the human health literature on particles. Although much can be learned from the extensive literature on the impact of particles on human health, caution is needed when making extrapolations to ecologic endpoints, because of the potential differences in exposure scenarios and in physiology and biochemistry among organisms. Development of ecologic risk-assessment and risk-management tools should progress in tandem with the research on fate, behavior, and toxicity already identified.

Conclusions

A strength of this section is that the major topics identified for research are appropriate. Each is critical for meeting the ultimate goal of risk assessment and material management.

Several important research topics have been overlooked. It is important that the research strategy be comprehensive so that high-priority research can be accomplished in a logical manner. Research needs must be comprehensive to ensure that ecologic risks can be assessed and nanomaterials managed objectively and with minimal uncertainties.

There was no justification for the setting of priorities of the research needs, nor were they set in relation to resource allocation. The priorities of research needs were not well justified, and even a cursory examination suggests that a different prioritization might be more logical. Projects funded in FY 2006 and identified as relevant to the research needs do not support the proposed prioritization.

Priority of research on factors that control transport, fate, and exposure should be expressed in a fashion that clarifies the need for this work to inform ecotoxicity studies. This is a critical inaccuracy in the document. The document suggests that ecotoxicity research should proceed immediately without attention to identifying species at risk on the basis of an understanding of nanoparticle behavior, fate, and transport. That could result in a substantial waste of resources.

Human and Environmental Exposure Assessment

Introduction

For nanomaterials to present a risk to human health or ecosystems, both exposure and hazard must exist. Without knowledge about exposure potential at some point in the life cycle of nanomaterials, it is not possible to assess risk appropriately or to implement well-founded risk-management practices. Research conducted with the goal of assessing potential exposure to nanomaterials must take into account the physicochemical properties of the nanomaterials because they affect partitioning from portal of entry to secondary compartments in the human body and the environment. The risk-assessment paradigm (NRC 1983) connects exposure to dose to response. This section focuses primarily on exposure and dose. Dose-response relationships are addressed in other sections of the report.

One of the strengths of the 2008 NNI strategy document is that it clearly identifies exposure research as a high-priority need and articulates its relevance to risk assessment. It also highlights the paucity of research in this regard and reflects on the nascent nature of nanotechnology (NEHI 2008, p. 34) and lack of exposure information.

Because exposure is a critical determinant of dose, exposure-assessment information will be necessary for informing the design of toxicologic and ecotoxicologic studies with respect to exposure in animal and *in vitro* studies.

But the exposure-dose relationship needs to be considered critically in assessing nanomaterial interactions with organisms and the environment. For example, most of the studies on the assessment of toxicity of nanomaterials have used extremely high exposure concentrations (doses), which are usually irrelevant in realistic exposure scenarios (Oberdörster et al. 2005) except possibly industrial exposures and accidents. Although such high-dose studies can identify a hazard, they also lead to identification of mechanisms that may not be relevant at lower exposures and thus may contribute to an unrealistic perception of risk. In addition, most of the studies have focused on acute exposures and neglected chronic and environmentally relevant exposures.

Evaluation and Assessment

The NNI document identified five research needs in the category of Human and Environmental Exposure Assessment (NEHI 2008, Figure 9, p. 36). The five research needs (see Box 4-6) are all important, but they are not well elaborated. As an organizing principle, the NNI document (p. 33) adopts the approach of identifying and characterizing exposed populations by categories and relating their exposures. The committee believes that the broader concept of human and ecologic exposure potential throughout the life cycle of nanomaterials (from manufacture to packaging, distribution, consumer use, and disposal) needs to be considered as an overarching research theme. In addition, with respect to human exposures, the document focuses mainly on occupational issues. Environmental exposures receive little attention in this section except as conceptualized in Figure 10 and wording in section III (p. 46) that calls out the need to characterize the health of and presumably identify exposures to environments. Issues related to environmental exposure are also addressed briefly in the category "Nanomaterials in the Environment."

BOX 4-6 Research Needs for Human and Environmental Exposure Assessment

1. Characterize exposure among workers.
2. Identify population groups and environments exposed to engineered Nanoscale materials.
3. Characterize exposure to the general population from industrial processes and industrial and consumer products containing nanomaterials.
4. Characterize health of exposed populations and environments.
5. Understand workplace processes and factors that determine exposure to nanomaterials.

Source: NEHI 2008.

The gap analysis presented in the document lacks substantive discussion of exposure except for a cursory treatment of occupational exposure. The committee noted that the NNI did not identify the lack of research on exposure throughout the life cycle of nanomaterials as an important gap. That omission appears to be due to the lack of research projects on this subject in the portfolio of FY2006 projects.

Understanding metrology and developing tools to characterize and measure attributes of nanomaterials—including particle size, number, and surface area—relevant to exposure is not identified as a research need, and it is implied that it is adequately addressed by a few projects in the instrumentation and metrology section (p. 33). Of particular concern is the challenge of assessing "dose" in toxicologically relevant terms. Although this is not a new challenge in the field of toxicology (appropriate dose metrics for particulate matter exposure have been studied for decades), whether nanomaterial "dose" is best assessed by particle mass concentration, surface area, concentration of reactive functional groups, or other means, will be an especially important area for standardization in nanotoxicology research.

Types of research that should be considered include the following:

- Developing instrumentation for personal monitoring.
- Monitoring air and water discharges in the workplace.
- Research on exposure associated with product use throughout the life cycle from manufacture to distribution and consumer use to disassembly and disposal (Thomas and Sayre 2005; Borm et al. 2006).
- Research on source apportionment, for example, exposure to materials of manufactured origin relative to exposure from naturally occurring or non-manufactured anthropogenic materials, such as combustion products.
- Research on contributions of specific nanoparticles to total exposure, including personal exposure (personal samplers) vs area exposure.
- Research on personal susceptibility because lessons learned from exposure to particulate matter (including ultrafines) suggest that such factors as age, sex, windows of exposure, genetic makeup, and pre-existing diseases can play a critical role in susceptibility.
- Research on routes of environmental exposure, including commercial trends and the potential for nanomaterial penetration into conventional material markets, with an assessment of the unintended and associated environmental losses.
- Development of methods of identifying environmental "hot spots," including fundamental studies of nanoparticle movement through the environment and interactions with known environmental pollutants.
- Research on trend forecasting, using tools from social sciences to allow gross exposure assessment and more targeted studies. Some nanomaterials have been produced and used for decades in large quantities, such as TiO_2 and carbon

black (although these are not "engineered"); in the case of carbon black in particular, several epidemiologic studies have begun to capture workplace exposures (Morfeld and McCunney 2007).

