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BEFORE
THE U.S HOUSE OF REPRESENTATIVES
COMMITTEE ON SCIENCE AND TECHNOLOGY

AT A HEARING ON

RESEARCH ON ENVIRONMENTAL AND SAFETY IMPACTS OF NANOTECHNOLOGY: CURRENT STATUS OF PLANNING AND IMPLEMENTATION UNDER THE NATIONAL NANOTECHNOLOGY INITIATIVE

31 OCTOBER 2007

Introduction[1]

Environmental Defense continues to believe that nanotechnology promises major health and environmental benefits. We also believe that implementation of a robust process to identify and address the potential risks of engineered nanomaterials is absolutely essential to ensuring that these benefits are in fact realized. A *concurrent* and balanced approach to addressing both the applications and implications of nanotechnology is the best hope for achieving the responsible introduction of this remarkable set of new technologies.

There has been a relatively strong consensus among large and small industry, academic researchers, think tanks and consumer and environmental NGOs that this balanced approach is needed. Unfortunately, however, the federal government is pursuing an approach under the National Nanotechnology Initiative (NNI) that is well out of balance.

To be sure, NNI and many of its member agencies are *talking and writing* a great deal about the need to address nanotechnology's risks as well as its benefits. One need only look at their websites and reports, especially those written by their scientists. But there is a continuing, and in some ways, growing disparity between NNI's words and actions.

Over the past two years, scientists at several NNI agencies and at NNI itself have published documents elegantly describing how little we know about nanomaterials' potential hazards and exposures and how much work will be needed both to address these gaps and to adequately assess risks.[2] These documents also repeatedly draw needed attention to three critical facts:

1) Because nanomaterials have different properties than their conventional counterparts, existing information on substances' conventional forms is of limited use in elucidating the behavior and biological activity of their nano forms.

2) Methods for testing nanomaterials or for measuring their presence in environmental media or in organisms have largely yet to be developed.

3) Current approaches to predicting the hazard, exposure potential or fate of chemicals cannot be applied to nanomaterials, because they do not account for the physical as well as chemical properties that determine the latter's behavior and biological activity.

These critical gaps severely hamper our ability to apply the usual risk assessment and risk management procedures.

For example, the Nanotechnology Task Force of the U.S. Food and Drug Administration (FDA) recently released a succinct summary of the state of the science of nanomaterials falling under its jurisdiction. Reversing its earlier position that suggested nanomaterials are really nothing new, FDA now acknowledges the inability to effectively predict nanomaterials' behavior and the need for direct testing:

> "[A]t this scale, properties of a material relevant to the safety and (as applicable) effectiveness of FDA-regulated products might change repeatedly as size enters into or varies within the nanoscale range. … Biological interactions influenced by the particular chemistry and physical configuration of the nanoscale material might also occur in ways that are unpredictable without specific test data for the material." [3]

Likewise, the thorough *Nanotechnology White Paper* published by the U.S. Environmental Protection Agency (EPA) notes the following:

> "The diversity and complexity of nanomaterials makes chemical identification and characterization not only more important but also more difficult. A broader spectrum of properties will be needed to sufficiently characterize a given nanomaterial for the purposes of evaluating hazard and assessing risk. … The limited studies conducted to date indicate that the toxicological assessment of specific intentionally produced nanomaterials will be difficult to extrapolate from existing databases. The toxic effects of nanoscale materials have not been fully characterized, but it is generally believed that nanoparticles can have toxicological properties that differ from their bulk material. … The sheer variety of nanomaterials and nanoproducts adds to the difficulty of developing research needs. Each stage in their lifecycle, from extraction to manufacturing to use and then to ultimate disposal, will present separate research challenges. Nanomaterials also present a particular research challenge over their macro forms in that we have a very limited understanding of nanoparticles' physicochemical properties." [4]

These reports also attach a considerable degree of urgency to the need to address these large and complex questions. FDA notes that "the science and applications are developing at a very rapid pace," while EPA highlights "the rapid development of nanotechnology and the increasing production of nanomaterials and nanoproducts," noting that hundreds of nanoproducts are already on the market and that "nanomaterials are already being used or tested in a wide range of products such as sunscreens, composites, medical and electronic devices, and chemical catalysts." [5]

Recognition of both the complexity of the task at hand and the urgency to get moving are widely shared beyond government. For over two years now, a coalition comprised of large and small companies, other industry groups and NGOs has publicly called for much greater attention to be paid to risk research, noting in particular the disparity between federal spending on applications versus implications research:

