Summary Report of the Peer Review Workshop on the *Nanotechnology White Paper: External Review Draft*

Washington, DC
April 19-20, 2006

Prepared for:
U.S. Environmental Protection Agency
Office of the Science Advisor
1200 Pennsylvania Avenue, N.W.
Washington, DC 20004

Prepared by:
Versar, Inc.
6850 Versar Center
Springfield, VA 22151

Contract No. 68-C02-061
Task Order 125

July 7, 2006

NOTICE

This report was prepared by Versar, Inc., an EPA contractor (Contract No. 68-C02-061, Task Order No. 125), as a summary of the discussion of the Peer Review Workshop on the *Nanotechnology White Paper: External Review Draft* (April 19-20, 2006). This report captures the main points and highlights of the meeting. It is not a complete record of all detailed discussion, nor does it embellish, interpret, or enlarge upon matters that were incomplete or unclear.

CONTENTS

CHAIR'S EXECUTIVE SUMMARY iii

1.0 INTRODUCTION 1
1.1 Meeting Purpose 1
1.2 Meeting Participants 1
1.3 Agenda 1
1.4 Organization of Summary Report 2

2.0 SUMMARY OF PRESENTATIONS AND DISCUSSION ON THE DOCUMENT 3
2.1 Goals of Workshop and Introductions 3
2.2 Background on Nanotechnology White Paper 3

3.0 PEER REVIEW COMMENTS ON THE DOCUMENT 5
3.1 General Comments 5
3.2 Response to Charge Questions 5
3.2.1 Charge Question A 6
3.2.2 Charge Question B 7
3.2.3 Charge Question C 8
3.2.4 Charge Question D 9
3.2.5 Charge Question E 10
3.2.6 Charge Question F 11
3.3 Summary 12

4.0 OBSERVER COMMENTS 15
4.1 First Comment Period 15
4.2 Second Comment Period 15

APPENDICES

APPENDIX A LIST OF PEER REVIEWERS AND BIOGRAPHICAL SKETCHES
APPENDIX B LIST OF OBSERVERS
APPENDIX C CHARGE QUESTIONS
APPENDIX D AGENDA
APPENDIX E POWERPOINT PRESENTATIONS
APPENDIX F WRITTEN COMMENTS FROM REVIEWERS
APPENDIX G OBSERVER COMMENTS

CHAIR'S EXECUTIVE SUMMARY

An external peer review of the U.S. Environmental Protection Agency (EPA) "Nanotechnology White Paper: External Review Draft" was conducted on April 19-20, 2006. The peer review panel consisted of eleven members with a broad range of expertise in nanotechnology science, human toxicology/risk assessment, and ecological risk assessment. The meeting was hosted by Versar, Inc. for EPA's Office of the Science Advisor, with the purpose of providing expert comments, suggestions, and recommendations for improvements to the draft document. The premeeting peer review process involved preparation of written comments by all experts, including responses to six charge questions and consideration of public comments that had been submitted to EPA during the public comment period. The charge questions and responses were used as the framework for face-to-face discussions, which took place in front of public observers over the course of two days in Washington, DC.

The prevailing opinion of the reviewers was that, as a first draft, the EPA has written a lucidly presented and rationally balanced document that appears to have engaged extensive cross-Agency involvement. The technology issues were reasonably well referenced and acknowledged. Key recommendations proposed by the Agency for their future role and activities in the scientific frontier of "nanoscience and technology" were duly noted. While the reviewers generally praised EPA's document, they provided general and specific recommendations for revisions that should significantly improve the document and lead to a very useful publication. One of the major suggestions from the reviewers concerned providing clear future direction for the Agency's nanotechnology research and regulatory programs. Many reviewers voiced the option that the Agency should prioritize the research needs and other activities, including determining resource needs and timelines, to help guide implementation of their programs. While some reviewers believed that this should be done within the White Paper, others felt that a separate strategic plan would be the more logical place to present such details. The Agency is encouraged to consider these suggestions and acknowledge the importance of developing a detailed plan for conducting these future efforts, whether they are presented in the final White Paper or in a separate strategic plan.

