January 5, 2009

NNI Response to the National Research Council Review of the "National Nanotechnology Initiative Strategy for Nanotechnology-Related Environmental, Health and Safety Research."

In coordination with the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the National Science and Technology Council, the National Nanotechnology Coordination Office offers the following comments on, and requests the factual corrections to, the National Research Council (NRC) review of the National Nanotechnology Initiative's (NNI) *Strategy for Nanotechnology-Related Environmental, Health, and Safety (EHS) Research.*

We would like to thank the National Research Council for its report. We're pleased that the NRC acknowledges and recommends continuation of "the successful interagency coordination effort" that led to the *Strategy for Nanotechnology-Related Environmental, Health and Safety Research*. NNI member agencies acknowledge the report's substantial and important recommendations for further progress on EHS research and will give them the careful and thorough analysis they deserve. Where provided, the constructive comments on the scientific and technological content of the NNI EHS Strategy document are particularly appreciated.

The NSET Subcommittee will carefully review the report, and as work continues on the NNI's coordinated interagency EHS research efforts, incorporate appropriate conclusions and recommendations from this NRC study. However, it is important to note several areas of significant concern and a number of factual errors that materially affect the recommendations and thus require correction.

Clarification of the Scope of the NRC Review

Strategy or Strategic Plan? The 2008 NNI EHS strategy document is not, and was never intended to be, a "strategic plan" or an implementation plan, but a higher-level description of the interagency approach to nanotechnology-related EHS research. The document is the result of two years of interagency review and analysis of current research, research needs, and gaps requiring attention. It was written as a strategy document for Federal agencies in order to coordinate, encourage cooperation, and where possible to implement collaborative research activities. The NRC committee spends significant text confirming what the NNI has already said that the document is not. However, contrary to statements in the NRC report, the NNI strategy does indeed include clear vision and goals towards responsible nanotechnology development. The establishment of implementation plans and milestones are appropriately maintained at the agency level in a manner that is consistent with the congressional authorities and appropriations with which the federal agencies are required to comply. To be maximally useful to the NNI, the

recommendations in the NRC report should be consistent with these authorities and appropriation guidelines of the federal agencies.

Moving Towards a National Strategy. The intent and scope of a strategy and a strategic plan are different and consequently, evaluation of these two documents would be different. For the evaluation of The 2008 NNI EHS Strategy, the NNI charge to the NRC committee (see attachment) focused on five areas for evaluation: 1) whether the areas of knowledge or information for supporting risk assessment and risk management were addressed appropriately or not; 2) are the priorities for the research needs appropriate; 3) were the proposed timing and staging of research appropriate; 4) an assessment of strengths and weaknesses of the NNI strategy and similar documents published by other governments and non-government bodies (re: their selection of research needs, priorities and staging of research); and 5) are collaborations with and inputs from other governments and non-government bodies described appropriate.

The NRC report provides a substantive argument for "a robust national strategic plan." NSET Subcommittee member agencies and the NNCO will continue to work with the NAS and all stakeholders in the pursuit of a national strategy to further EHS research. Through refinement and integration of agency research strategies, the NNI is confident that many recommendations expressed in the NAS report are being, or will be, addressed. In fact, there are a number of related activities that were not directly linked to/incorporated in the NNI research strategy. For example: testing and assessment under regulatory programs; research, testing and assessment internationally (e.g., ISO, OECD); testing and research being conducted by other governments; research strategies developed by individual agencies; and testing and research conducted by academia and industry not otherwise captured by the above. The NNI strategy was assembled in the context of these other initiatives.

Lines of Accountability. Lines of accountability in the report should be consistent with congressionally-assigned authorities and appropriations. Funding allocations—as with all areas of the Federal science and technology budget—are established in consultation with the Office of Science and Technology Policy and the Office of Management and Budget. There is no question as to the lines of accountability for Federal research. The director of OSTP is ultimately responsible not just for nanotechnology-related EHS research, but *all* of nanotechnology research (not to mention the breadth of Federal R&D).

Factual Errors and Misleading Conclusions.

Based on our review of the prepublication manuscript, the factual errors and omissions noted below should be corrected in the final report. In most cases we have suggested reasonable corrections. However, it appears that a number of the report's conclusions were based on these factual errors. Therefore, it is incumbent on the NRC to analyze the correlation between the errors and the conclusions. In the cases where there is a direct relationship between obvious

errors and the report's conclusions, the committee should reconsider those conclusions and any related recommendations.