> "While industry, academic, and government scientists continue to vigorously explore nanotechnology's potential *applications* in a wide variety of fields, such as groundwater cleanup and cancer therapy, research on nanotechnology's potential health and environmental *implications* has failed to keep up. Federal research is essential to providing the underlying methods and tools critical to developing a fundamental understanding of the risk potential of nanomaterials and nanotechnologies – methods and tools that all producers and users can then use to fulfill their appropriate responsibility to identify potential risks of their own materials and applications." [6]

This same coalition has also called for development of a federal risk research roadmap and strategy.[7]

Unfortunately, the words in the FDA and EPA reports I referenced earlier have not translated into meaningful and sufficient actions by the federal government, even though they have been bolstered by the remarkable and unusual consensus among key stakeholders just noted. Too little is being spent on risk research, too little is known about what current funds are being spent on, and the pace at which the federal government is moving to produce a coherent risk research strategy borders on glacial. Let me address each of these concerns in more detail.

What is being spent

NNI's 2007 budget is estimated at $1.35 billion and its 2008 budget request is $1.45 billion. NNI reports that the fraction of those totals to be spent on environmental, health and safety (EHS) research and development (R&D) are 3.5% for 2007 and 4.1% for 2008[8] – a trend line that has remained nearly flat for the last several years in percentage terms and is only a modest increase in absolute dollars. In contrast, Environmental Defense has called for much more – at least 10% – of the federal nanotechnology R&D budget to be specifically directed, for the foreseeable future, to targeted EHS research (exclusive of applications research that may tangentially shed light on implications questions).[9] For more than two years, many others have joined us in making this call. In June 2005, the CEO of DuPont and the President of Environmental Defense coauthored an opinion editorial in the Wall Street Journal calling for an increase in such funding to at least 10% of the federal nanotechnology R&D budget.[10] Indeed, the coalition of industry and NGOs to which I just referred has also pressed Congress for a significant increase in federal appropriations. Yet NNI has never publicly called for or indicated its support for such an increase.

How current funds are being spent

NNI's budget numbers for EHS research must be considered suspect, unfortunately. There is currently no way to know what research NNI is counting when it provides its totals, because NNI has not made public any listing of the projects it includes. In addition, NNI has itself noted that it has trouble drawing the line between direct EHS implications research and applications research that it maintains is "relevant" to understanding implications. Last year, the Project on Emerging Nanotechnologies (PEN) at the Woodrow Wilson International Center for Scholars used NNI's 2005 budget numbers and its inventory of ongoing federal risk research to try to answer these questions. Of the roughly $40 million NNI said it was spending on "relevant" EHS research that year, PEN could identify as "highly relevant" only $11 million of research and about $30 million as "generally relevant." [11] While PEN's analysis has not been updated, the lack of transparency on the part of NNI as to what projects it counts in tabulating EHS spending creates unnecessary confusion and uncertainty over how much is actually being spent and on what.

To date, the only detail provided by NNI as to how this money is being spent is a breakdown by agency or department. From this breakdown, we know that the National Science Foundation (NSF), which funds basic research but has no public or occupational health or environmental mission, continues to receive the lion's share (>50%) of federal risk research dollars. While there is certainly a role for basic research, environmental or public health research should be conducted primarily by, and ideally directed and overseen by, federal agencies that have such missions, such as EPA, the National Institute for Environmental Health Sciences (NIEHS), or the National Institute for Occupational Safety and Health (NIOSH).

In addition, the great majority of federal risk research dollars is being spent on extramural research, through grants to academic and other institutions. Both extramural and intramural research have important roles to play, but to date too few funds have been devoted to building

the needed intramural research capacity. Federal funding for both intramural and extramural research can and should reflect research priorities by more tightly focusing calls for proposals on key environmental and health research objectives. Increased funding for intramural research at federal agencies and laboratories is needed to conduct more applied research and to address specific priorities that are less likely to be efficiently addressed by academic or institutional research.

Although such federal research institutions may not have the capacity now to fully absorb the resources needed for intramural research, immediate priority should be placed on building that capacity as rapidly as possible. This capacity-building and research agenda should be viewed as an investment that will facilitate the responsible development of emerging nanotechnologies.

Need for a comprehensive federal risk research strategy – and the means to implement it

While NNI has been promising to deliver a risk research strategy that is coordinated across its agencies for well over a year, such a strategy has yet to materialize. Its issuance was just delayed again and is now projected for release in January 2008.

Based on the process NNI has laid out for developing such a strategy, it still has a considerable way to go:

- Step 1 – Identify EHS research needs and priorities. This step took the form of a report issued in September 2006, which was subjected to public comment.[12] Environmental Defense's comments on this document are attached to this testimony.
- Step 2 – Further prioritize research needs. This step came in a report issued in mid-August of this year, nearly a year after the first one, and was again subjected to public comment.[13] The 8-page second report was essentially a boiled-down version of the first, 60-page report.

