DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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NSET Subcommittee:

The National Institutes of Health (NIH)'s Institute and Center members of the Trans-NIH-Nanotechnology Task Force have reviewed the NSET/NEHI Working Group paper entitled, "Prioritization of Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials: An Interim Document for Public Comment," and provide the following comments for consideration.

We appreciate NEHI's efforts in developing 25 key research priority needs for nano EHS. We offer a few suggestions and additions that might serve to further strengthen the report. For example, it might be useful to provide a paragraph or so of context, in order to highlight the urgency of addressing these research priorities will all deliberate speed, both to ensure the future scientific progress of the field, and to secure the economic generativity that Congress expects from this home-grown technology. In addition, some reference to the major EHS initiatives presently underway on the international front might also be important to attend to, as John Marburger noted at the PCAST meeting on Nanotechnology on September 10th.

It is possible that some opportunities for additional integration and ordering of the research needs may have been overlooked. For example, a reader who is unfamiliar with the process of the report's development might find priority 4, under the Health and Environmental Exposure Assessment ("Characterize health of exposed populations and environments") to overlap with priorities already articulated under the categories of Nanomaterials and Human Health and under Nanomaterials and the Environment, respectively. Although the report states that the subcommittee worked hard to integrate overlapping needs, perhaps another look at possibilities for highlighting cross-cutting themes might be beneficial.

It might also prove helpful to include a brief discussion of the scientific rationale underlying the prioritization of the 5 topics in each section, in order to provide additional

clarification about how these decisions were made. Some reference to the manner in which the science was discussed and the assumptions which guided the selection of each chapter's unique ordering would further advance the transparency of the report.

In addition, perhaps some reference to development of a risk communication plan, with specific attention accorded to the health of population groups likely to be at high risk for exposure, might also be in order here.

Finally, we have included a few suggested edits in the attached Word document.

In summary, we believe this document represents a useful first step, and suggest that the addition of several factors, pertaining to policy context, cross-cutting themes, decision-making transparency and risk communication, might serve potentially to make the report a more valuable and informative document for members of Congress.

Please direct questions about these comments to: Nancy E. Miller, Ph.D., Executive Secretary, Trans-NIH Nanotechnology Task Force, Office of Science Policy Analysis, Office of the Director, NIH, 1 Center Drive-- MSC 0166, Building 1, Room 218, Bethesda, MD 20892-0166, Telephone 301-594-7742, Fax 301-402-0280, Email nm68k@nih.gov .

Thank you for the opportunity to review and comment on this important effort.

Nancy E. Miller, Ph.D.

Attachment

PRIORITIZATION OF ENVIRONMENTAL, HEALTH, AND SAFETY RESEARCH NEEDS FOR ENGINEERED NANOSCALE MATERIALS

AN INTERIM DOCUMENT FOR PUBLIC COMMENT

August 2007
Released for Public Comment on August 16, 2007
Deadline for Comments September 17, 2007
Submit Comments at http://www.nano.gov/html/society/ehs_priorities/
Nanotechnology Environmental and Health Implications Working Group
Nanoscale Science, Engineering, and Technology Subcommittee
Committee on Technology
National Science and Technology Council

Report prepared by
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OVERVIEW

The September 2006 National Nanotechnology Initiative (NNI) document *EHS Research Needs for Engineered Nanoscale Materials* (http://www.nano.gov/NNI_EHS_research_needs.pdf), hereafter referred to as the *EHS Research Needs* document, identified for the Federal government five broad categories of environmental, health, and safety (EHS) research and information needs. Within these five categories, the *EHS Research Needs* document defined seventy-five specific needs related to risk assessment and management of nanoscale materials. It also provided principles for prioritizing EHS research.

Following release of the *EHS Research Needs* document, the interagency Nanotechnology Environmental and Health Implications (NEHI) Working Group solicited public comment on the prioritization principles and continued to assess the research needs. As a result, the Working Group has refined the prioritization principles and has reorganized and, in some cases, revised slightly the statement of the research needs and categories. The Working Group used the updated principles to identify five priorities within each of the five categories of EHS research and information needs. This document defines these twenty-five priorities along with the revised principles and the process used for prioritizing EHS research needs.