The ordering of research needs in exposure research appears incongruous. For example, although characterizing workplace exposure appears to have the highest priority for research in this category, it seems misplaced with respect to research need 2, which aims to identify population groups and environments that may be exposed to engineered nanoscale materials. Similarly, research need 5 seems to be required to arrive at the conclusion that characterization of workplace exposure should be important for research. Indeed, understanding which population groups and environments may be exposed appears to be a prerequisite for selecting the type of workplace settings that should be the focus of research to characterize exposures among workers. Both research needs 1 and 5 appear to have been eliminated in the final list in Section III (p. 46). In general, research priorities seem to have been simply an articulation of the collection of existing research in FY 2006, not priorities for research required to address knowledge gaps. Appropriate priority-setting of research would enable proper allocation of resources. That does not necessarily imply a chronology of research; many types of important research can and should be addressed in parallel.

As presented, there will be large gaps in exposure-assessment information needed for EHS risk assessment and management. There appears to be a lack of clarity as to how and where exposure issues need to be addressed. They are scattered among several sections of the document with no apparent linkage. And the critical linkage between environmental and human exposure is overlooked. Because ecologic exposures may be more difficult to assess than occupational exposures because there are more uncontrolled variables, it is important that environmental exposure research be a priority, and greater recognition of the commonalities of this research need to both the Human and Environmental Exposure Assessment and the Nanomaterials in the Environment categories is needed.

The research priorities described in the NNI document will potentially support environmental health and safety research needs, but they are largely insufficient to allow for rigorous exposure assessment. Information on exposure to engineered, incidental, and natural nanoparticles is critical for development and implementation of effective risk-management plans.

Conclusions

The NNI acknowledges the importance of exposure research (primarily in occupational settings), but the research portfolio, gap analysis, and priority order do not adequately reflect attention to it.

The 2008 NNI document does not address human and environmental exposure potential throughout the life cycle of nanomaterials. It focuses primarily on occupational exposure.

The exposure-assessment section is imbalanced and does not adequately connect with research on environmental processes that determine environmental exposures.

Understanding metrology and developing tools to characterize and measure attributes of nanomaterials—including particle size, number, and surface area—relevant to exposure is not identified as having high priority, and it is implied that it is adequately addressed by the projects listed in the instrumentation and metrology section.

The document does not consider exposure in the context of susceptible populations in humans and the environment, nor does it consider the need to identify such populations. An exposure that may be harmless for a healthy organism may be detrimental to a susceptible population.

The NNI document does not address the importance of exposure studies in the design of toxicologic and ecotoxicologic studies. Repeat or chronic studies in relevant experimental animal models and model systems using realistic exposure concentrations should be an essential component of risk assessment of nanomaterials (including considerations of susceptibility, mechanisms, and mode of action).

Risk-Management Methods

Introduction

By including risk-management methods as one of its five research categories, the 2008 NNI document recognizes that research on risk management can not only broaden available options but also inform risk-assessment research. For an emerging set of technologies, such as nanotechnology, with great uncertainties regarding hazards and exposures, the rapid and active development of risk-related information for risk management should have very high initial priority.

The NNI document identifies five research needs (see NEHI 2008, Figure 11, p. 42 and Box 4-7) that, with several exceptions, subsume the twenty-four research needs in NEHI (2006). There is no description of the process by which these changes occurred. NEHI (2007) provides a limited description of the combining and prioritization of the 2006 research needs, but does not account for why some identified needs (for example, packaging needs, spill containment methods) are not mentioned. In addition, many of the specific research needs

subsumed under the five research needs in NEHI (2008) are only evident in the report's Figure 11 and are not discussed in the text.

Responsible nanotechnology-related risk management requires not only research to support risk assessment and to develop new knowledge about risk-management methods and technologies but data collection on trends and practices and dissemination of risk information. A research strategy for risk-management methods should lay out clearly the boundaries between research activities and risk-management data-collection activities. Those boundaries are not defined in the 2008 NNI document. Instead, some essential data-collection and information-dissemination activities are listed as research projects. Such activities are critical for effective risk management, but they do not constitute risk-management research. For example, collecting information on nanoparticle type, composition, and physicochemical characteristics is not research; development of a control banding method[3] based on those characteristics would be.

Evaluation and Assessment

The NNI document lacks a rationale for the selection of research needs and assignment of specific projects related to risk-management methods. That is evident from the statement on p. 41 that indicates that this category has been used as a catchall for projects otherwise not classifiable: "issues not typically thought of as pertaining directly to risk management needs, such as ethics and societal considerations, are included in the projects that fall under this category." Nearly half the already small number of projects, and 62% of the total funding, could not be assigned to any of the other four categories so were placed here. The text does not describe how the unclassifiable projects contribute to meeting research needs.

Ideally, the NNI and the Nanotechnology Environmental and Health Implications Working Group (NEHI) would constitute a useful structure for bringing the needs of risk managers in the regulatory agencies to the attention of scientists in the primary research agencies. The NNI strategy states that "input about the needs of regulatory decision makers expedites the development of information to support both risk assessment and risk management of nanomaterials" (p. 3). That might be true, but there is no description of input from agency risk managers in the 2008 NNI document. Moreover, this section addresses only occupational settings; risk managers for the Food and Drug Administration and EPA would most likely have included environmental and consumer exposure settings as well. The focus of the research may be partly due to NNI's own data collection methods, as NNI acknowledges on p. 38, "the apparent lack of fund-

[3]"Control banding is a qualitative risk-assessment and risk-management approach to promoting occupational health and safety." For additional information, see NIOSH (2005).

BOX 4-7 Research Needs for Risk Management Methods

1. Understand and develop best workplace practices, processes, and environmental exposure controls.
2. Examine product or material life cycle to inform risk reduction decisions.
3. Develop risk characterization information to determine and classify nanomaterials based on physical or chemical properties.
4. Develop nanomaterial-use and safety incident trend information to help focus risk management efforts.
5. Develop specific risk communication approaches and materials.

Source: NEHI 2008.

ing by regulatory agencies for risk management methods research could be due to the data call having been focused primarily at grant-related efforts for a topic that may not always be addressed through research."

There is very little indication of priorities among research needs in this section. Most of the text describes the existing studies that have been placed in this category and the substantial gaps in most of the research needs. There is no textual description of priorities among the many gaps or of how the gaps will be strategically filled.

The only indication of priority among the research needs is in Figure 11. Of the 13 subjects in the five research needs, all but two indicate high priority for immediate emphasis. That is appropriate for risk management of an emerging technology, but it is not informative, especially given the poor description of what is involved in the research needs. Moreover, in a research field characterized by uncertain risks and poor-quality information about risks, it is not appropriate to stall the development of essential risk communication, but this is the only research need that is put off to the intermediate term.

In reviewing this research category, the committee compared the description of research and research needs in risk-management methods in the 2006 NNI report with the research needs, listed projects, and text discussion on risk-management research in the 2008 NNI document. Research gaps were identified through the comparison and with expert judgment, and the evaluation of priorities was based on the descriptions in the 2008 document. Because the content is explicitly related to risk management, the question of relevance to risk management was not considered separately.