Four more steps remain to be completed, according to NNI:

- Step 3: Evaluate in greater detail the current NNI EHS research portfolio.
- Step 4: Perform a "gap analysis" of the NNI EHS research compared to prioritized needs.
- Step 5: Coordinate and facilitate among the NNI agencies' research programs to address priorities.
- Step 6: Establish a process for periodic review of progress and for updating the research needs and priorities.

It is not clear whether each of these steps is to be taken on sequentially, with a corresponding pause for public comment. In any event, as a journalist for the New York Times recently put it: "No one can accuse them of acting rashly." [14]

Key impediments to progress

Unfortunately, in Environmental Defense's view, NNI has core structural impediments that prevent it from acting expeditiously to identify and address potential risks and from adopting a more balanced overall approach. The problems are two-fold. First, NNI lacks any overarching budgetary and oversight authority to shape and direct the research activities undertaken by its

member agencies and departments. The part of NNI that is mounting current efforts in this area is the Nanoscale Science, Engineering and Technology Subcommittee (NSET), which serves primarily in a facilitation and coordination role and simply has not been given the necessary authority to devise and implement a coherent, cross-agency risk research strategy. Additional authority to oversee and direct federal risk-related research is essential to ensure two things: a) that the right questions are asked and answered, and b) that identified risks are comprehensively assessed and do not fall through the cracks between statutes, departments and agencies.

Second, we have become convinced that a conflict of interest has arisen from the decision to house within NNI the dual functions of both seeking to develop and promote nanotechnology and its applications, while at the same time aggressively pursuing the actions needed to identify and mitigate any potential risks that arise from such applications. That conflict of interest is both slowing and compromising efforts by NNI and its member agencies and departments to effectively address nanotechnology's *implications*. The conflict manifests itself in the continuing budget disparity I have already discussed. It is also apparent in NNI's evident inability or unwillingness to clearly identify research activities devoted specifically to EHS concerns and sufficiently distinguish them from applications research that may incidentally yield data relevant to understanding implications. And it may help explain what's taking so long.

The conflict also appears to be manifesting itself at the individual agency level. Some NNI agencies, including FDA and EPA, are themselves charged with both promoting and regulating nanotechnology applications, sometimes even within the same office. In addition, all agency proposals pertaining to addressing nanotechnology's potential risks must now be vetted through a White House nanotechnology policy group. These factors may be responsible in part for the growing disconnect between, on the one hand, the recognition by agencies of the magnitude of and urgent need to address the risk question, and on the other hand, the tepid response of those same agencies in terms of actions to be taken.

For example, the FDA Nanotechnology Task Force's recommendations are vague and lack critical details on actions needed to close identified research and regulatory gaps. While there is a call for the agency to promote and participate in research, there is no mention of the level of resources needed, the timeframe within which this is – or needs – to be accomplished, or even an indication that there is any urgency to advance the collection of data. While the recommendations call on the agency to issue various forms of guidance for manufacturers to use on a voluntary basis, they propose that the evaluation of products continue on a case-by-case basis, which is essentially the status quo. There is no description of how the agency will or should address two key points: a) the greater uncertainties it has identified that are posed by using nanomaterials in products for which the agency has pre-market authority, or b) the considerable gaps in information for classes of products, such as cosmetics, for which the agency has no pre-market authority.

Similarly, we can look at how EPA has responded to growing public concern over the lack of nanotechnology oversight and its own scientists' identification of the enormous data gaps that must be filled if risks are to be effectively identified and addressed. EPA has taken two recent steps. First, it issued a policy decision that considers the nano forms of existing chemicals to be no different than their bulk counterparts, and by so doing effectively eliminates the only opportunity EPA has to review or require testing of such nanomaterials prior to their

manufacture and use.[15] Second, it issued a "concept paper" that proposes an open-ended, voluntary program to encourage companies to submit any information they already happen to possess. EPA proposes what its own advisory committee proposed nearly two years ago – except it has removed the strict deadlines for the voluntary program and the simultaneous development of mandatory reporting rules as a regulatory backstop, which the committee had included.[16]

Recommendations: Can the NNI approach be made to work?

If NNI is to effectively address the potential risks of nanotechnology, two changes are essential.

First, a new entity needs to be created, or an existing entity elevated, and given responsibility, ample authority and resources to do the following:

- Ensure the development of an overall federal research strategy to identify, assess and address the potential risks of nanomaterials.
- Shape and direct the overall federal risk research agenda across agencies to ensure all critical needs are being addressed.
- Ensure that individual agencies have sufficient dedicated staff and resources to conduct or commission the needed research in their areas, and sufficient authority to identify, assess and address potential risks.