The broad factual errors in the NRC review, detailed below, relate to five claims that the NRC report makes:

1. That the 2008 NNI strategy formulation process did not include an evaluation of the state of science
2. That the NNI did not seek public input and that "in essence the strategy has been conducted in a federal vacuum" (p. 33)
3. That the research needs and priorities were determined based on existing research efforts
4. That the most recent PCAST review of the NNI did not comment on the NNI EHS research strategy
5. That the health applications studies identified in the NNI list of FY 2006 EHS projects are misapplied and are not directly related to EHS

The following text outlines the broad factual errors and suggests some remedies to correct them.

Claim 1 about the 2008 NNI strategy formulation process not including an evaluation of the state of science.

In the summary of the NRC Review document, the NRC states, "The NNI document does not provide an evaluation of the state of science in each of the five research categories;" (page 3). The NRC was asked to review three documents; each built on the other and finally leading to the FY 2008 document. The first of these three, *Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials* (identified in the NRC report as NNI 2006) provides an evaluation of the science in all five research categories. Specific examples of an evaluation of the science in "instrumentation, metrology, and analytical methods" are provided on pp. 16-17 of NNI 2006; in "nanomaterials and human health" on pp.19-20; in "nanomaterials and the environment" on pp. 29-30; in "health and environmental surveillance" on p. 40 and pp. 47-48; and in "risk management methods" on p. 44.

RESPONSE AND RECOMMENDATION: Thus it should be clear that the 2008 NNI Strategy document was founded on the 2006 NNI EHS Research Needs document, which included an evaluation of the state of science. The NRC committee could take the view that this review of the science was inadequate or not done well, but it is factually inaccurate to make a blanket statement that this was not done. The NRC committee should qualify statements concerning the NNI's efforts to evaluate the state of science in the five categories of research chosen in the 2008 NNI Strategy document.

Claim 2 that the NNI did not seek public input and that "in essence the strategy has been conducted in a federal vacuum."

One of the most glaring errors in the NRC report is the statement that the NNI strategy document had, "essentially no stakeholder input outside these federal agencies." (Page 33)

In addition, there are several other statements in the report that convey the erroneous implication that the NNI did not engage stakeholders in the process of developing the NNI Strategy document, for example:

> "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." (Page 4)

In fact, stakeholder input was received at the interagency level prior to the preparation of the 2006 document, through a series of NNI workshops, through a formal liaison with the electronics and chemical industries, which combined forces to prepare a recommended list of EHS research needs as input to the NNI process, and through a review of scientific literature and documents produced by other governments, all referenced in the 2006 document. Further stakeholder and public input was received after the release of the 2006 document, during a formal Federal Advisory Committee Act (FACA) public meeting held in January '07, and through a public docket that remained open for several months after the public meeting. Finally, the NNCO published a document in 2007 (also part of the documentation we asked the NRC committee to review) entitled *Prioritization of Environmental, Health, and Safety Research Needs For Engineered Nanoscale Materials: An Interim Document For Public Comment*. As the title makes clear, this document was intended specifically to elicit comments from the public, the scientific community, and other stakeholders, on how the NNI was proposing to approach prioritization of EHS research needs. We received many useful comments during all of these phases of public and stakeholder comment, and that input was incorporated as the NEHI Working Group prepared the research strategy document published in early 2008.

In addition to all of the coordinated NNI public and stakeholder input efforts discussed above, individual participating agencies also extensively solicited outside input on their agency-specific approaches to nanotechnology-related EHS research, which correlate directly with and extend from the overall NNI strategy. In sum, the following is a list of the NNI's extensive stakeholder engagement efforts as part of the NNI's ongoing adaptive management strategy for EHS research:

- EPA's voluntary stewardship program (several public meetings);
- NIOSH's efforts to reach out concerning safety in the workplace (several documents published as drafts for public comment including an overall nanotechnology strategic plan; formal review by NIOSH's outside advisory bodies);

- FDA's public meetings and responses to inquiries, including a draft report of the FDA Nanotechnology Task Force and a formal FACA meeting to obtain public and stakeholder input on that document;
- NIH/NIEHS meetings attended by representatives from industry, nongovernmental organizations and the federal government to develop the NanoHealth and Safety Enterprise, a public-private partnership for nanomaterials EHS research.
- Combined input from the semiconductor and chemical industries, providing a list of recommended EHS research needs;
- Numerous other interactions with industry groups including the Consultative Boards for Advancing Nanotechnology and attendance at industrial sector conferences (e.g., foods, forest products, semiconductors);
- A series of NNI technical workshops held between 2003 and 2005 seeking input from the research community and other stakeholders on the NNI research agenda, including specific workshops on societal implications of nanotechnology, nanotechnology and the environment, and nanobiotechnology (see http://www.nano.gov/html/res/pubs.html, list of workshop reports)
- The public meeting on the 2006 Research Needs document and subsequent public comment period;
- The on-line publication and open comment period on the 2007 NNI interim document on prioritization of research needs;
- Annual meetings with the NanoBusiness Alliance.