Analysis of Individual Risk-Management Research Subjects

The strategy briefly describes 14 projects in the risk-management methods

research category, with a total funding of $3.3 million, primarily from NSF and the National Institute for Occupational Safety and Health.

In many cases, it is difficult to discern from the information provided in the 2008 NNI document what is intended by the category; this complicates an independent analysis of the appropriateness of the research needs. For example, research need 3, "Develop risk characterization information to determine and classify nanomaterials based on physical or chemical properties," implies development of a banding or other screening-level categorization of nanomaterials for risk-management purposes on the basis of readily available physical or chemical characteristics. That is a highly relevant and appropriate research need for risk management that is referred to in the 2006 NNI report. The 2008 document, however, does not describe the research need in any detail or how it is to be met. The text combines the research need with the unrelated research need 4, "Develop nanomaterial-use and safety-incident trend information to help focus risk management efforts," apparently because one 2006 project was believed to address the two rather disparate research subjects equally. In place of a thorough description of the research needs, the text describes the severe limitations of the one project placed in this grouping.

The discussion of research need 3 (risk-characterization information) and research need 4 (trend information) also illustrates the failure of the section to distinguish between risk-management method research and risk-management activities. Compiling information on use, trends, and products is essential for developing appropriate risk-management strategies. However, it is not clear why developing a Web-based library (research need 3, project E3-1 in Appendix A, p. 87) or collection of trend information (research need 4) is considered as filling a "research need" instead of as an infrastructure or surveillance activity, especially when it is only a voluntary activity and therefore unlikely to be comprehensive or representative in its characterization. Moreover, the information collected is stated to be "nanomaterial-characterization" rather than "risk-characterization" information identified as a research need. That is another example of how the document is compromised by its efforts to make existing projects fit into the research needs previously identified as critical even when the projects are neither truly research projects nor designed to develop information pertinent to the research need.

Research need 1 (workplace practices and environmental controls) has a primary focus on inhalation exposure; only respirators and personal protective equipment are mentioned. Projects assigned to this research need were relevant and designed to provide essential information. The committee notes, however, that studies of workplace design and other engineering controls, dermal and other routes of exposure, and workplace hygiene and disposal practices should also be discussed in the section. There are large gaps in worker-protection research, and little in this document indicates strategies or priorities for filling them.

Research need 2 deals with life-cycle analysis and comprehensively considers, "manufacturing, incorporation into an integrated product, consumer use,

and recycling or disposal" (p. 4). It is essential that not only the finished product but the materials, byproducts, and waste in producing the materials be considered with regard to EHS. But the description of this research need does little to explain the strategic approach to understanding product or material life cycles. The 2006 portfolio identified only two projects in this category, one of which is a life-cycle analysis of manufacturing technologies rather than products or materials (project E2-2 in Appendix A, p. 87); the other is limited to a small sector of products (project E2-1). The strategy itself identifies a clear research gap in life-cycle analysis for product classes not considered in the two current research projects. The document suggests that the research gap is so large, "a systematic evaluation . . . is needed to evaluate where the most critical of such gaps would exist" (p. 40). However, there is no further discussion of conducting such an evaluation. Thus, although including life-cycle analysis is appropriate, a clearer description of specific research and of how the extensive gaps are to be filled is needed.

Only one project is identified in research need 5 (risk-communication approaches). It is restricted to workplace-related issues, and this indicates a large gap in risk-communication approaches for the general public. In addition, the single project listed describes an information-dissemination project rather than a two-way risk-communication project. The document should consider risk communication as a useful information-gathering process and give higher priority to problem scoping and formulation processes with interested and affected parties (NRC 1996).

The section on risk-management methods identifies four gaps on p. 41 of NNI (NEHI 2008): trend information, exposure controls, flammability or reactivity changes due to particle size, and material-safety data sheets. In the broader summary of research needs on p. 46, the 2008 NNI document identifies three major risk-management research gaps to be addressed in the near term: "develop risk characterization information to determine and classify nanomaterials based on physical or chemical properties," "develop nanomaterial-use and safety-incident trend information," and "expand exposure route-specific risk management methods research and life cycle analysis research on the basis of nanomaterial use scenarios expected to present greatest exposure and potential for health or environmental effects." The committee agrees that these seven research priorities, some of which are identical with the research needs mentioned in the document and some not, are reasonable. The lack of concordance between the two lists of identified gaps, however, and the lack of discussion of how the NNI and the NEHI intend to promote research to address them preclude useful evaluation of whether the NNI document provides a useful strategy for filling gaps and meeting short-term and long-term risk-management needs.

Risk-management topics and kinds of research areas in addition to the gaps identified by the document should be considered in this section. They include identifying nanotechnology-enabled products that can assist in managing risks posed by conventional hazards, and permitting the replacement of hazardous chemicals with less hazardous materials. For example, the document indi-

cates that the properties of nanomaterials can be used to "clean contaminated soil and groundwater" (p. 3). That suggests an important risk-management activity for EPA. Although this kind of research was mentioned in the 2006 NNI report and research project C4-8 in Appendix A (p. 82) appears to support it, there is no further discussion of it in the 2008 document. Identifying and developing nanotechnology-enabled risk-management approaches to environmental problems should be addressed as a separate research need.

Conclusions

The criteria for setting priorities for risk-management methods research were not clearly stated. Information was only implicit in the graphical timelines, not described explicitly in the text. Descriptions of high-priority research needs and how they are to be met are lacking; in their place are descriptions of the FY 2006 projects and their limitations in meeting the needs. There is inadequate description of the process by which the 24 research needs identified in the 2006 NNI report were culled to the five in the 2008 NNI document. The graphical timeline gives high priority to nearly all research needs, providing little strategic guidance for meeting them within resource constraints.

The gap analysis for risk-management methods is flawed and limited by the decision to use the 2006 research portfolio as its basis. Major gaps, including management of environmental and consumer risks with emphasis on potential risks to infants and children, are not addressed. The small number of research projects in this category and the smaller number of research projects that actually address the identified research needs underscore the enormous gaps between what is needed and what the agencies are doing. The failure to distinguish carefully between risk-management methods research and risk-management data-collection activities further hampered the gap analysis. The lack of consideration of management of environmental and consumer risks constitutes another considerable gap. It pertains to consideration of risk-management approaches to both general population exposures and specific potential exposure settings, such as accidents and spills, environmental discharges, and exposure through consumer products with the likelihood of exposure of infants and children; it also pertains to the development of life-cycle analyses, which must encompass not just manufacturing processes but the entire product life cycle from resource extraction through disposal. In general, approaches to risk management, such as control banding, that can help to address risks in the absence of completed traditional risk assessments are not adequately addressed in the document. Although the focus on workplace risk management is reasonable given that the occupational setting is likely to be the initial setting where important exposures occur, and the few projects that assess the adequacy of exposure-control measures are critical and appropriate, the overall risk-

management research portfolio and strategy are inadequate to address societal needs.