This entity, whether independent or housed in an existing agency, should have a core public health and/or environmental mission. Congress should also request that the National Academies' Board on Environmental Studies and Toxicology (BEST) take a lead role in developing the needed strategy, and in overseeing its implementation over a number of years. BEST has successfully played an analogous role in the formulation and execution of the U.S. Environmental Protection Agency's research strategy for assessing the risks of airborne particulate matter.[17]

The second essential step is to establish a firewall between the parts of the federal government whose mission is to help develop and advance nanotechnology, and those parts charged with ensuring a thorough and objective examination of its potential risks and taking the steps needed to mitigate those risks. Ensuring that both goals receive equal consideration would require, at a minimum, that the responsibility to address the two distinct goals be assigned to different offices and senior staff members, who are given parallel and comparable degrees of authority, and who report directly to the highest levels within their individual agencies and within NNI. We believe that a clear division of labor and interests is critical if public confidence in the ability of the federal government to facilitate the responsible development of nanotechnology is to be restored.

In sum, the activities within NNI devoted to identifying and mitigating the potential risks of nanotechnology need to be both substantially elevated in importance and clearly separated from those dedicated to promoting its development and application.

Thank you for the opportunity to present our views today. Environmental Defense stands ready to assist the Committee as it considers what changes are needed in legislation to be developed to reauthorize NNI.

[1] A biography of Dr. Denison is attached.

[2] For example, see: U.S. Food and Drug Administration, *Nanotechnology: A Report of the U.S. Food and Drug Administration Nanotechnology Task Force*, July 25, 2007, at www.fda.gov/nanotechnology/taskforce/report2007.pdf ; and U.S. Environmental Protection Agency, *Nanotechnology White Paper*, February 2007, at www.epa.gov/osa/nanotech.htm; National Institute for Occupational Safety and Health, *Strategic Plan for NIOSH Nanotechnology Research: Filling the Knowledge Gaps*, at www.cdc.gov/niosh/topics/nanotech/strat_planINTRO.html; and National Nanotechnology Initiative, *Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials*, September 2006, at www.nano.gov/NNI_EHS_research_needs.pdf.

[3] FDA, *op. cit.*, pp. ii, 11.

[4] EPA, *op. cit.*, pp. 31, 70, 77.

[5] FDA, *op. cit.*, p. 8; EPA, *op. cit.*, pp. 4, 13, 21.

[6] Letter signed by 14 companies and organizations sent to Chairs and Ranking Members of the House and Senate Appropriations Committees, dated June 7, 2006, at www.environmentaldefense.org/documents/5067_nano-appropsLetter.pdf. Emphasis in original.

[7] Letter signed by 19 companies and organizations sent to Chairs and Ranking Members of the House and Senate Appropriations Committees, dated February 22, 2007, at www.environmentaldefense.org/documents/6015_Approps_2007NASLetter.pdf.

[8] *The National Nanotechnology Initiative: Research and Development Leading to a Revolution in Technology and Industry, Supplement to the President's FY 2008 Budget*, Tables 2 (p. 7) and 6 (p. 11), at www.nano.gov/NNI_08Budget.pdf.

[9] Denison R.A. "A proposal to increase federal funding of nanotechnology risk research to at least $100 million annually." Environmental Defense, Submitted to the National Academy of Sciences' Committee to Review the National Nanotechnology Initiative (April 2005), at www.environmentaldefense.org/article.cfm?ContentID=5131.

[10] See Fred Krupp and Chad Holliday, "Let's Get Nanotech Right," *Wall Street Journal*, June 14, 2005, p. B2, at www.environmentaldefense.org/documents/5177_OpEd_WSJ050614.pdf. That same month, the American Chemistry Council's Panel on Nanotechnology and Environmental Defense issued a Joint Statement of Principles stating: "A significant increase in government investment in research on the health and environmental implications of nanotechnology is essential." At www.environmentaldefense.org/documents/4857_ACC-ED_nanotech.pdf. And in a 2005 report on nanotechnology, Innovest, a leading investment research and advisory firm, said: "We strongly support calls by others in the investment community for increased government funding of toxicology research. The NNI's lack of priority for this issue represents a missed opportunity to minimize uncertainty." See Innovest (2005). *Nanotechnology: Non-traditional Methods for Valuation of Nanotechnology Producers*. New York, NY. Page 56. At www.innovestgroup.com/images/pdf/final%20nano%2010-30-06.pdf.

[11] Maynard, A.D. (2006) *Nanotechnology: A Research Strategy for Addressing Risk*, pp. 3, 20, at www.nanotechproject.org/file_download/77.

[12] NNI, 2006, *op. cit.*

[13] National Nanotechnology Initiative, *Prioritization of Environmental, Health and Safety Research Needs for Engineered Nanoscale Materials — An Interim Document for Public Comment*, at www.nano.gov/Prioritization_EHS_Research_Needs_Engineered_Nanoscale_Materials.pdf.