The NNI and the individual Federal agencies will continue to develop increasingly robust efforts to engage stakeholders in the process of formulating, validating, and adapting the NNI approach to nanotechnology R&D, including EHS.

RESPONSE AND RECOMMENDATION: From this list, we hope it is clear that the NSET Subcommittee did launch an aggressive public and stakeholder engagement effort and did so, not after, but during the process of formulating the strategy. The suggested remedy for this error is either to remove the statement on page 33 or reword it to state it in terms of the committee's view of the adequacy of stakeholder input and what the NSET Subcommittee should have done beyond what was done. An acknowledgement of what was done by the NSET Subcommittee to obtain stakeholder input along the lines described should be a part of this text.

Claim 3 that the research needs and priorities were determined based on existing research efforts.

The report repeatedly claims that the 2006 NNI EHS projects shaped the development of the priorities, rather than the other way around.

> "The NNI document does not provide an evaluation of the state of science [see earlier responses on this statement] in each of the five research categories, rather the research needs are evaluated against research projects that were funded in FY2006 …"(Page 3)
> "Federal agencies may have a vested interest in justifying the value of current efforts rather than critically assessing what needs to be done and how deficiencies might be addressed." (Page 4)
> "The document resembles a laundry list of ad hoc projects that some agencies have shoe-horned into relevance for environmental health and safety." (Page 29)

This claim was further stated during the briefing sessions conducted on December 10th and December 15th. An example follows:

> One NRC committee member's statement on December 15th: "...when you read the actual gap analysis and how it relates to research goals, you see the actual inventory of the research shaping the priorities rather than the other way around."

RESPONSE AND RECOMMENDATION: Contrary to this claim, the research needs and priorities in the 2008 NNI Strategy Document were based on stakeholder input and a review of the state of science. They were also developed and released in the 2006 and 2007 NNI Research Needs and Prioritization documents long before the availability of data on the 2006 funded projects. The committee should correct the statements stating or implying that the research needs were shaped by the 2006 NNI EHS project data call.

Claim 4 that the most recent PCAST review of the NNI did not comment on the NNI EHS research strategy

The report asserts that the most recent PCAST review of the NNI did not comment on the NNI EHS research strategy.

> 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 2008): this report did not comment on the federal strategy being reviewed by the committee. (page 14)

This is not correct. The PCAST report stated that PCAST would issue a letter addendum to their report later in 2008 explicitly reviewing the 2008 NNI EHS strategy document. That letter addendum was released by PCAST in July 2008. The PCAST review on the overall NNI approach to nanotechnology-related EHS issues was favorable.

RESPONSE AND RECOMMENDATION: It is a major omission in the NRC review that it does not include mention of the PCAST addendum report. Footnote 4 on p. 14 of the NRC review document should be revised to reflect the PCAST addendum report. The NRC review document should note also that PCAST's review was generally favorable. A reference should be added at

the end of that chapter to the PCAST addendum report:
http://www.ostp.gov/galleries/PCAST/PCAST%20Addendum%20Letter.pdf

Claim 5 that the health applications studies identified in the NNI list of FY 2006 EHS projects are misapplied and are not related to EHS

In challenging the overall EHS relevance of the 2006 projects, the report repeatedly asserts that NIH grants to develop novel diagnostic and therapeutic applications of nanotechnology have no direct relevance to EHS considerations. The NRC report says while this area of study is important it does not relate directly to EHS. For example, in the report summary the committee says,

> "Use of the FY 2006 data is probably the greatest deficiency in the 2008 document" …"because most of the listed FY 2006 projects were focused on understanding fundamentals of Nanoscience that are not explicitly associated with risk or the development of nanotechnology." (Page 4)

This assessment is inaccurate on several fronts. First, we should clarify that only a small percentage of the budgets for many of these projects that corresponded directly to EHS assessments, such as toxicology testing of these potential health applications of nanotechnology, were counted in the EHS research funding total. Explicit statements of this approach to reporting project funding are provided in Appendix A of the NNI EHS Strategy document in the last paragraph on page 55 and at the end of page 56. The practice of <u>not</u> counting the safety testing that is routinely included in NIH clinical research projects, which this report implies the NNI should be doing, would result in a far less accurate accounting of projects relevant to the NNI EHS research portfolio. In other words, if the safety testing (and the knowledge gained from such testing) supported by this funding were excluded from all of the NIH nanotechnology projects, what are the chances that any of those projects would ever be approved by FDA for clinical use? We therefore argue strongly that it is simply incorrect to assert that these projects have no relevance for risk assessment and regulatory decision making. Without the EHS information developed as part of these projects, the process of regulatory review would be significantly hindered.