Presented below are summaries of the major suggestions provided during the peer review meeting, which generally fall into the following three categories: (a) enhancements for clarity and focus, (b) expert-driven suggestions for technical enhancement of the White Paper, and (c) EPA's technical niche capabilities in the nanotechnology movement.

(a) Suggestions for Enhancements of the White Paper for Clarity and Focus

1. Prioritize and fine tune EPA's list of research needs and recommendations, presented in Chapters 5 and 6, and add specific timelines for implementation.
2. Rewrite the Executive Summary – The Executive Summary should be revised to report major conclusions and present an introduction to the scope and coverage of the paper, rather than presenting an overview of the structure of the document.
3. Remove redundancy and provide more even coverage of all topics.

4. Utilize a technical editor to improve consistency across the sections.
5. Reorganize the discussion of EPA's future plans and activities so that regulatory needs and authorities are clearly communicated.
6. Consider dropping Appendix C.
7. More clearly place this document in the context of EPA's overall plan to address nanomaterials, including succinctly describing the Agency's plans in the executive summary, and in more detail in a next steps section.
8. Add a dedicated Appendix that outlines current EPA efforts in nanotechnology, an organization chart showing EPA's offices and their different responsibilities in this subject area (collaboratively and otherwise), and a list of publications, reports, patents, etc.

(b) Expert-Driven Suggestions for Enhancement of the Technical Content of the White Paper and EPA's Strategic Plan for Nanotechnology

1. Determine relevance of *in vitro* assays for predicting *in vivo* effects of nanomaterials for both ecological and human health effects.
2. Outline and diagram a "roadmap" for specific statutes/authorities, and how they apply to nanomaterials, and their limitations for application to nanomaterials.
3. Complete full *in vivo* characterization of several key (1-3) nanomaterials.
4. Describe present and future collaborations at all organizational levels: intraagency, interorganizational, and international.
5. Place EPA research in context of national nanotechnology strategic plan.
6. Focus on supporting research for EPA-specific regulatory needs that other organizations and agencies would not address.
7. Discuss the use of multi-criteria decision analysis, value of information analysis, and adaptive management that supplement a risk assessment framework which can be used to prioritize nanotechnology research needs.
8. Develop and utilize a framework to methodically identify potential releases of nanomaterials and assess their associated risks through the complete product life-cycle.
9. Expand on environmentally beneficial applications of nanotechnology and integrate risk assessment approaches to ensure that nanomaterials are safe.
10. Develop a "nano periodic table" that defines a framework or a roadmap for assessing patterns and structure activity and physio-chemical properties.

(c) EPA's Technical Niche Capabilities

The reviewers provided the following suggestions for activities that EPA should consider, because of their niche capabilities and specific needs:

1. Mechanistic studies on inhaled or pulmonary exposures to nanoparticles.
2. Environmental fate and transport, and ecological studies.
3. Partnering with other agencies (NCI, NCL, NIST, FDA, NIEHS, etc.) for toxicity testing.

4. A broad look at sources, pathways for ambient exposure to humans and other organisms (e.g., linking w/FDA for pharmaceutical exposure to the environment).
5. Basic research necessary for development of models (including quantitative structure-activity relationship (QSAR), absorption, distribution, metabolism, and excretion (ADME), physiologically based pharmacokinetic (PBPK), and fate/transport models).
6. Examine how nanotechnology can be applied to control the release of pollutants, and remediate and protect the environment.
7. Develop risk assessment and policy guidance for nanotechnology that incorporates multi-criteria decision analysis tools.
8. Develop methods and tools for routine use in environmental monitoring, and determination of persistence and bioaccumulation potential.
9. Support development and application of “green” principles in all nanotechnology development.
10. Play a primary role to play in development of methods and tools that it and others can use to execute 1 through 9.
11. Use its authority through the Toxic Substances Control Act (TSCA) and other relevant statutes to call in data on use, production, releases, toxicity and other information from manufacturers and producers of nanomaterials.