[14] Barnaby J. Feder, "No one can accuse them of acting rashly," August 17, 2007, at bits.blogs.nytimes.com/2007/08/17/no-one-can-accuse-them-of-acting-rashly/.

[15] US Environmental Protection Agency, "TSCA Inventory Status of Nanoscale Substances – General Approach," released for public comment on July 11, 2007, at www.regulations.gov/fdmspublic/component/main?main=DocumentDetail&d=EPA-HQ-OPPT-2004-0122-0057.

[16] US Environmental Protection Agency, "Concept Paper for the Nanoscale Materials Stewardship Program under TSCA," released for public comment on July 11, 2007, at www.regulations.gov/fdmspublic/component/main?main=DocumentDetail&d=EPA-HQ-OPPT-2004-0122-0058. The 2005 proposal made by EPA's National Pollution Prevention & Toxics Advisory Committee (NPPTAC) is at www.epa.gov/oppt/npptac/pubs/nanowgoverviewdocument20051125.pdf. Environmental Defense's comments on both of EPA's recent proposals are at www.environmentaldefense.org/documents/7010_ED_WrittenCommentsonEPANanoDocs09072007.pdf.

[17] Board on Environmental Studies and Toxicology, *Research Priorities for Airborne Particulate Matter: I. Immediate Priorities and a Long-Range Research Portfolio*, Committee on Research Priorities for Airborne Particulate Matter, National Research Council, 1998; and *Research Priorities for Airborne Particulate Matter: IV. Continuing Research Progress*, 2004, both at: books.nap.edu/catalog/6131.html, and books.nap.edu/catalog/10957.html.

Attachment 1

Biography of Richard A. Denison, Ph.D.

Dr. Denison is a Senior Scientist in Environmental Defense's Washington, DC office. With more than 20 years of experience in the environmental arena, he specializes in chemicals policy, hazard and risk assessment and management for industrial chemicals, and responsible development of nanotechnology.

Dr. Denison has managed Environmental Defense's participation in and oversight of the U.S. High Production Volume (HPV) Chemical Challenge Program, initiated by Environmental Defense, the U.S. Environmental Protection Agency and the American Chemistry Council to provide basic hazard data on the 2,200 chemicals produced in the U.S. in the largest quantities. He also represents Environmental Defense on the Chemicals Committee and on the Working Party on Manufactured Nanomaterials of the Organization for Economic Cooperation and Development (OECD). Dr. Denison was recently appointed to the Science Advisory Panel for California's Green Chemistry Initiative. Until recently, he was a member of the National Pollution Prevention and Toxics Advisory Committee (NPPTAC), which advises EPA's toxics office. Dr. Denison is part of Environmental Defense's team that worked jointly with the DuPont Corporation to develop a framework governing responsible development, production, use and disposal of nano-scale materials.

Dr. Denison has authored numerous papers and reports, and he is active in a variety of activities and forums, pertaining to chemicals and nanomaterial regulation and policy at the federal and state levels and internationally. Dr. Denison is the author of a major report, titled ***Not That Innocent***, that provides a comparative assessment of existing and emerging industrial chemicals policies in the U.S., Canada and Europe.

Dr. Denison earned a Ph.D. in Molecular Biophysics and Biochemistry from Yale University in 1982. He joined Environmental Defense in 1987, after several years as an analyst and assistant project director at the Office of Technology Assessment, United States Congress.

Attachment 2

ENVIRONMENTAL DEFENSE COMMENTS[1] ON:

Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials, released September 15, 2006

January 31, 2007

Federal Register: December 8, 2006 (Volume 71, Number 236)
DOC ID:FR08DE06-135

Introductory Statement

Environmental Defense appreciates this opportunity to submit comments on the National Nanotechnology Initiative's document Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials, which was released on September 15, 2006.

Environmental Defense is a leading national environmental nonprofit organization representing more than 400,000 members. Since 1967, we have linked science, economics, law, and innovative private-sector partnerships to create pragmatic solutions to the most serious environmental problems. Among our other activities related to nanotechnology, we are currently working with DuPont to develop a comprehensive, practical and transparent approach to proactively evaluate and address the risks of nanomaterials across their lifecycle.

The National Nanotechnology Initiative's Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the Committee on Technology, National Science and Technology Council (NSTC) has requested comment on the research needs and prioritization criteria that were identified in the NSET Subcommittee document *Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials*.

We commend the NSET subcommittee on the preparation of this report, which identifies critical research and information needs for nanoscale materials. The subcommittee emphasizes that these research needs were not presented in any priority research order, and requests feedback on the development of criteria for establishing priority research.