RESPONSE AND RECOMMENDATION: As argued here, health studies do relate and are supportive of EHS research. The remedy for this problem in the NRC Review is for the committee to include language correctly acknowledging that only a small percentage of the health applications projects were included in the estimated EHS research funding and to add language better explaining the committee's understanding of how these projects inform regulatory decision making. A similar request is made for language to clarify the committee's understanding of the relevance of instrumentation and metrology research projects.

Additional Technical Errors and Misstatements

Technical: Appendix 1 provides a representative, partial list of errors in the NRC report's technical analysis of the NNI 2008 Strategy, mostly from the section on Nanotechnology and the Environment. The NEHI working group of the NSET Subcommittee is continuing its effort to identify the full set of factual errors and provide detailed, public responses to the NRC report over the next month. This is consistent with the NNI's adaptive management process and will improve the foundation for incorporating recommendations and engaging stakeholders.

On p. 5, in the center of the third paragraph, lines 4-6 state, "For example, in the 'Instrumentation, Metrology, and Analytical Methods' category the development of a sub-angstrom-resolution microscope is said to fulfill the need "to detect nanomaterials in biological matrices." To the best of our records there is no project listed in the 2006 EHS projects to develop a sub-angstrom-resolution microscope. Similarly on p. 41, second from last paragraph, lines 6-7 imply that the NNI has been counting as EHS research investments "hundreds of millions of dollars on instrumentation with a resolution of 0.01 nm…" This is simply not true. The total investment in the 2006 "snapshot" of EHS research projects for instrumentation, metrology, and analytical methods was only $26.6 million. We have no idea where the "hundreds of millions of dollars" figure for sub-angstrom resolution microscopy research came from and request clarification as to which project this comment – repeated in the press releases about the NRC committee report and during the briefing session – refers. This hyperbole should be removed.

Structural: The report contains several misstatements about the history and structure of the NNI. For example, Box 1-1 states that the NNI was formally established in January 2000. That is when President Clinton made the NNI proposal; the NNI itself began when Congress authorized the increased budgets for nanotechnology research in the participating Federal agencies for fiscal year 2001. Those appropriations were signed into law in November 2000. In another example, p. 10 misstates the number of agencies participating in the NNI budget crosscut as twelve. There are 13 agencies that participate in the NNI budget crosscut.

Typographical: In addition to the above, the document contains a number of typographical errors and "non-sequitur" statements that should be corrected—a list of these is provided in Appendix II.

Conclusion

While the NRC review acknowledges that it was outside the scope of the review to offer recommendations, there are a number of implied solutions to the shortcomings cited in the NNI strategy document. The report does conclude that a "robust national strategic plan is needed," but does not suggest which entity or mechanism should create and manage the effort. Please note also that the list of items to be included in the proposed new national strategic plan (included on p. 69 of the NRC report, prepublication draft) does not include all the elements of a

successful EHS strategic plan against which this same report measures the NNI documents (see list on pp. 2-3 of the NRC report).

The report indicates a recommendation for structural changes to grant the NNI new independent budgetary authority, "As an interim step, the NNI Amendments Act of 2008 establishes a separate authority within the NNI with accountability for EHS research." This recommendation was not within our agreed upon charge that formed the basis for this review. To be maximally useful to the NNI, the recommendations in the NRC report should be consistent with the authorities and appropriation guidelines of the federal agencies.

The report claims that "the NNI document does not …contain a clear set of goals and does not have a plan of action for achieving the goals…" The 2008 NNI Strategy document spells out in great detail five major categories of research needs, a clear plan of action for implementing the NNI Strategy for Nanotechnology-Related EHS Research, and actions for interagency coordination to address the identified research needs. These are spelled out briefly in the Executive Summary, and more extensively in the Section III where a summary, prioritization of selected research needs, and next action steps are all described in some detail. As stated earlier, it is clear that the NRC committee and the NSET Subcommittee took different perspectives on the interpretations of what constitutes goals and plans of action. The NRC committee may well take the view that the proposals by the NSET Subcommittee are inadequate or do not meet the needs for their proposed National Plan. However, we recommend that the committee qualify their statements concerning the NNI's efforts to develop a "plan of action" relative to the thrust of the 2008 NNI Strategy document.

Finally, the report calls on the NNI to continue its inter-agency coordination, "with an 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." The NSET, Subcommittee will continue to revise and adapt its interagency EHS research strategy in a manner consistent with the state of the science as well as current research needs and opportunities. The NNI will also continue to facilitate development of detailed implementation plans at the agency level, consistent with agency missions. In so doing, we will closely review the NRC report to determine which elements can be employed productively to assist in that effort. We look forward to working with the academies and we request that you address the corrections outlined above.