1.0 INTRODUCTION

1.1 Meeting Purpose

The peer review of the draft U.S. Environmental Protection Agency (EPA) document "Nanotechnology White Paper: External Review Draft" was held on April 19-20, 2006, at the Marriott at Metro Center in Washington, DC. This two-day meeting was organized and hosted by Versar, Inc. for EPA's Office of the Science Advisor.

As nanotechnology emerges and evolves, potential environmental applications and human health and environmental implications are under consideration by the EPA. The White Paper describes these considerations. The purpose of the meeting was to provide a peer review of the draft document by a group of expert scientists.

The reviewers were experts in nanotechnology science, human health toxicology/risk assessment, and ecological risk assessment and included individuals from academia, consulting, industry, environmental groups, non-governmental organizations, and the Federal government. The reviewers were charged with providing technical feedback, recommendations, and input to the document. EPA developed six charge questions to help guide and focus the discussion. The reviewers made recommendations throughout the meeting as they responded to each charge question.

1.2 Meeting Participants

Eleven experts were convened by Versar to review and provide input on the document. Versar selected experts having broad experience and demonstrated expertise in the scientific areas related to nanotechnology science, human health toxicology/risk assessment, and ecological risk assessment. The reviewers certified that they had no conflicts of interest relative to this document prior to being selected by Versar for the peer review. The list of reviewers and short biographical sketches describing their areas of expertise are presented in Appendix A and a list of external observers is listed in Appendix B.

1.3 Agenda

The agenda for the peer review meeting is presented in Appendix D. The meeting began with a welcome, introductions, and outline of the goals of the meeting. Background on the document's purpose, intended audience, and scope was provided by EPA. The peer review consisted of a panel review of the document, observer comments, and discussion of observer comments. The reviewers discussed responses to the charge questions and suggested revisions and additions of text, figures, and references to improve the technical content and clarity of the document. Reviewers also participated in wrap up discussions to highlight the major suggested changes to the document, research needs, and EPA's technical niche capabilities in nanotechnology.

1.4 Organization of Summary Report

This report presents information on the presentations and discussions from the meeting:

- Section 2 of this report summarizes the opening presentations and discussion on the purpose and procedures for the conduct of the peer review workshop. Section 3 contains summaries of the reviewers' general comments, responses to charge questions, and summary points from the two day discussion. Section 4 summarizes observer comments.

- The appendices to this report are as follows:

  Appendix A - List of Peer Reviewers and Biographical Sketches
  Appendix B - List of Observers
  Appendix C - Charge Questions
  Appendix D - Agenda
  Appendix E - PowerPoint Presentations
  Appendix F - Written Comments from Participants
  Appendix G - Observer Comments

2.0 SUMMARY OF PRESENTATIONS AND DISCUSSION ON THE DOCUMENT

This section presents summaries of the opening presentations and introductions by David Bottimore, Versar, Inc., Dr. George Gray, Assistant Administrator for Research and Development (ORD), White Paper lead authors Jim Willis, EPA Office of Pollution Prevention and Toxics (OPPT), and Jeff Morris, EPA/ORD, and peer review chair Dr. Donald Tomalia, Dendritic Nanotechnologies, Inc. Slides supporting the presentations can be found in Appendix E.

2.1 Goals of Workshop and Introductions

Mr. David Bottimore, of Versar, Inc., provided welcoming remarks and outlined meeting objectives and procedures. He noted that the goal of the peer review was to provide feedback on the scientific content and utility of the White Paper. He reviewed the materials that the participants should have received in advance of the meeting, which included a compilation of premeeting comments from the expert reviewers, the list of charge questions, and the agenda for the meeting. He then initiated introductions by each of the reviewers.