Almost every research need identified in this report addresses a critical data gap. To this end we urge the US government to provide the necessary funds to implement an aggressive and broad research strategy. However, we recognize that available funds are limited and it is necessary to prioritize research needs.

[1] These comments are available online at www.nano.gov/html/meetings/ehs/uploads/20070131_0752_ED_comments_on_NNI_EHS_Research_Needs_FINAL.doc

The NNI proposes using a "value of information strategy" to prioritize research needs. This approach is predicated on how to assign value to different kinds of information. The NNI document identifies the following factors as indicators of research value:

- The extent to which the information will reduce uncertainty about benefits or risks.
- The extent to which information can be expected to lead to broad knowledge about the property and behavior of nanomaterials.
- The extent of expected use of the nanomaterial.
- The exposure potential for workers, consumers, or the environment.
- The potential to leverage relevant existing data.

While we agree that these are useful criteria for evaluating research priorities, we are concerned about applying some type of formal "value of information" methodology to the prioritization of nanoscale material toxicity research. At this stage, it is not possible to apply a typical "value of information" methodology to predict what type of research will optimally reduce uncertainty about risks or lead to broader knowledge and understanding of nanomaterial behavior without broadly speculating on potential risks and the types of information needed to reduce them. Value of information methodologies rely on quantifying the harms being reduced, which is not possible at this time for nanomaterial risks. Moreover, in the setting of an emerging technology such as nanotechnology, the economic consequences of obtaining or failing to obtain critical information on toxicity are in reality so unpredictable that formalizing the costs and benefits through a value of information analysis is artificial and potentially misleading. While some of the principles of a value of information approach are valid for prioritizing nanomaterials risks, we recommend that reference to this formal methodology be removed. In our comments below, we provide additional recommendations on how to proceed with prioritization in the face of multiple major knowledge gaps, and on the relative roles for industry and government research programs.

Based on our assessment of the report Environmental Defense would like to provide support for the EHS research portfolio, and present specific comments and recommendations pertaining to the need to prioritize the EHS research. The summary outline of EHS research needs is reproduced here, with numbering and lettering added to facilitate direct references in the text below to the research needs identified in the NNI document.

1. Instrumentation, Metrology, and Analytical Methods
    a) Methods for detection nanomaterials in biological matrices, the environment, and the workplace
    b) Methods for standardizing particle size and size distribution assessment
    c) Methods and standardized tools for assessing shape, structure, and surface area
    d) An inventory of engineered nanomaterials and their uses

2. Nanomaterials and Human Health
    a) Understanding the absorption and transport of nanomaterials throughout the body from different exposure routes - methods development
    b) Understanding the properties of nanomaterials that elicit a biological response
    c) Identification and development of appropriate in vitro and in vivo bioassays
    d) Methods to quantify and characterize exposure to nanomaterials in biological matrices

3. Nanomaterials and the Environment
   a) Evaluation of testing schemes for ecological effects
   b) Evaluation of factors affecting fate and transport
   c) Understanding the transformation of nanomaterials under different conditions

4. Health and Environmental Surveillance
   a) Understanding exposures in the workplace and factors that affect them
   b) Quantification of exposure from industrial, consumer, and other sources
   c) Establishment of environmental monitoring protocols

5. Risk Management
   a) Improve understanding of process design and engineering controls
   b) Develop "green design" techniques
   c) Determine product life cycles and potential impact on EHS
   d) Evaluate current risk communication strategies for known and anticipated risks

Below we present four overarching criteria that we believe should be used to prioritize the many research needs identified by NNI. These criteria are:

- Research that will develop the "enabling infrastructure".
- Information that will facilitate "look back" studies.
- Selection of materials should focus on key concerns related to toxicity and biological response.
- Selection of relevant materials and methods.

Criterion 1: Research that will develop the "enabling infrastructure".

We strongly recommend that federal funds be used first and foremost to **acquire fundamental knowledge that is needed to develop the "enabling infrastructure" for nanomaterial EHS, which is best addressed by the federal government.** This "enabling infrastructure" includes developing and standardizing, for routine application, the methods, tools (e.g., instrumentation) and basic scientific understanding needed to measure and assess:

- Physical-chemical characterization of nanomaterials;
- Sampling and analysis;
- Detection and monitoring: in workplaces, air/waterborne releases, humans and other organisms, environmental media;
- Biological and environmental fate and behavior;
- Acute and chronic toxicity; and
- Hazard, exposure and risk.

Development of the enabling infrastructure will advance industry research in risk assessment and materials design and testing of specific materials and products, and will facilitate independent researchers in pursuit of general and applied nanoscale research.