Appendix I.
Examples of Technical/Analysis Errors in the NRC Committee Review of the NNI EHS Strategy Document.

The NRC report (pages 51 – 55) contains factual errors that result in several recommendations that are either already followed in the NNI document or are not supported. As indicated in the body of this document we have included a few examples of such errors here. Most the factual errors are from the Nanomaterials and the Environment category and can be seen by reference to Figure 7 of the NNI document (reproduced below), and the accompanying text in the NNI document at pages 26 – 32. A few other examples are also included as well.

1. On page 5 of the NRC Report Summary, the report notes "In many cases, the NRC committee concluded that the sequencing of research needs was generally appropriate but not adequately justified. In a number of cases the NRC committee questioned the rationale for a sequence..... In the 'Nanomaterials and the Environment" category, **"**the NRC committee questioned whether resources could be used more efficiently if the characterization of exposure and transformation processes occurred prior to characterization of higher-level ecosystem effects." This recommendation is repeated on the top of page 52 of the NRC Report.

RESPONSE:

- This is criticism that is based on a factual error.
- The Bottom Set of Heat Diagrams associated with Research Need 5 (see Figure 7 on page 31of the NNI document : please see the Attachment on the last page of this document for easy reference to all comments made in this set of comments) places the focus of ecosystem effects in the beyond 10 yrs timeframe, while the focus of exposure work in Research Area 2 is in the Near Term (0-5 years) and the focus of both Transport and Transformation research (Research Needs 3 & 4) are in the Near to Mid Term (0 - 10 years): therefore, the NNI report clearly notes that the work on exposure, transformation, and transport precedes ecosystem level research.

<u>Recommendation:</u> *The criticisms on pages 5 and 52 should be retracted from the final version of the report.*

2. On page 52 (first full paragraph) the NRC report states that "Exposure scenarios should precede toxicity testing for ecosystem risk assessments." Later in the same paragraph, the NRC report notes that "it is prudent to perform both exposure and toxicity evaluations in tandem, but that the performance and interpretation of toxicity tests is predicated on an understanding of the relevant concentrations to which organisms will be exposed".

RESPONSE:

- These statements in the NRC report are self-contradictory, and not in keeping with the need for research that underpins new product reviews by regulatory agencies.
- What is missing in the NRC analysis is incorporation of an understanding of the differences in needs for a regulatory decision, vs. longer term research: when a new nanomaterial is reviewed for regulatory approval, both the toxicity results for testing on an individual organism must be on hand (and the appropriate protocol for testing followed) and some reasonable estimate of the exposures to arrive – in a short timeframe -- at an overall conclusion on potential risk. It states on page 29 of the NNI document that research on test protocols for effects "…is considered of highest priority due to: (1) the need to better understand potential impacts on receptors prior to their commercialization." In a longer-term research context, more realistic exposure information would be critical, but at the current time there is almost no information on environmental concentrations for most manufactured nanomaterials.

Recommendation: The inherent contradictions on page 52 should be reconciled to be useful to the NNI planning process. In regard to the sequencing of exposure and effects research: these two research areas both start with heavy emphasis in the near term as shown in the Heat bars for Research Areas 1 & 2 in Figure 7 of the NNI document.

3. A. On page 52 (second full par.) the NRC report states that "…it is critical that research priorities **include investigations that focus on nontraditional ecotoxicologic endpoints** that are more appropriate for particles."

B. The same paragraph also notes "In addition to different endpoints, toxicity assessments must include exposure characterizations." The report then goes on to note that " …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."

RESPONSE:

- *These statements noted in items A and B above are offered as criticism – implying that they are not already addressed in the document, -- when in fact they are already agreed to in the NNI document, Hence, these criticisms are based on factual errors.*
- On item A, The NNI document on page 29 states that "In the near term, test protocol research can be addressed by a concentrated emphasis on evaluation of exiting protocols for their adequacy for nanomaterial testing." Also, see Research Area 1 in Figure 7 and the associated heat bar on "test protocols" which is linked to text in NNI report: review of existing protocols occurs in the near term; based on this review, modifications are subsequently considered] This addresses

endpoints' concerns raised by the NRC, species selection, exposure issues with dosing, dose-response metrics, and more.

- On item B, the NNI document suggests that exposure characterizations should be addressed and that other aspects of particle characterization should also be considered. The NNI document on page 29, second full paragraph states that "…(1) a fundamental enabler of work under this research category is the physical/chemical characterization research that enables identification of nanomaterials in biological and environmental matrices….(3) research should address key products of reactions between nanomaterials and the environment following contact with environmental matrices." The NNI document also emphasizes the need for dose-response characterization work (page 29, 3rd paragraph; and Figure 7, Research Area 1) which cover the concerns noted by the NRC.