The document does not provide evidence of a strategic approach to risk-management research. The need for the rapid development and validation of effective risk-management methods is great for a set of rapidly emerging technologies like nanotechnology, but the narrow focus on 2006 studies and failure to describe adequately what is meant by the research categories and how projects are to be given priority constitute a failure to develop a strategic plan to meet the need.

COMMITTEE'S ASSESSMENT OF CURRENT DISTRIBUTION OF FEDERAL INVESTMENT IN NANOTECHNOLOGY-RELATED ENVIRONMENTAL, HEALTH, AND SAFETY RESEARCH

The NNI comments on the distribution of nanotechnology-related EHS research investment by illustrating the amount of money it was spending on each of the five research categories in FY 2006 (see Table 4-1). It states that "it is appropriate that investments at this time are predominantly in the categories of Instrumentation, Metrology, and Analytical Methods, Nanomaterials and Human Health, and Nanomaterials and the Environment. The balance of spending will evolve in time as research programs mature and efforts that are undertaken sequentially are initiated" (p. 44).

On the basis of the breakdown in funding, the NNI concludes that, "in short, the analysis demonstrated that the Federal Government is supporting more EHS research than has been previously identified, and the research is well-distributed across key priority areas" (p. 2). However, the analysis does not address how well the funded studies are addressing the specific research needs for a science-based assessment of the human health and environmental risks posed by the production, use, and distribution of nanoscale engineered materials. In the committee's opinion, examining what is funded (Appendix A, pp. 55-58) leads to a different research portfolio that is heavily slanted to specific medical-imaging applications, therapeutic nanomaterials, and targeted drug delivery, especially cancer chemotherapeutics, and to studies focused on understanding fundamentals of nanoscience that are not explicitly associated with the EHS aspects of the risks posed by nanomaterials.

The nanomedicine projects are not basic toxicologic studies of potential human response to nanomaterials in general. Rather, much of this research focuses on finding new applications of nanotechnology-related therapeutics. That does not lead to the general understanding of factors governing absorption, distribution, metabolism, elimination, and toxicity of manufactured nanomaterials needed for a comprehensive risk assessment of manufactured nanomaterials with respect to environmental, occupational, and consumer exposure (for example, cosmetics).

TABLE 4-1 NNI Evaluation of Federal Grant Awards in FY 2006 That Are Directly Relevant to EHS Issues

Category	Number of Projects	$ Invested (Millions), FY 2006
Instrumentation, Metrology, and Analytical Methods	78	26.6
Human Health	100	24.1
Environment	49	12.7
Human and Environmental Exposure Assessment	5	1.1
Risk Management Methods	14	3.3
TOTAL	246	67.8

Source: NEHI 2008.

Many of the funded projects will not generate the information needed to support EHS risk assessment and risk management or provide critical data for regulatory agencies. It makes no sense to include many of the projects listed in Appendix A only because incidental knowledge, procedures, or techniques obtained from that research might be relevant to one or another aspect of research relevant to EHS needs in nanotechnology. The committee notes that the NNI chose to include an additional 116 projects in Appendix A that were not included in the president's budget even though they were aimed primarily at medical applications or at characterization and measurement of nanomaterials (NEHI 2008; Teague, unpublished material, 2008).

The committee conducted its own informal reassessment of the current balance of nanotechnology-related EHS-research investment by using its professional judgment. The committee reviewed the titles and abstracts of the projects to determine which are *primarily* aimed at understanding the potential risks posed by engineered nanomaterials or would otherwise be reasonably expected to provide data that are directly relevant to EHS evaluation. The results are presented in Table 4-2. (Only the percentages of projects in each broad category are presented, because the funding of each project was not readily available.)

Table 4-2 shows that roughly one-fifth to two-fifths of research projects in the instrumentation, metrology, and analytic methods category and about one-third of projects in the human-health category are directly relevant to understanding the potential risks posed by engineered nanomaterials or would otherwise be reasonably expected to provide data that are directly relevant to EHS evaluation. The ranges in Table 4-2 reflect the variability in professional judgment among committee members; such an evaluation has elements of subjectivity. Nevertheless, what is critical is that fewer than half the projects listed in Appendix A are relevant to understanding of EHS issues related to nanomaterials. Therefore, the amount of money being spent by the federal government specifically to address EHS needs in nanotechnology is certainly far less than the

TABLE 4-2 NRC Committee's Estimate of Percentage of FY 2006 Projects That Are Aimed Primarily at Understanding Potential Risks Posed by Engineered Nanomaterials

Category	Committee's Professional Judgment
Instrumentation, Metrology, and Analytical Methods	18-40%
Human Health	30-32%
Environment	67-84%
Human and Environmental Exposure Assessment	100%
Risk Management Methods	57-78%
TOTAL	36-48%

$68 million indicated in the NNI strategy document. It should be noted that that conclusion is supported by other independent analyses of the issue (for example, GAO 2008; Maynard 2008).

CONCLUSIONS

Cross-cutting observations that are relevant to all research categories in the 2008 NNI strategy document include the following: generally appropriate research needs are identified, priorities among research needs are not clearly articulated, and the gap analysis contributes to overstating the amount of relevant federal research being conducted to support EHS research needs related to nanomaterials.

The organization of research into five topical categories is necessary, but it obscures the interrelationships among research needs and creates the possibility that research needs that fall between categories will be overlooked. It is important that the research categories not be viewed as silos. For example, environmental exposures is a common thread in both research categories; Nanomaterials and the Environment and Human and Environmental Exposure Assessment. An example of a research need that may have been omitted because it falls between categories is the omission of characterization methods that consider specific biologic settings. Additional examples are discussed in Section II.

Inventories of the research needs are sufficient for some topical categories, but they are poorly defined and incomplete in risk management and exposure assessment. For example, the discussion of exposure assessment does not address exposures throughout the life cycle of nanomaterials and the discussion of risk-management methods does not cover management of environmental and consumer risks, including specific potential exposure scenarios, such as accidents and spills, environmental discharges, and exposure through consumer products.

Poor gap analysis is a problem in all sections of the document, but it is particularly severe in the discussions of human health and metrology. Table 4-2 offers the committee's collective expert judgment of the extent to which the NNI strategy document miscounts research projects in its gap analysis. As is apparent, this problem was particularly severe with respect to the instrumentation, metrology, and analytic methods category and the human-health category. The extent of the problem is so great that the committee is concerned that the current funding or allocation of funding for EHS research needs related to nanomaterials may not be adequate to address current uncertainties in the manner needed to understand the risks posed by nanomaterials.