There are several lines of research discussed in the NNI document that can be included in this category. For example, we agree there is a critical need for the development of **methods to detect, quantify and characterize nanomaterials in biological matrices, the environment, and the**

workplace (1a, 2d)[2]. The development of these methods will facilitate a cascade of additional research pertaining to fate and transport in humans and non-human organisms from different exposure routes, and fate, transport, and transformation in the environment, which are also of high priority, and addressed in more detail below.

Another critical data need identified by the NNI is the development of **methods for the standardized characterization of nanomaterials: particle size, size distribution, shape, structure, and surface area** (1b, 1c). This will, in turn, advance government research on risk assessment, development of quantitative structure-activity relationships, and ultimately identification of the key properties of nanomaterials that elicit biological responses.

The federal government also needs to plays an important role in the **identification and development of key *in vitro* and *in vivo* bioassays** (2c) for acute and chronic toxicity testing, and **testing schemes for ecological effects** (3a).

A high priority should be placed on **developing methods to identify nanomaterials that exhibit environmental persistence and/or bioaccumulation potential**. These characteristics are critical indicators of concern for both environmental and human health, and nanomaterials exhibiting these properties require additional scrutiny. With such methods, research agencies could assess a broad array of materials and subsequently focus other lines of research on those materials presenting greater potential risk on the basis of their persistence and accumulation potential.

Testing protocols developed by the government can then be used by industry to demonstrate the safety of their product or to identify risks requiring mitigation. They are also the key step required for the development of robust and health protective risk assessment and risk management protocols.

The status of available assays for nanomaterials was recently reviewed in a workshop sponsored by Environmental Defense, the Center for Biological and Environmental Nanotechnology at Rice University, and the Woodrow Wilson Center, and attended by scientists from government, academia, industry, and non-profit organizations. The consensus of the attendees was the highest priority methods development needs include physical chemical characterization (structure, concentration, and surface properties, addressed above), and ADME/Translocation methods, which is equivalent to **understanding the absorption and transport of nanomaterials throughout the body from different exposure routes** (2a), particularly for *in vivo* bioassays (e.g., nanoparticles tracking, aggregation, transformation, solubility and stability, transmembrane movement, and bioaccumulation/bio persistence). The workshop proceedings are in preparation, and will be provided to the NNI upon acceptance for publication.

Although we can and should expect industry to address product-related research needs, the research listed above will be critical in generating the means by which industry can most effectively evaluate its own products. This is *not* to say that there is no role for industry prior to the development of the enabling infrastructure, as most standard apical bioassays will allow for the evaluation of potential toxicity, even in the absence of tissue quantification methods. For

[2] Numbers/letters in parentheses here and in the remainder of the text refer to items in the research outline provided above, to indicate the category and subcategory from the NNI document to which they refer.

instance, both inhalation and instillation rodent bioassays have been very useful for elucidating toxicity for inhaled nanomaterials. Advancing research methods will require an iterative approach, measuring the outcome of new bioassays against standard apical bioassays. There is certainly the potential for government-industry and other stakeholder involvement in government-led initiatives in partnerships for methods development, and industry co-funding of such research should be pursued, as long as the government retains the ability to manage and direct it.

Other considerations: Primary environmental or public health research, whether conducted intramurally or extramurally, should be directed and overseen by federal agencies that have an environmental or public health mission, such as the Environmental Protection Agency (EPA), the National Institute for Environmental Health Sciences (NIEHS), or the National Institute for Occupational Safety and Health (NIOSH). Currently, the National Science Foundation (NSF) funds and oversees more than 50% of the nanomaterials environmental health and safety research. NSF, which lacks any public health or environmental mission, may not be in the best position to identify and oversee such research.

Both extramural and intramural research have important roles to play, but to date too few funds have been devoted to building the needed intramural research capacity. Federal funding for both intramural and extramural research can and should reflect research priorities by more tightly focusing calls for proposals on key environmental and health research objectives. Increased funding for intramural research at federal agencies and laboratories is needed to conduct more applied research and to address specific priorities that are less likely to be efficiently addressed by academic or institutional research.

Although such federal research institutions may not now have the capacity to immediately fully absorb the resources needed for intramural research, immediate priority should be placed on building that capacity as rapidly as possible. This capacity-building and research agenda should be viewed as investment that will facilitate the responsible development of emerging nanotechnologies.

Criterion 2: Information that will facilitate "look back" studies.