<u>Recommendation:</u> *The criticisms on page 52 of the NRC report should be modified to recognize that these issues are already addressed in the NNI document.*

4. The NRC reports (last full par. On page 52) that research on understanding "…exposure by identifying principal sources and exposure routes….should have high priority and should be done quickly…."

RESPONSE:

- *This criticism is based on a factual error:*
- The NNI document clearly identifies this research on sources and exposure routes as one of the top 2 near term research priorities – please see Figure 7 Heat Diagram: work on both of these areas have a heavy emphasis during the first 0-5 years of the research proposed and hence are almost equally ranked relative to priorities.

<u>Recommendation:</u> *The suggestion that sources of exposure, and exposure route, research do not have a high priority should be amended in the NRC document as this is the same recommendation that is in the NNI document.*

5. On page 53 (5th paragraph) the NRC report notes "Additional needs for characterization methods to identify nanomaterials in biological and environmental matrices and the products of nanomaterial-environment interactions are also appropriate. The call to focus on "as manufactured" nanomaterials may misdirect interim risk assessments by creating…"

RESPONSE:

- *This criticism is based on a factual error.*
- Page 29 of the NNI document clearly states that one "overarching consideration" that must be taken into account is " …(3) research should address key products of reactions between nanomaterials and the environment following contact with environmental matrices…."

<u>Recommendation:</u> The NRC report should be amended to reflect the concurrence of its conclusions with those of the NNI.

6. Page 53 of the NRC report suggests **a re-ordering of research priorities:** " …estimates of transport and transformation are required to assess environmental exposure and should therefore have higher priority than evaluation of ecosystem-wide effects because of the latter cannot be usefully studied without knowing what the likely environmental concentrations will be and what organisms might be exposed. Therefore, the NRC committee recommends the research be rearranged as (2) [sources of exposures and exposure routes], (4) [Transformation], (1) [Effects on individuals of a species], **(** 5) [Abiotic, and ecosystem-wide effects], and (3) [environmental transport]. Exposure and transport processes would be characterized before effects."

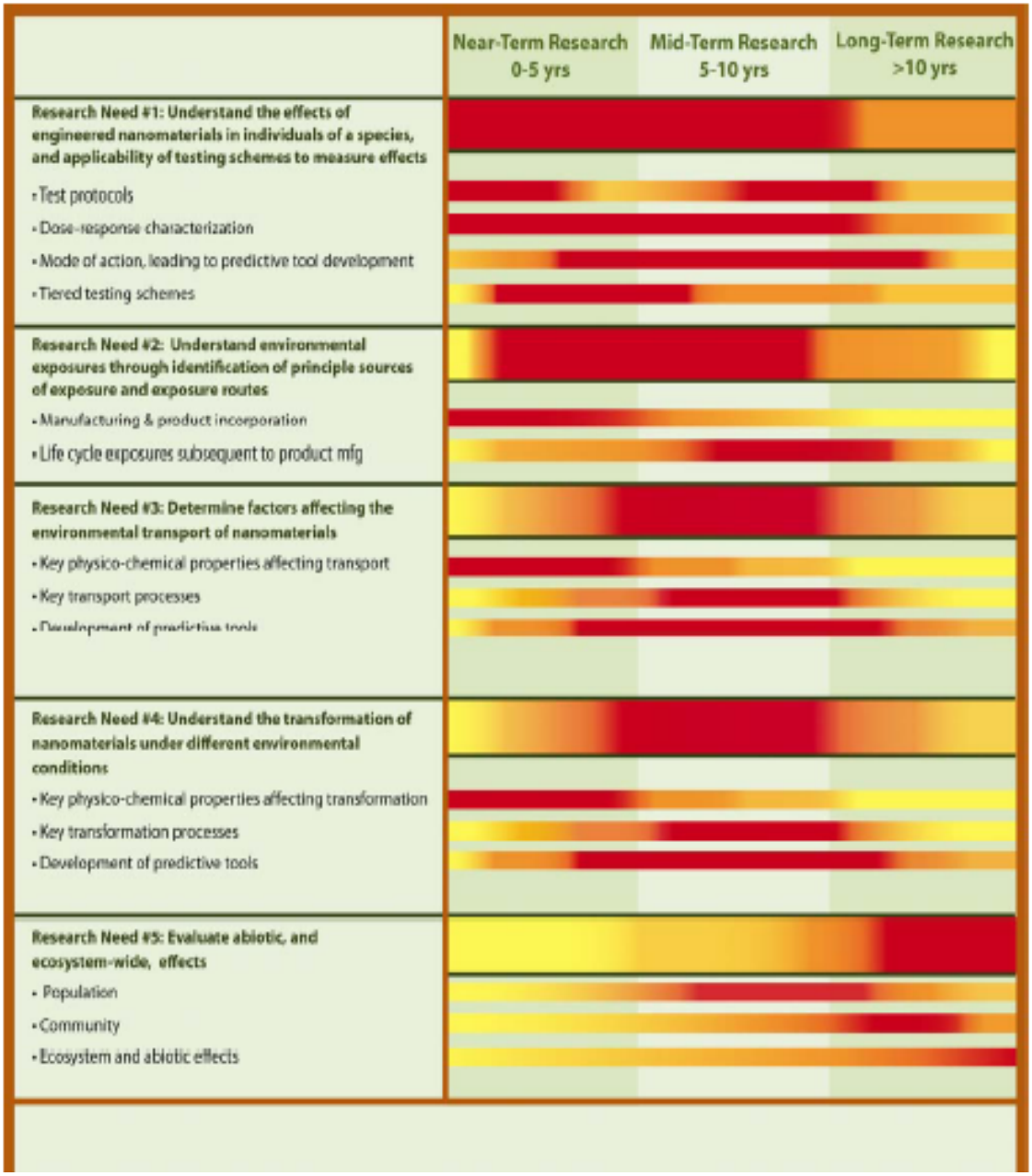
RESPONSE:

- *The above recommendations appear to be self-contradictory* in two respects: environmental transport research (lowest priority according to NRC recommendation) cannot be the lowest priority given the last statement in the quote directly above. In addition, the earlier text noted that ecosystem effects should be a focus after exposure/transport/sources work is well underway: the ranking above has ecosystem level effects preceding environmental transport.
- The research needs for the NNI are intended to support regulatory decisions on new product approvals which have short turn-around times for many of the decisions made. Such decisions in the near term require balanced consideration of both ecological effects information and exposure information in order to formulate an appropriate risk characterization of individual nanomaterials submitted for regulatory review. With this in mind**, appropriate toxicity protocols must be in place for at least some of the common aquatic receptors for which there is already a large database of data for existing chemicals (and a growing database for nanoparticles, such as daphnid toxicity publications). This is necessary to provide good protocols to industry for testing and receipt of meaningful hazard information. If hazard is low, there may be little need for precise exposure information to make a conclusion**. In fact, examination of the Figure 7 Heat Diagram indicates that Priority 2 (Exposures and Exposure routes) is almost identically as high in priority as Priority 1 (Effects on Individuals of a Species), and only slightly lower due to the need to understand toxicity in the short term (and due to the ability to review existing protocols for their relevance and achieve significant results in the very near term that can be applied to approval processes for commercial products).

<u>Recommendation:</u> The NRC should adjust its priority ranking of the recommended research. Taking into account the above discussions, a reasonable order of priorities from highest to lowest would be 1=2, 3, 4, 5.

7. Please correct spelling of National Institute for Occupational Safety and Health on pp. xiii and 10.
8. Please correct spelling of “Murashov” on page 36.

Figure 7. Relative emphasis as a function of time for EHS priority research needs: Nanomaterials and the Environment category



Appendix II

"Typographical" Errors Noted During Review of the NRC Report

[referencing the Dec. 9 prepublication print]

- P. 6, second to last para:
  - Lines 5-6 state that the NNI is not a research program
  - Line 10 refers to the NNI's "robust research and development program"

  (The committee might want to explain or rectify this evident inconsistency in the report.)
- P. 6, second to last para, and also repeated on pp. 35 and 68: text sets up "straw man" that there is an evident conflict of interest between the NNI being responsible for both promoting and regulating nanotechnology. Then in all three places it goes on to say this is a "false dichotomy" – tearing down the straw man. Why does the report then conclude that a separate regulatory authority may be needed, based on this "false dichotomy"? The first and third of these statements is in direct conflict with the second. Why should a "false dichotomy" be the basis for a major recommendation?
- P. 9, box 1-1, includes several inaccurate statements about the NNI history. As indicated above, the Jan. 2000 date referred to in the first paragraph here is the date of Pres. Clinton's speech at Caltech proposing the NNI. "In August 2000, as the NNI got underway" should be changed to "In August 2000, as the NNI proposal matured." Lines 3-4 of the second paragraph should be re-worded to say, "starting from eight agencies in 2001, the subcommittee now includes representatives of over 25 Federal agencies and R&D programs…" Otherwise, the reader may get the impression that the NSET Subcommittee has involved 25 agencies from its inception.
- P. 9, last para., discussion of PL 108-153 is inaccurate. The second sentence should say that the law "calls on" or "requires" rather than "requested" – this is the law so "request" is not the correct verb. The remainder of the sentence would more accurately be worded, "that the President establish or designate…" – that is the language in the legislation, not "establish and designate." This is an important nuance in the law that allows an existing body [i.e., PCAST] to be designated, rather than requiring the establishment of a new body.
- P. 11, second para., line 5, change "workgroups" to "working groups."
- P. 14, lines 2-3: it is correct as currently worded that "In 2005 NSET… formally established… NEHI," but this statement leaves the incorrect impression that this was the inception of NEHI. As at least one of your panel members knows very well, the history of NEHI goes back to August 2003, when Dr. Teague organized the first meeting. NEHI was very active as an "informal" group before it received its formal charter. It is a significant distortion in the NRC report to leave out this important fact, since the