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5

Conclusions and Recommendations

The National Nanotechnology Initiative document *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* could be an effective tool for communicating the breadth of federally supported research associated with developing a more comprehensive understanding of the environmental, health, and safety implications of nanotechnology. It is the result of considerable collaboration and coordination among 18 federal agencies and is likely to eliminate unnecessary duplication of their research efforts.

***The Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* does not describe a strategy for nano-risk research. It lacks input from a diverse stakeholder group, and it lacks essential elements, such as a vision and a clear set of objectives, a comprehensive assessment of the state of the science, a plan or road map that describes how research progress will be measured, and the estimated resources required to conduct such research.**

There remains an urgent need for the nation to build on the current research base related to the EHS implications of nanotechnology—including the federally supported research described in the 2008 NNI document—by developing a national strategic plan for nanotechnology-related environmental, health, and safety research.

Having reviewed the National Nanotechnology Initiative (NNI) strategy document, the committee has concluded that it does an excellent job of identifying numerous specific topics on which more research is needed to adequately address the environmental, health, and safety (EHS) concerns associated with engineered nanoscale materials. The committee found that, with some exceptions, the specific research needs in each research category were appropriate for nanotechnology-related EHS research. However, although the inventories of the research needs are sufficient for some research categories, they are poorly de-

fined and incomplete in others, specifically risk management and exposure assessment. The committee also believes that some research needs that fall between categories could be overlooked.

The research needs in the NNI strategy document are not presented as concrete, measurable objectives, and the implementation plan fails to provide any sense of how success toward specific goals will be measured or what resources might be needed to achieve them.

The committee carefully considered the "gap analysis" in the NNI document, which was based on identifying FY 2006 funded projects as relevant to one or more of the five broad research categories. The committee concluded that the gap analysis is flawed and is neither accurate nor complete in laying a foundation for a research strategy. The approach used does not provide an accurate picture of current resource allocations even among the five broad categories. The committee concluded that the use of the FY 2006 data to conduct the gap analysis is perhaps the greatest flaw identified in the document. It is particularly problematic in the discussions of human health and metrology, in which it resulted in the inclusion of research projects that are not directly relevant to understanding the EHS needs related to nanomaterials. The issues arising from the gap analysis led to important deficiencies in all the research categories described in Section II of the 2008 NNI document. Because of the flaws in the gap analysis, it is difficult to understand the priorities of selected research needs and the logic for the priorities.

The NNI document states (p. 46) that "the EHS research strategy fundamentally depends on sustaining the broad spectrum of basic research. . . . The current balance of research funding addresses such basic investigations and supports regulatory decision making." However, although the committee has no reason to doubt the value of the compelling nanotechnology research described, it notes that probably less than half the grants and resources counted in the inventory will provide any useful data to support regulatory decision-making. The analysis suffers universally from a lack of coherent and consistent criteria for determining the value of information provided by various research activities. Such criteria would ideally be founded on an understanding of the uncertainties in each of the various research fields and the interrelationships among them.

The federal funding specifically addressing nanotechnology-related EHS issues is far less than portrayed in the NNI document and may be inadequate. The committee concludes that if no new resources are provided and the current agency funding continues, the implementation plan described in the NNI document will not ensure that engineered nanomaterials are adequately evaluated for potential health and environmental effects. Such an evaluation is critical to ensure that the future of nanotechnology is not burdened by uncertainties and innuendo about potential adverse health and environmental effects of engineered nanoscale materials. Those concerns have been voiced recently by both the nanotechnology industry and a variety of environmental and public-health interest groups.

In many endeavors, society looks to the scientific community for insights, data, and recommendations for establishing policies or regulations. In the broad swath of nanoscience and nanotechnology, the present committee considers that the emerging field of nanotechnology is one such endeavor. The scientific input needed for understanding the potential effects is not necessarily that produced by exploratory research (although it has its place) but rather often relies heavily on generating, identifying, and applying specific knowledge. In this respect, scientific input into developing policies for risk assessment and risk management of currently available and emerging nanotechnology bears a closer resemblance to the approval process for new drugs and medical devices than to the general advancement of new knowledge through exploratory research.

The current nanotechnology risk research portfolio is dominated by agencies traditionally focused on exploratory and investigator-driven research, such as the National Institutes of Health and the National Science Foundation. If these agencies are to continue to lead research efforts in this area, the scope of research requests and the review criteria used to assess the relative merits of submitted proposals may need to be modified if the agencies want to ensure that the research they support feeds into an effective EHS risk research strategy based on appropriate, targeted research.

There are several possible ways to accomplish such a change in criteria, for example, through joint initiatives, including requests for proposals with explicit statements of need, between federal agencies focused on fundamental or investigator-driven science and mission-driven agencies responsible for protecting human health and the environment (such as the Environmental Protection Agency, the National Institute for Occupational Safety and Health, the Food and Drug Administration, and the Consumer Product Safety Commission). Ultimately, any useful strategic plan for addressing EHS aspects of nanotechnology will have to focus on obtaining timely research results that can assist all stakeholders, including federal agencies, in planning, controlling, and optimizing the use of purposely engineered nanomaterials while minimizing and controlling the potential EHS effects of concern to society.

What is needed, the committee concludes, is an effective *national strategic plan* for nanotechnology-related EHS research that involves more stakeholders than the federal government. Such a plan would have to identify research needs clearly and estimate the financial and technical resources needed to address identified research gaps. A national strategic plan would be focused on providing solutions to challenges that do not necessarily fit neatly into disciplinary and institutional silos, and ensure important research does not fall between the gaps. Such a plan would also provide specific, measurable objectives and a timeline for meeting them.

The committee finds that the 2008 NNI document represents excellent input into a national strategic plan. A national strategic plan would ensure the timely development of engineered nanoscale materials that will bring about great improvements in the nation's health, its environmental quality, its economy, its security, and the quality of life without the unintended consequences of

damage to the environment and to the health of the very workers and consumers who stand to benefit from the technology.

Reducing the burden of uncertainty through targeted, effective research that identifies and eliminates potential environmental and health hazards of engineered nanoscale materials should have high priority for the nation. An effective national strategic plan is essential for the successful development of and public acceptance of nanotechnology-enabled products. A value-of-information approach should be used to determine the research that is needed to reduce the current uncertainties with respect to the potential health and environmental effects of nanomaterials. A national strategic plan would need to address nanotechnology-based products that are entering commerce and nanotechnology-based products that are under development. It would provide a path for developing the scientific knowledge to support nanotechnology-related EHS risk-based decision-making. It would lay the scientific groundwork for addressing future materials and products arising out of new research, new tools, and new cross-fertilization between previously distinct fields of science and technology.

The committee chose the term *national strategic plan* rather than *federal strategic plan* because it concluded that one of the weaknesses of the 2008 NNI document is that it focuses only on federal government agency activities. Federal programs are essential and in the national interest, but the nongovernment research community should also contribute research and knowledge to the understanding of the EHS implications of nanotechnology.