The prioritization of federal research should be undertaken with the understanding that we have **critical knowledge gaps in the face of ongoing and growing exposures**. In order to lay a foundation for understanding potential risks that may only manifest themselves well after exposures start, we need to know what types of nanomaterials are present in products, who is and has been employed in production, and who may be coming into contact with nanomaterials now. As we move forward in research to fill the knowledge gaps in the laboratory, the federal government should also address current and emerging exposures in the workplace by **developing a registry of workers who have worked with or used nanomaterials for at least 4 weeks.** This will not only aid in helping to understand "**exposures in the workplace and the factors that affect them**" (4a), but will also facilitate future epidemiologic studies of workers, a critical research need that is not sufficiently emphasized in the report. In addition, **EPA, FDA and CPSC should collaborate in developing nanomaterial and nanomaterial-containing product registries and inventories, which will also facilitate additional "look back" research to the extent it is needed in the future**. This will help to meet the following research needs identified in the NNI report: **an**

inventory of engineered nanomaterials and their uses (1d), and the identification and **quantification of exposure from industrial, consumer, and other sources** (4b).

Criterion 3: Selection of materials should focus on key concerns related to toxicity and biological response.

Companies can and should be expected to concentrate their environmental health and safety research and testing programs on nanomaterials used in commercial applications, where they should employ lifecycle approaches to identify all known and reasonably anticipated exposure scenarios. In contrast, government sponsored research should focus more on nanomaterials that will best **elucidate general principles of toxicity and biological response** (similar to 2b), for example, seeking to understand mechanisms whereby nanomaterials may readily translocate across biological interfaces, bioaccumulate, interact with cells or specific macromolecules (e.g., the stimulation of collagen formation in fibroblasts noted with carbon nanotubes), or generate reactive oxygen species. By focusing research on those nanomaterials that exhibit these and related characteristics of biological relevance and concern, federal research will advance knowledge of the features and characteristics most associated with biological responses, and also may facilitate the development of structure-activity relationships. Acquisition of these data not only can contribute to the construction of general principles regarding nanomaterials toxicity, but will also provide nanomaterial developers with important information that can be used to design "green" nanomaterials that do not exhibit these properties.

While the costs and characteristics of some nanomaterials make the conduct of chronic bioassays or multigenerational testing challenging, in general there is likely much greater potential for nanomaterials to cause more subtle, chronic effects rather than acute toxicity – effects that may well be missed by only conducting acute testing. We therefore recommend that a number of nanomaterials with high potential for chronic exposure be tested for chronic toxicity to begin to gain understanding of potential long-term effects.

The government should also pursue and fund research in a manner that provides not only an in-depth characterization of specific categories of nanomaterial, but also fully elucidates the effects of variations (in manufacturing processes, surface modifications, etc.) among materials within those categories on key biological properties. The NIEHS has begun this process by testing at least two variations of each category of nanomaterials it is studying. Only by expanding this approach will we begin to develop the much needed *predictive capability* to interpolate or extrapolate among structurally related materials.

The NNI report indicates that government research efforts at the National Cancer Institute, National Institute for Environmental Health Sciences, National Institute for Occupational Safety and Health, the Food and Drug Administration, and the National Toxicology Program are focused on metal oxides (particularly TiO2 and ZnO), quantum dots, fullerenes, and carbon nanotubes. While it can be useful for discussion purposes to group nanomaterials into broad categories such as metal oxides, carbon-based materials, etc., the assumption that the members of such categories possess the same or similar biological properties is at this stage a hypothesis. For example production by different processes or surface modifications of the same basic material can dramatically alter the characteristics and behavior of a nanomaterial. Considerable empirical test data will be needed to test any "category hypotheses," i.e., to determine the actual extent of

similarity, or the regularity and predictability of trends, among category members, with respect to both hazard and exposure characteristics.

Criterion 4: Selection of relevant materials and methods.

Research should also consider the need to test materials and applications that are now or are projected to be the **most relevant, based on likelihood of release and exposure – *examined on a lifecycle basis*.** As noted in the report, "…the exposure potential for some nanomaterials will be limited to nonexistent whereas exposure potential for other materials will exist at one or more stages of their product life cycle." Selection of the most relevant materials should be based on a systematic assessment of nanomaterials with known or reasonably anticipated human and environmental exposure potential over the lifecycle of a broad array of materials.

Additional Comments: Need for public database for nanomaterial EHS data.
The development of a publicly available database containing the results of environmental health and safety testing data is an urgent need that can be readily addressed through government funding. There is precedent to make this information available. One recent example of such a database is the EPA's High Production Volume Information System (HPVIS), which is providing access to hazard data on hundreds of chemicals. Directly relevant to nanoparticles are: 1) the NIOSH Nanoparticle Information Library (http://www2a.cdc.gov/niosh-nil/index.asp), which includes physical chemical and toxicological data on a select number of nanomaterials, and 2) the National Cancer Institute's Nanotechnology Characterization Laboratory's publication of the results of the testing of nanomaterials, performed at the request of private companies (http://ncl.cancer.gov/index.asp). The reports are issued following a 90-day lag to allow for the management of confidential business information. These efforts should be consolidated and expanded to include the results of testing performed by industry laboratories to facilitate the dissemination of EHS data.