Dr. George Gray, Assistant Administrator for Research and Development, also welcomed and thanked the panel and praised the authors for all the hard work on the document. Dr. Gray noted that EPA is excited about the possible application of nanotechnology providing environmental benefits; but the Agency is also well aware of the potential human health and environmental impacts. In addition to answering the charge questions, Dr. Gray asked the panel to provide suggestions of where internal ORD efforts could be most beneficial while keeping in mind the Agency's unique capabilities. The reviewers' comments in response to Dr. Gray's request are presented in the third list (c), EPA's Technical Niche Capabilities, both in the executive summary and summary section (3.3) of this report.

2.2 Background on Nanotechnology White Paper

Mr. Jim Willis, EPA/OPPT, and Mr. Jeff Morris, EPA/ORD, lead authors of the "Nanotechnology White Paper," thanked and welcomed the panel and provided background information on EPA's efforts on the issue of nanotechnology and the white paper. Mr. Willis noted that in December 2004 EPA's Science Policy Council (SPC) charged the Agency with the creation of a nanotechnology workgroup to identify science policy issues. The workgroup identified the White Paper as an initial Agency-wide product. The document is intended to inform EPA mangers of the technology, activities both internal and external to EPA, potential environmental applications, potential human health and environmental implications, and research needs. While the initial charge was to develop a science based document, as more research was conducted, it became clear that policy issues also needed to be discussed.

Mr. Morris acknowledged that the draft does not present the purpose clearly because the White Paper was evolving as it was being written. Mr. Morris also noted that the purpose statement will be revised in the final draft. Mr. Morris asked the panel to provide feedback on the adequacy of the potential science and research issues outlined, balance between benefits and impacts, and provide additional resources/studies, and any other potential issues with the document. He also noted that the paper was not meant to provide a ranking of priorities because it was intended to be a starting point for EPA's strategic planning in the field of nanotechnology.

Dr. Tomalia, the workshop chair, thanked EPA for convening the workshop and its efforts on addressing the implications of nanotechnology use in environmental applications. He described some of his experience in developing and handling nanomaterials and acknowledged that nanotechnology has received increased attention in recent years and, therefore, it is necessary to define all possible risk boundaries.

3.0 PEER REVIEW COMMENTS ON THE DOCUMENT

Dr. Tomalia started the peer review workshop with general comments from each reviewer. The reviewers prepared premeeting comments (Appendix E), which established the starting points for discussion at the meeting. The following general comments and specific responses to charge questions were developed by the reviewers.

3.1 General Comments

Reviewers generally felt that the White Paper was well written, informative, and serves as a good background document. The document was seen to be a very good first draft that acknowledged there is a realistic potential for risks while not being overly alarmist. Many reviewers stated that the document could be informative to the public and should be released for public consumption as soon as possible, because the field of nanotechnology is growing faster than EPA's ability to capture all the issues. A couple of the reviewers stated that the document does a very good job outlining the majority of the research needs and gaps and several also felt that it was the most comprehensive document to do so.

Reviewers noted that the White Paper can be improved by adding clear guidance on how to make decisions given the large uncertainty in understanding and characterizing the basic properties of nanomaterials, let alone toxicity, fate and transport in the environment, and other important factors necessary for risk characterization. Several reviewers felt that the research needs and recommendations, presented in Chapters 5 and 6, should be prioritized in order to better aid a strategic plan for addressing nanotechnology issues. A few reviewers specifically suggested that EPA collaborate with other Federal and international agencies in developing a strategic plan. One reviewer suggested the need for modifying a risk assessment paradigm for nanomaterials prior to prioritization since existing methods and tools are not adequate to deal with uncertainty related to nanomaterial exposure assessment and characterization. Reviewers felt that developing an agreed-upon nomenclature to group nanomaterials might be useful to guide product-specific regulations. Other reviewers noted that beneficial applications of nanotechnology were limited to only a couple of examples. Some believed that the paper reads as if the document was meant only for internal EPA purposes. Several reviewers suggested that the purpose be redefined, particularly revisiting the executive summary to more accurately state the document's scope, coverage, and purpose. Two reviewers suggested that the document look further into the relevance of *in vitro* assays for predicting *in vivo* effects. One reviewer noted that EPA is the only agency that deals specifically with ecological effects and that the Agency could be most beneficial in the field by identifying and characterizing the ecological effects of nanotechnology.