The committee concludes that a truly national strategy cannot be developed within the limitations of the scope of research under the umbrella of the NNI. The NNI can produce only a strategy that is the sum of the individual agency priorities, many of which are not aligned with EHS research related to nanomaterials. The structure of the NNI makes the development of a visionary and authoritative research strategy extraordinarily difficult. Because the NNI is a coordination mechanism, not a research funding program, it has no central authority to make budgetary or funding decisions, and it relies on its member agencies to gather resources or influence to shape the overall federal nanotechnology-related EHS research activity. The NNI is responsible for ensuring U.S. competitiveness through the development of a rapid and robust nanotechnology-related research and development program while ensuring the safe and responsible development of nanotechnology itself, and these two missions may be perceived as being in conflict. But the conflict is a false dichotomy in that strategic research on potential risks posed by nanotechnology can be an integral and fundamental part of its sustainable development. Nonetheless, a clear separation of accountability for development of applications and assessment of potential EHS implications would help to ensure that the public-health mission is given appropriate priority.

Having considered those conclusions with respect to the 2008 NNI document and what is needed for a path forward, the committee offers the following two recommendations.

A robust national strategic plan is needed for nanotechnology-related environmental, health, and safety research that builds on the five categories of research needs identified in the 2008 NNI document. The development of the plan should include input from a broad set of stakeholders across the research community and other interested parties in government, nongovernment, and industrial groups. The strategy should focus on research to support risk assessment and management, should include value-of-information considerations, and should identify

- **Specific research needs for the future in such topics as potential exposures to engineered nanomaterials, toxicity, toxicokinetics, environmental fate, and standardization of testing.**
- **The current state of knowledge in each specific area.**
- **The gap between the knowledge at hand and the knowledge needed.**
- **Research priorities for understanding life-cycle risks to humans and the environment.**
- **The estimated resources that would be needed to address the gap over a specified time frame.**

As part of a broader strategic plan, NNI should continue to foster the successful interagency coordination effort that led to its 2008 document with the aim of ensuring that the federal plan is an integral part of the broader national strategic plan for investments in nanotechnology-related environmental, health, and safety research. In doing so, it will need a more robust gap analysis. The federal plan should identify milestones and mechanisms to ascertain progress and identify investment strategies for each agency. Such a federal plan could feed into a national strategic plan but would not itself be a broad, multistakeholder national strategic plan. Development of a national strategic plan should begin immediately and not await further refinement of the current federal strategy.

Appendix A

Biographic Information on the Committee for Review of the Federal Strategy to Address Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials

David L. Eaton *(Chair)* is associate vice provost for research at the University of Washington, where he holds faculty appointments as professor of environmental and occupational health sciences, professor of public health genetics, and adjunct professor of medicinal chemistry. He also serves as director of the University of Washington-National Institute of Environmental Health Sciences (NIEHS) Center for Ecogenetics and Environmental Health and directs a large, multi-investigator center grant from NIEHS in toxicogenomics. Dr. Eaton's research interests include the molecular basis of chemically induced cancers and the effect of human genetic variation in biotransformation enzymes on individual susceptibility to natural and synthetic chemicals. He was president of the Society of Toxicology in 2001-2002. He has served as chair of several National Research Council committees, including the Committee on Emerging Issues and Data on Environmental Contaminants and the Committee on EPA's Exposure and Human Health Reassessment of TCDD and Related Compounds. Dr. Eaton has been awarded many distinguished fellowships and honors, including the Achievement Award of the Society of Toxicology in 1990. He is an elected fellow of the Academy of Toxicological Sciences and of the American Association for the Advancement of Science. He earned his PhD in pharmacology and toxicology from the University of Kansas Medical Center.

Martin A. Philbert *(Vice Chair)* is a professor of toxicology and executive director of the Center for Risk Science and Communication at the University of Michigan. Dr. Philbert's research interests include the development of nanotechnology for intracellular measurement of biochemicals and ions and for the early detection of and treatment for brain tumors. He is actively engaged in the investigation of mechanisms of chemically induced energy deprivation syndromes in the central nervous system. He has published more than 100 scholarly manuscripts, book chapters, and abstracts and is the recipient of the 2001 Society of Toxicology Achievement Award. Dr. Philbert serves on the Institute of Medicine's Food and Nutrition Board and the Roundtable on Environmental Health Sciences, Research, and Medicine. He earned his PhD in neurochemistry and experimental neuropathology from the University of London.

George V. Alexeeff is deputy director for scientific affairs of the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency. He oversees a staff of more than 80 scientists in multidisciplinary evaluations of the health effects of pollutants and toxicants in air, water, soil, and other media. His activities include reviewing epidemiologic and toxicologic data to identify hazards and derive risk-based assessments, developing guidelines to identify chemicals hazardous to the public, recommending air-quality standards, identifying toxic air contaminants, developing public-health goals for water contaminants, preparing evaluations for carcinogens and reproductive toxins, issuing sport-fish advisories, training health personnel on pesticide-poisoning recognition, reviewing hazardous-waste site risk assessments, and conducting multimedia risk assessments. He was chief of the Air Toxicology and Epidemiology Section of OEHHA from October 1990 through February 1998. Dr. Alexeeff has over 50 publications in toxicology and risk assessment. He has been a member of previous National Research Council committees including Evaluating the Efficiency of Research and Development Programs in the Environmental Protection Agency and the Scientific Review of the Proposed Risk Assessment Bulletin from the Office of Management and Budget. He earned his PhD in pharmacology and toxicology from the University of California, Davis.

Tina Bahadori is the managing director of the Long-Range Research Initiative (LRI) at the American Chemistry Council (ACC). Dr. Bahadori manages the development, implementation, and direction of the LRI research portfolios in environmental health with specific expertise and responsibilities in exposure and risk analysis. She is the LRI lead for developing a global research program on interpretation of biomonitoring data. Dr. Bahadori is the president-elect of the International Society of Exposure Analysis. She serves as an expert and reviewer on a number of scientific panels, including the National Academy of Sciences (NAS) panel for review of particulate-matter research; as a peer reviewer for the Environmental Protection Agency Science to Achieve Results grants; on the NAS interacademy panel on the ecology of the Caspian Sea; on

the Advisory Panel for the Aerosol Research Inhalation Epidemiology Study; and on the internal steering committee and as one of the principal investigators for the St. Louis-Midwest PM Supersite. She was also a member of the Chemical Exposure Working Group for the National Children's Study. Before joining ACC, she was the manager for air-quality health integrated programs at the Electric Power Research Institute. Her research was related to health implications of environmental pollution and included integration of atmospheric chemistry, exposure assessment, and epidemiology. She was responsible for the design, implementation, and promotion of collaborative research with emphasis on policy and regulatory decision-making. At Arthur D. Little, Inc., where she was a consultant in the Environmental Risk Management Unit, she assisted clients with technical and management problems related to environment, health, and safety matters. She holds a doctorate in environmental science and engineering from the Harvard School of Public Health.