The NNI has recognized from its inception the need to support research on the potential risks of specific nanomaterials in parallel with research on related basic science and applications. Federal agencies that have a responsibility to protect human health and the environment need information about the potential hazards associated with nanomaterials in order to provide appropriate guidance and oversight. The NEHI Working Group, under guidance of the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the National Science and Technology Council, has created and continuously assesses a framework under which to broadly consider EHS research needs specific to nanomaterials and nanotechnology. Federal agencies that regulate and/or conduct research and development with nanomaterials are involved in this ongoing assessment. Important to this assessment are inputs from non-Federal experts on risk assessment issues and from previously published reports relevant to [or focused on] this topic. Such resources are particularly important to the strategic planning undertaken by the NNI to identify priority research and coordinate among agencies in support of such research.

PRINCIPLES FOR PRIORITIZING EHS RESEARCH

Based on public comments, the original principles for prioritizing research needs, as described in the *EHS Research Needs* document, were refined and elaborated upon and were used as guidelines in setting the priorities that are central to this document. The three major principles presented in the *EHS Research Needs* document are outlined below, followed by a clarification of these principles in response to the public review of the *EHS Research Needs* document.

1. *Prioritize research based on the value of information.* This overarching principle calls for the following factors to be taken into consideration:
– the extent to which information gained from investment in research funding will reduce uncertainty about both benefits and risks of nanomaterials
– the extent to which information may lead to broad knowledge about properties and behavior of nanomaterials or classes of nanomaterials
– the extent of use expected for a nanomaterial or groups of nanomaterials; potential of worker, consumer, or environmental exposure to nanomaterials

2. *Where appropriate, seek to leverage research funded by other governments and the private sector.* Other nations and various industries support EHS research that can address research needs identified by the NEHI Working Group. This principle seeks to avoid unnecessary duplication of research and to leverage investments by identifying opportunities to collaborate or build upon efforts of other stakeholders.
3. *Use adaptive management for nanomaterial EHS research.* The emerging nature of nanomaterials research, development, and commercialization means that EHS research priorities need to be evaluated and updated periodically.
The NEHI Working Group received approximately 40 public comments, written and oral, during its comment solicitation period in December 2006 and January 2007 and at a public meeting on January 4, 2007 (http://www.nano.gov). Most of the comments expressed support for the prioritization criteria identified in the *EHS Research Needs* document (http://www.nano.gov /NNI_EHS_research_needs.pdf). Of particular value to the work of prioritizing EHS research and information needs were the comments that addressed specific elements of the proposed prioritization principles. Addressing these comments helped to clarify the importance and meaning
of those principles. The discussion below summarizes the comments and responses related to the principle of "prioritizing research on the basis of value of information." Comments suggested examining two broad prioritization areas with respect to this principle:
1. *Short-term urgency and/or existing problems*. A number of commenters suggested prioritizing short-term research based on (a) opportunities to complete findings in the near term, (b) necessity of work to enable further developments (e.g., metrology), or (c) urgency due to current commercial use of specific nanomaterials or current occupational exposures. Prioritization of research to address existing exposures and nanomaterials with the greatest likelihood of exposure or that is required to enable future research is consistent with the originally stated criteria for assessing "value of information." However, these existing, high value research needs may have near-term solutions or require longer-term research. For example, occupational exposure measurement and mitigation is an existing, high-priority area with near-term research opportunities and is reflected in several top research priorities in this document. In contrast, longer-term research—research that can be expected to take many years to complete or that requires the development of new technology—may be important for addressing some of the existing problems. Thus, the length of time required to complete a research need was recognized in the research priorities here, but not emphasized in the valueof-information or other prioritization principles.
2. *Align risk assessment research with risk management needs*. Some comments encouraged prioritizing EHS research based on its relevance to risk management decisions. This, in fact, was the starting point for development of the *EHS Research Needs* document. The regulatory and research agencies of the NNI evaluated their information needs based on the risk management responsibilities that are integral to protecting public health and the environment. Through an adaptive management process, the risk management needs of those who assess and manage risk will be evaluated in an ongoing manner, and the NNI EHS research priorities will