deliberate process of developing the strategy that this report reviews began during the period when the NEHI Working Group was informal.

- P. 22, 5th para, last line, refers to a published EC implementation report, as an example of what the U.S. should be doing. Recommend the addition of a reference to or URL for the document.
- P. 34, second para. from the bottom, line 3, refers to the "National Science Engineering and Technical Subcommittee." I think you are referring to the NSET Subcommittee, correct? If so that is correctly spelled out, "Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the National Science and Technology Council." See comment below about inconsistencies throughout the report in references to the NSET Subcommittee and its subsidiary working groups.
- P. 38, second para. from the bottom, line 5: "research agencies which comprise NEHI" is incorrect on several levels. First of all, grammatically it should be "that" instead of "which". Secondly, "agencies" do not "comprise" NEHI. A better wording would be "… agencies that participate in the NEHI Working Group."
- P. 42, second para. from the bottom, lines 2-3 read, "Many of the FY 2006 advancement of nanoscience and nanotechnology—have little obvious relevance to EHS issues." There are obviously some missing words or characters here…. Doesn't make sense as currently worded.
- P. 46, second para. from the bottom, line 8, there is a missing end paren after "Organizations."
- P. 47, last para. above Box 4-4, inconsistent use of italics in spelling out "*in vivo*" and "*in vitro*." We usually italicize, but either is o.k. now, as long as the usage is consistent. There are several other examples of Latin words like this throughout the document – e.g., "*in situ*" on the next page.
- P. 51, last para., lines 8-9 state that "Strategic planning for research is also in Figure 7." What does this mean? There is no figure 7 in the NRC report. Figure 7 in "NNI 2008" is probably what is being referred to, but the words "strategic planning" do not appear on that figure.
- P. 52, first para. under Box 4-5, line 2, refers to "goals laid out for this section." Elsewhere the NRC report states that the NNI strategy does not lay out goals. Which is it?
- P. 56, last bullet, line 3, the "2" in Ti02 should be subscripted, i.e., "$Ti0_2$".
- P. 58, first para., first sentence is very confusing; intended meaning unclear. Do you mean that research on risk management can both broaden available options AND inform risk assessment research? Or do you mean that it cannot do either or both of these things? The sentence should be reworded.
- P. 58, second para., second line states that "There is no description of how the culling occurred." This is incorrect. NNI 2007 (as called out in the NRC report), p. 6-7, describes the process by which the research needs originally identified in NNI 2006 were

all subsumed under one of the broader categories identified in NNI 2007. This same error is repeated on P. 61 of the NRC report draft, second para.

- Throughout the document, there are inconsistent references to the NSET Subcommittee, the NEHI Working Group, etc. It would be more formal and correct to spell out "NSET Subcommittee" and "NEHI Working Group" in all references to these two bodies in the document (and obviously spelling out the NSET and NEHI acronyms on first use).
- Also throughout the document, it is incorrect to reference our publications as "NNI 2006", "NNI 2007", "NNI 2008," etc. This is an indicator of a broader misunderstanding among the report drafters about what the NNI actually consists of. The NNI is not a publisher, nor an author. On the "NNI" publications prepared by the NSET Subcommittee (e.g., the NNI 2007 Strategic Plan), the NSET Subcommittee should be listed as author, and NNCO as the publisher. In the case of the three key documents that this NRC panel reviewed, all three were "prepared" (i.e., authored) by the NEHI Working Group, under the supervision of the NSET Subcommittee and with assistance from NNCO. So the NEHI Working Group should be listed as author, and NNCO as publisher on those three documents.
- Re: Appendix D, proposed to start on p. 78 of the prepublication draft, why is it necessary to reproduce the NNI document when it is easily referenced via the Web? This would appear to be a waste of paper and time.