John M. Balbus is the chief health scientist and health program director at the Environmental Defense Fund and an adjunct associate professor of environmental health sciences at Johns Hopkins University. His expertise is in epidemiology, toxicology, and risk science. He spent 7 years at George Washington University, where he was the founding director of the Center for Risk Science and Public Health and served as acting chair of the Department of Environmental and Occupational Health. He was also an associate professor of medicine there. Dr. Balbus has served as a member of the Environmental Protection Agency (EPA) Children's Health Protection Advisory Committee, as a core peer consultation panel member for EPA's Voluntary Children's Chemical Exposure Program, and as a member of EPA review committees on air-toxics research, computational toxicology, and climate-change research. He serves on the National Research Council's (NRC) Board on Environmental Studies and Toxicology and is a member of the Committee on Improving Risk Analysis Approaches Used by the U.S. EPA. He previously served on the NRC Committee on Applications of Toxicogenomics Technologies to Predictive Toxicology. Dr. Balbus received his MD from the University of Pennsylvania.

Moungi G. Bawendi (NAS) is the Lester Wolfe Professor of Chemistry in the Department of Chemistry at the Massachusetts Institute of Technology. His research interests include the chemistry, physics, and applications of nanometer-size semiconductor and metal particles exhibiting quantum mechanical size effects. He is interested in the science and applications of nanocrystals, especially semiconductor nanocrystals. Previously, he was a member of the National Research Council Committee on the Review of the National Nanotechnology Initiative. In 2007, Dr. Bawendi was elected to the National Academy of Sciences. He earned a PhD in chemistry from the University of Chicago.

Pratim Biswas is the Stifel and Quinette Jens Professor and chair of the Department of Energy, Environmental and Chemical Engineering at Washington

University in St. Louis. Dr. Biswas's research interests include aerosol science and engineering, nanoparticle technology, air quality and pollution control, combustion, environmentally benign energy production and materials processing (with applications in environmental and energy technologies), and thermal sciences (heat transfer and fluid mechanics). Dr. Biswas was appointed president of the American Association for Aerosol Research for 2006-2007 and had been the technical program chair at the International Aerosol Conference in St. Paul, MN. He received his PhD in mechanical engineering from the California Institute of Technology.

Vicki Colvin is professor of chemistry at Rice University and director of its Center for Biological and Environmental Nanotechnology (CBEN). CBEN is one of the nation's six nanoscience and engineering centers funded by the National Science Foundation. One of CBEN's primary interests is the application of nanotechnology to the environment. Dr. Colvin has received numerous accolades for her teaching abilities, including Phi Beta Kappa's Teaching Prize for 1998-1999 and the Camille Dreyfus Teacher Scholar Award in 2002. In 2002, she was also named one of Discover magazine's "Top 20 Scientists to Watch" and received an Alfred P. Sloan Fellowship. Dr. Colvin is a frequent contributor to Advanced Materials, Physical Review Letters, and other peer-reviewed journals and holds patents to four inventions. She received her PhD in chemistry from the University of California, Berkeley, where she was awarded the American Chemical Society's Victor K. LaMer Award for her work in colloid and surface chemistry.

Stephen J. Klaine is a professor in the Department of Biological Sciences and the director of the Institute of Environmental Toxicology at Clemson University. His research focuses on the fate and effects of contaminants in the environment, specifically contaminants that migrate from various land uses into aquatic ecosystems and their effects on aquatic plants and animals. His laboratory studies contaminant effects on fish, aquatic invertebrates, plants, and algae. Currently, it is studying the toxicity of metals, pesticides, pharmaceuticals, and nanomaterials. Dr. Klaine received the Sigma Xi Researcher of the Year Award at Clemson University in 2007 and has been named to Who's Who in Technology, Environmental Science and Engineering. He has served on the National Research Council Panel on Life Sciences and is aquatic-toxicology editor for Environmental Toxicology and Chemistry. He received his PhD in environmental science from Rice University.

Andrew D. Maynard is the chief science adviser at the Woodrow Wilson International Center for Scholars for the Project on Emerging Nanotechnologies. He also holds an associate professorship at the University of Cincinnati and is an honorary senior lecturer at the University of Aberdeen, UK. Dr. Maynard's research interests revolve around aerosol characterization and the implications of nanotechnology for occupational health. His expertise covers many facets of

aerosols and health implications, from occupational aerosol sampler design to state-of-the-art nanoparticle analysis. Previously, he worked for the National Institute for Occupational Safety and Health (NIOSH) and represented the agency on the Nanoscale Science, Engineering and Technology Subcommittee (NSET) of the National Science and Technology Council; he also cochaired the Nanotechnology Health and Environment Implications Working Group of the NSET. Recently, he was a recipient of the NIOSH Alice Hamilton Award (Biological Sciences). He is a member of the Executive Committee of the International Council on Nanotechnology and until recently chaired the International Standards Organization working group on size-selective sampling in the workplace. He earned his PhD in aerosol physics from the Cavendish Laboratory, University of Cambridge, UK.

Nancy Ann Monteiro-Riviere is a professor of investigative dermatology and toxicology at the Center for Chemical Toxicology Research and Pharmacokinetics at North Carolina State University (NCSU). Dr. Monteiro-Riviere is also a professor in the Joint Department of Biomedical Engineering of the University of North Carolina (UNC)-Chapel Hill and NCSU and research adjunct professor of dermatology in the School of Medicine at UNC-Chapel Hill. She is a past president of the Dermal Toxicology Specialty Section and the In Vitro Toxicology Specialty Section of the Society of Toxicology. Dr. Monteiro-Riviere is a fellow of the American Academy of Nanomedicine, the Academy of Toxicological Sciences, and the American College of Toxicology. She serves on several toxicology editorial boards and national panels, including many in nanotoxicology, and she is coeditor of *Nanotoxicology: Characterization and Dosing and Health Effects*. She received her PhD in anatomy from Purdue University.

Günter Oberdörster is professor in the Department of Environmental Medicine at the University of Rochester, director of the University of Rochester Ultrafine Particle Center, principal investigator on a multidisciplinary research initiative in nanotoxicology, and head of the Pulmonary Core of a National Institute of Environmental Health Sciences center grant. His research focuses on the effects and underlying mechanisms of lung injury induced by inhaled nonfibrous and fibrous particles, including extrapolation modeling and risk assessment. His studies of ultrafine particles influenced the field of inhalation toxicology, raising awareness of the unique biokinetics and toxic potential of nanoscale particles. He has served on many national and international committees and is a recipient of several scientific awards. He is on the editorial boards of the Journal of Aerosol Medicine, Particle and Fibre Toxicology, Nanotoxicology, and the International Journal of Hygiene and Environmental Health and is associate editor of *Inhalation Toxicology and Environmental Health Perspectives*. He earned his DVM and PhD (in pharmacology) from the University of Giessen, Germany.