3.2 Response to Charge Questions

The following subsections summarize the reviewers' responses to the six charge questions. It should be noted that the reviewers' discussions often overlapped into topics

addressed in other charge questions. Consequently, the responses from the reviewers may incorporate aspects of other subjects being discussed and might repeat comments from other charge questions.

3.2.1 Charge Question A

Is the paper written in a clear, concise, and readable manner?

The reviewers, with the exception of one expert, generally felt that the White Paper is written in a clear, concise, and readable manner. Because the document was written by a number of authors, the document could be improved with the use of an editor. The points addressed below will help to improve certain aspects of the document.

Several reviewers suggested that the executive summary needs to be rewritten. The executive summary should contain the main topics from each chapter and demonstrate how each chapter is interconnected. Reviewers also felt that the scope of the document needs to be restated to demonstrate more appropriately what the document actually discusses. In particular, it should be clearly stated that the document is not a strategic plan but is intended to inform the Agency's development of such a plan. The eight bullets in Section 5.3, Chemical Identification and Characterization, seemed to be ill defined and Sections 5.2, Research Needs for Environmental Applications, and 6, Recommendations, need to be reviewed to limit intermixing of topics and objectives. One reviewer suggested the removal of Appendix C, Additional Detailed Risk Assessment Information, and that the literature review should be conducted by one author/editor to maximize consistency and thoroughness.

Reviewers felt that the section on research needs and gaps, Section 5.0, was not well organized. Several reviewers suggested that the research needs should be prioritized and incorporated into a larger strategic plan for the Agency. It was also recommended that EPA should also work with other Federal and international agencies in developing a larger strategic plan on nanotechnology. Examples included the Food and Drug Administration (FDA) in the pharmaceutical arena, the National Institute of Occupational Safety and Health (NIOSH) when dealing with personal protective equipment and occupational exposures, and the National Institute of Environmental Health Sciences (NIEHS). One reviewer suggested providing a 5-year forecast on each research area and show how each step will affect another. It was also suggested that each need could have short-, intermediate-, and long-term goals. Another reviewer added that the document should contain a next steps section to help the reader to understand how the information gained will be used by EPA in policy and regulatory decision making.

Reviewers also pointed to uneven treatment of topics and noted that topics not discussed in depth need to be expanded for better balance. The document seems to focus attention on occupational exposure and very little on consumer exposures. Environmental exposure modeling and associated limitations are well developed, but human exposure modeling is not as well developed. One reviewer also stated that EPA is the only Federal

agency that looks at ecological effects; and therefore, should address issues like transformation and fate once in the environment.

Reviewers noted that the document fails to identify policy issues facing the Agency when regulating nanotechnology. It was suggested that a flow diagram be added that follows a nanomaterial through the Agency's organizational structure noting which regulation is being addressed by that particular Program Office. The chart should also include research needs that will need to be met in order to fulfill each Program Office's regulatory obligations. It also would be helpful to create nomenclature to group similar types of nanomaterials (structure: carbon materials, nanotubes, dendrimers, metal materials; or physical type: aerosol, particles, materials etc.) and classify nanomaterials based on properties (see additional discussion under Charge Question C).

3.2.2 Charge Question B

Do the issues identified adequately address the breadth of potential science and research issues related to nanotechnology. If not, please identify additional issues that you believe should be addressed?