be updated to reflect the most pressing needs. Relevance to risk management is not a separate prioritizing principle but is, rather, a foundational principle when defining EHS research needs. Some comments also called for focusing Federal investment on enabling infrastructure, including the development of tools and methods as well as basic scientific understanding to support EHS research broadly. The NEHI Working Group agrees that such infrastructure is of high value and is a worthy supplement to the value-of-information principle because it is useful to industry and academia, as well as to the Federal Government and bodies with EHS responsibilities at State and other levels of government.

An overall challenge to the appropriateness of the NNI prioritization criterion of "value-ofinformation"
indicated that a typical value-of-information methodology might not be appropriate
for the state of development of nanomaterials. It was argued that "value-of-information methodologies rely on quantifying the harms being reduced, which is not possible at this time for nanomaterial risks." The NEHI Working Group agrees with this assessment that predicting which materials might be used commercially is challenging, as is quantifying the potential harms posed by the introduction of specific materials. The Working Group also notes, however, that the valueof-
information principle was not intended to prescribe a formal methodology for inference, learning, and sequential decision-making processes, but rather is intended to convey a broad and expansive theme that is fundamental to decisions regarding use of Federal funds in general. Moreover, the principle can be adapted for early stage technology development. With close monitoring of the relevant EHS research and the commercial introduction of materials—activities that will involve ongoing communication and cooperation with industry—the NEHI Working Group believes that attempting to anticipate the commercial introduction of potentially harmful nanomaterials is a worthy goal.

Many comments also included suggestions for research and information priorities for the NNI, as opposed to prioritization principles, which was the subject of the comment solicitation. Recommendations for research priorities will be considered with recommendations received in response to the call for comments on this document. Other recommendations addressed how the research needs are framed and communicated and how the research is to be conducted and reported. All of the recommendations were evaluated and will be considered in the relevant activities of the NEHI Working Group and NNI participating agencies.

PRIORITIZATION PROCESS

The NEHI Working Group formed a task force for each of the five research categories to prioritize
the needs within that category. NEHI member agencies were invited and encouraged to participate
in all of the task forces. The prioritization process for each task force was based on the principles described above. The task forces also deliberated on further considerations for prioritization, including the availability of research tools, current barriers for each need, possible approaches to overcome such barriers, and agency-specific regulatory, research, and mission needs for EHS research.

When overlapping research needs were identified within or across research categories, they were integrated into revised statements of research needs reflecting the overlap. Other research needs that appeared in various forms in multiple categories were consolidated in the prioritization process. In particular, the cross-cutting needs to develop methods and instrumentation to quantify or characterize nanomaterials in biological and environmental media and to develop standardized sampling methods are now appropriately captured as priority needs in the Instrumentation, Metrology and Analytical Methods research category.

Twenty-five priority research needs across the five research categories have been identified and are
presented below. The needs are listed from highest to lowest priority for each category, with the exception of those presented in the category Nanomaterials and Human Health. The Nanomaterials
and Human Health task force gave equal weight to identified research needs under an overarching research priority for the category.
The sequence of research categories does not reflect prioritization among the categories, and the order of priorities for each category is not intended to imply sequential funding or to suggest a sequence for conducting research. Rather, the top priority research and information needs presented
are those identified as critical to understanding and managing potential risks of engineered

nanoscale materials that may be used in commercial or consumer products, medical treatments, environmental applications, research, or elsewhere. Detailed descriptions of each of the research categories and the research and information needs within each category are provided in the original
EHS Research Needs document.