Mark A. Ratner (NAS) is the Morrison Professor of Chemistry and professor of materials science and engineering at Northwestern University. His research focuses on structure and function at the nanoscale and on the theory of fundamental chemical processes. Specific interests include molecular electronics, electron transfer, self-assembly, nonlinear optical response in molecules, and theories of quantum dynamics. He is a fellow of the American Association for the Advancement of Science and a member of the American Academy of Arts and Sciences. Dr. Ratner was elected to the National Academy of Sciences in 2002 for his contributions to molecular materials theory and modeling. He earned his PhD in chemistry from Northwestern University.

Justin G. Teeguarden is a senior research scientist with the Pacific Northwest National Laboratory where he conducts research within a multidisciplinary team studying the relationship between the physicochemical properties of nanomaterials and their biocompatibility. His major research focus is in the areas of nanomaterial pharmacokinetics and dosimetry, both *in vivo* and *in vitro*, and the development of integrated computational models of cellular and tissue dosimetry and biologic response. He is the principal investigator of pharmacokinetic studies of organic chemicals and metals and develops physiologically based pharmacokinetic models of chemical kinetics for application in study design and risk assessment for both private companies and the EPA. Through Society of Toxicology symposia, specialty sections and continuing education courses, Dr. Teeguarden has promoted the application of the fundamental sciences in nanomaterial risk assessment. He serves on the National Toxicology Program Board of Scientific Councilors, and on a variety of EPA and NIH review panels. Dr. Teeguarden received his PhD in toxicology from the University of Wisconsin, Madison, and is board certified in toxicology.

Mark R. Wiesner is the James L. Meriam Professor of Civil and Environmental Engineering in the Pratt School of Engineering at Duke University. He was previously Chair of Excellence in the Chemical Engineering Laboratory at the Institute Nationale Polytechnique, Toulouse, France. His research interests include membrane processes, nanostructured materials, transport and fate of nanomaterials in the environment, colloidal and interfacial processes, and environmental systems analysis. Dr. Wiesner has received the Association of Environmental Engineering and Science Professors Frontiers in Research Award, the American Institute of Chemical Engineers Graduate Research Award for Membrane-Based Separations, and the Charles Duncan Award for Scholarship and Teaching at Rice University. He served on the Scientific Advisory Board and was the U.S. director for the European Union-United States University Consortium on Environmental Engineering Education from 1993 to 2005. Dr. Wiesner received his PhD in environmental engineering from Johns Hopkins University.

Appendix B

Statement of Task

The National Research Council shall conduct a scientific and technical review of the draft document entitled "Federal Strategy for Environmental, Health, and Safety (EHS) Research Needs for Engineered Nanoscale Materials," expected to be publicly released by the U.S. National Nanotechnology Initiative in September 2007. An ad hoc committee will plan a workshop and evaluate the scientific and technical aspects of the draft strategy and comment in general terms on how this strategy will develop information needed to support the EHS risk assessment and risk management needs with respect to nanomaterials. In its evaluation the committee will take into consideration the report, *Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials* (NEHI 2006) and other governmental and non-governmental reviews identifying EHS research priorities.

Appendix C

Workshop Agendas of the National Research Council Committee for Review of the Federal Strategy to Address Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials

1st Workshop: March 31, 2008

Lecture Room
National Academy of Sciences
2100 C Street, NW
Washington, DC

Public Agenda

2:30 PM	Welcome and Introductory Remarks *David Eaton, Chair, NRC Committee for Review of the Federal Strategy to Address Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials*
2:40 PM	Dr. Clayton Teague – Introduction to the NNI Strategy and Expectations for the Review *Director, National Nanotechnology Coordination Office*

Committee – Panel Discussion with Members of the Nanotechnology Environmental Health Implications (NEHI) Working Group

Environmental Protection Agency
Jeffrey Morris, *Acting Director, Office of Science Policy*
Phillip Sayre, *Associate Director, Risk Assessment Division, Office of Pollution, Prevention, and Toxics*

Food and Drug Administration
Norris Alderson, *Associate Commissioner for Science*
Richard Canady, *Senior Science Policy Analyst, Office of the Commissioner*

National Institute of Environmental Health Sciences
Sally Tinkle, *Senior Science Advisor*

National Institute for Occupational Safety and Health
Paul Schulte, *Director, Education and Information Division*
Vladimir Murashov, *Special Assistant to the Director*

National Institute of Standards and Technology
Dianne Poster, *Policy Analyst*

4:40 PM Public Comments

5:30 PM Adjourn Public Session

2nd Workshop: May 5, 2008

Room 100
Keck Center of the National Academies
500 5th Street, NW
Washington, DC

Public Agenda

8:45 AM Welcome and Introductory Remarks
David Eaton, Chair, NRC Committee for Review of the Federal Strategy to Address Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials

9:00 AM Discussion of the development of the EU framework for EHS research on nanotechnology (videoconference)

	Dr. Philippe Martin, *Directorate General, Health and Consumer Protection, European Commission* Dr. Pilar Aguar, *Program Officer, Directorate General for Research, European Commission*
10:00 AM	Committee – Panel Discussion on the Federal Strategy to Address Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials Carolyn Cairns, *Program Leader, Product Safety, Consumer's Union* Thomas Epprecht, *Director of Products, Swiss Re* (video conference) William Gulledge, *Senior Director, Chemical Products and Technology Division, ACC* Michael Holman, *Research Director, Lux Researc*h William Kojola, *Industrial Hygienist, AFL-CIO* Terry Medley, *Global Director of Corporate Regulatory Affairs, DuPont* Jennifer Sass, *Senior Scientist, Natural Resources Defense Council*
1:15 PM	Committee – Panel Discussion on the influence of the Federal strategy on decision making and priority setting Altaf Carim, *Program Manager, Office of Science, Department of Energy* William Rees, *Deputy Under Secretary of Defense for Laboratories and Basic Sciences* Mihail Roco, *Senior Advisor for Nanotechnology, National Science Foundation*
2:15 PM	Public Comments
3:00 PM	Adjourn Public Session

Appendix D

National Nanotechnology Initiative Strategy for Nanotechnology-Related Environmental, Health, and Safety Research[1]

The National Nanotechnology Initiative's *Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* is available on CD-ROM on the inside of the back cover of this report.

[1]NEHI (Nanotechnology Environmental Health Implications Working Group). 2008. National Nanotechnology Initiative Strategy for Nanotechnology-Related Environmental, Health, and Safety Research. Arlington, VA: National Nanotechnology Coordination Office. February 2008 [online]. Available: http://www.nano.gov/NNI_EHS_Research_Strategy.pdf [accessed Aug. 22, 2008].