SUMMARY OF RESEARCH PRIORITIES

Research Category: Instrumentation, Metrology, and Analytical Methods

The priority research needs for this category provide an integrated approach essential to understanding, predicting, and quantifying the chemical and physical properties and behavior of nanomaterials. The priorities under this research category underpin, and are fundamental to, all five
categories of EHS research and information needs. The priorities are:

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 as well as pore size, shape and connectivity
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

In establishing these priorities, the task force considered research and other activities on terminology, definitions, and inventories or databases of nanomaterials and their uses. The task force noted that these support the development of instrumentation and analytical methods and all aspects of the measurement process and that there is active work in these areas by Federal agencies,
international and other standard development organizations, academia, and the private sector.

Research Category: Nanomaterials and Human Health

Research on human health often involves complex, interrelated scientific concepts that are investigated most efficiently by a parallel, rather than serial, research paradigm. This parallel structure permits the investigation of single or integrated research questions and the leveraging of progress in related areas. Evaluation of the human health research needs against this paradigm and
the value-of-information principle led to identification of an overarching research priority. The task
force identified five broad research needs that are critical to addressing this overarching priority

and to establishing the fundamental principles for nanomaterial interactions with living systems.
Overarching Research Priority: Understand generalizable characteristics of nanomaterials in relation to toxicity in biological systems.
Broad Research Needs

- Develop methods to quantify and characterize exposure to nanomaterials and characterize nanomaterials in biological matrices
- Understand the absorption and transport, and degradation of nanomaterials throughout the human body
- Establish the relationship between the properties of nanomaterials and uptake and secretion 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 tissue levels, including immunological response.
- Identify or develop appropriate *in vitro* and *in vivo* assays/models to predict *in vivo* human responses to nanomaterials exposure

These broad research needs were considered equally critical to achieving the overarching goal of understanding the potential for and mechanisms of engineered nanomaterials' toxicity in humans. They are also essential for the development of predictive models of toxicity and for risk management.

Research Category: Nanomaterials and the Environment

The priority research needs for this category represent those that were presented in the *EHS Research Needs* document, with revisions to ensure complete coverage of environmental issues. The priorities are:

1. Understand the effects of engineered nanomaterials in individuals of a species and the applicability of testing schemes to measure effects
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 and degradation of nanomaterials
5. Understand the transformation of nanomaterials under different environmental conditions

The first research need comprises research necessary for determining the adverse effects in individuals of both aquatic and terrestrial species and for evaluating the applicability of testing protocols, organisms, and associated testing schemes to determine such effects. Consideration should be given to measuring toxicity, mechanisms such as metabolism, and the development of structure-activity relationships.

The second research need is to identify sources of nanomaterials and their routes to the environment, which should provide insights into which environmental receptors, such as individual species, are exposed. Work in this area also would include research to assess the extent to which nanomaterials bioaccumulate in those receptors, and it would identify relationships between environmental exposure and the absorbed doses in relevant receptors.

The third research need is to determine effects of nanomaterials beyond those in individuals of a species, including those exhibited at the population, community, and ecosystem level, such as alterations to nutrient cycling. This need also includes the study of effects of nanomaterials on other abiotic processes in the environment, such as changes to air quality or photo-oxidative or catalytic effects.

The fourth research need, to determine the factors that affect the transport and degradation of nanomaterials in the

environment, includes research to understand and predict the transport and degradation within and between all
environmental media, as well as studies to gain better understanding of the effects of nanomaterials
on the transport and partitioning of other environmental chemicals such as metals.
The fifth research need focuses on research to examine transformations of nanomaterials under different environmental conditions, for example, alterations of a material due to changes in groundwater pH or exposure to sunlight.

Research to address all five of the needs in this category should consider not only the parent nanomaterial but also the environmentally altered forms and any by-products caused by reactions, either physical or chemical, of nanomaterials with environmental chemicals or matrices.

Research Category: Health and Environmental Exposure Assessment

Research in this category is aimed at assessing exposure to, rather than hazards of, nanomaterials and the title has been revised from its original (Health and Environmental Surveillance) to better reflect the scope of research. The priority research needs for this category identify work to enable the collection of exposure information. Data collection should group individuals into exposure categories and relate groups potentially exposed to nanomaterials, including workers, patients, consumers, and neighbors of production or utilization plants. Research should consider exposure assessment studies to quantify any general population exposures to nanomaterials resulting from the use of consumer products and to identify cases of unusual injury and patterns of health outcomes suspected of being associated with exposure to nanomaterials. Information on the process, task, and location variables should be evaluated to understand how nanomaterials behave in workplace environments and what factors determine the exposures to nanomaterials in such environments. The original wording of selected priorities in this research category was changed to better reflect the goal and to broaden the scope, for example, to include environmental effects and to reflect uncertainty about potential exposure in the workplace. The priorities are:

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

Research Category: Risk Management Methods

The many research needs for this category, as identified in the *EHS Research Needs* document, were grouped by the risk management methods task force into five broad research needs, which were then prioritized. The broad research needs are listed below, ranked from highest to lowest priority. The task force recognized one of the research needs identified in the *EHS Research Needs*
document as encompassing the overarching research priority for this category.

Overarching Research Priority: Evaluate the appropriateness and effectiveness of current and emerging risk management approaches for identifying those nanomaterials with the greatest potential risks.

Broad Research Needs

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

The first broad need includes research to further understand and as needed adapt oversight approaches and methods to nanotechnology. This need also captures research to assess, develop, or
improve: physical methods of control, such as personal protective equipment; process design and engineering control systems; spill mitigation technologies; and appropriate packaging requirements.
The second broad research need regarding material life cycle includes research on methods to evaluate and, if needed, develop procedures for life cycle assessment that are suitable for engineered nanomaterials. Research in life cycle assessment would include a focus on determining
the stages in a product's life cycle that introduce the greatest potential for risk. This need also captures research and information to develop or enhance material choices so that risks may be reduced. For example, this would include research to understand and develop manufacturing approaches that minimize environmental impact through "green design" principles or to determine
if there should be any limitations or restrictions when using certain modes of transportation or waste disposal.
The third broad research need comprises research on methods to develop an improved understanding of potential impacts of nanomaterials based on their properties to facilitate risk management. For example, research to understand factors influencing flammability and reactivity will allow for an accurate hazard determination and classification and facilitate material transport and worker protection considerations.
The fourth broad research need addresses the development of nanomaterial trend information, including material flow analysis, nanomaterial use in products, and accident or incident investigations, to help focus risk management approaches with respect to reducing exposure to nanomaterials from consumer products during use, disposal, or recycling, and by way of transportation methods, spills or accidents.
The fifth broad research need includes research to develop effective methods for communicating information on hazards from and potential for exposure to nanomaterials, as well as methods for managing associated risks. This need includes research to evaluate whether current risk communication methods are adequate for known risks and for risks that can be anticipated from currently available information; research to develop effective methods to communicate risk or safety information to potentially affected populations; and research to determine how best to communicate hazard to the emergency response community under real-world accident scenarios.

NEXT STEPS

Toward the development of an NNI EHS research strategy, the NEHI Working Group has identified research needs and priorities and is now in the process of evaluating the current NNI EHS research portfolio. After obtaining public comments on the priorities described in this document, the NEHI Working Group will perform a gap analysis to identify priority research areas
that are not being addressed by currently funded research. With this background of analysis and public input, the NEHI Working Group will develop a strategy to address EHS research priorities. This NNI EHS research strategy will report the finalized priorities, summarize current research activities, describe the unmet research needs identified by the gap analysis, and will identify opportunities for interagency collaboration. Finally, the research strategy will establish a process for periodic review of progress and for updating the research needs and priorities.
The NNI EHS research strategy also will create a science-based framework that can be used by

individual agencies as guidance for the development of their mission-related research plans. The research strategy will guide NNI participating agencies in coordinating their research plans,

developing research plans that are complementary, and supporting joint research efforts of mutual interest and benefit.

The NSET Subcommittee is pursuing a dynamic, open, and transparent process in developing an NNI EHS research strategy. This public document is one aspect of that effort. Input on this and other elements of the research strategy from all stakeholders, including citizen and industry groups,
academia, and other research entities and end-users of scientific information, such as public policymakers
and resource managers, has enhanced and will continue to enhance the impact and value of EHS research for engineered nanoscale materials.