As mentioned above, some of the reviewers felt that the White Paper is possibly the most comprehensive paper written on the environmental issues of nanotechnology. While the document authors should be commended for acknowledging both environmental benefits and potential environmental and human health risks, additional environmentally-related applications should be mentioned (see charge question C). The major recommendations provided to improve the document, included: an approach to address environmental risk through the product life cycle, a "nano periodic table," a framework to help evaluate nanomaterials based on their unique physical/chemical characteristics, and a framework for making policy decisions under uncertainty with multiple lines of incomplete information available.

The reviewers generally agreed that the document lacks details on how the EPA plans to deal with the materials as they travel through the full life cycle (i.e. utilizing a life cycle analysis framework[1] to identify potential releases to the environment) of the product from manufacturing, use, recycle, disposal, and transformation through environmental weathering (through rain, sunlight, pH etc.). A few reviewers felt that the document should contain a risk assessment paradigm designed to deal with significant information gaps for nanomaterials. The classic dose metric in terms of mass might not be the best measure in addressing toxicity concerns of nanomaterials. Until the properties that determine the biological effects of nanomaterials are better understood, it should be recommended that dose be routinely characterized by several properties, such as surface

[1] Life cycle analysis (LCA) is a technique to assess the environmental aspects and potential impacts associated with a product, process, or service. LCA are often done by compiling an inventory of relevant energy and material inputs and environmental releases and evaluating the potential environmental impacts associated with identified inputs and releases. Even though the reviewers recommend LCA considerations for nanotechnology in general, specific applications will require significant modification of the LCA framework and developing new analytical tools and methods.

area or particle size, which might present a closer link to risk. In the effort to identify better dose metrics, *in vitro* studies could be used to establish the extent of correlation with *in vivo* effects, in addition to toxicokinetic research. The White Paper could also benefit from detailing information on health hazard issues by discussing pulmonary studies with carbon black and ultrafine titanium dioxide and exposure assessment data (from Kulbush or others) assessing the occupational exposures in carbon back factories. Furthermore, additional ecological exposure and effects information is needed to balance the document.

In creating a risk management plan, the Agency should review plans/documentation and work with other agencies (e.g. NIOSH, FDA, NIEHS). It was noted by one reviewer that a typical weight of evidence analysis may not be sufficient due to large uncertainty. The Agency may need to incorporate quantitative decision analysis tools into the overall risk management paradigm.

3.2.3 Charge Question C

Does the Nanotechnology White Paper strike an appropriate balance between its discussion of benefits and risks? If not, what would improve that balance?

Several reviewers felt that that paper's discussion of the beneficial applications of nanomaterials could be expanded. One reviewer suggested discussing broader societal benefits in addition to environmental benefits. Beneficial examples include the capture of mercury from stack emissions, reduction of nitrogen oxide in ambient air, dendrimer use in the detection of heart attacks, and dendrimer products used to prevent the spread of HIV. One reviewer suggested that Section 2.0 should be titled nanotechnology applications and present side-by-side the potential risks and benefits, instead of separating them in two sections. Although reviewers listed a number of beneficial applications, many also noted the potential risks of such applications and the importance of "engineering out" or reducing the risks during the research and development phase, to encourage the design of inherently safe nanomaterials. It was also noted that the cost analysis presented in the document was incorrect in that the cost of production was not included. One reviewer also suggested that the energy cost be reviewed for errors.

One reviewer suggested that nanotechnology effects need to be treated as unknowns until risk and exposure boundaries have been identified. Several reviewers believe that nanomaterials need to be classified or grouped according to basic properties in order to avoid overburdening the different programs such as toxicology. It was also suggested that EPA's biggest contribution might be to help in developing a framework for assessing and characterizing and assessing risks, which would help manufacturers to assess the potential impacts of their products. One reviewer stated that small companies may not have the same resources or capabilities as larger companies to aid in providing product information to the Agency. Most reviewers agreed that to be of greatest utility to these companies, the public in general, and EPA internally, the White Paper should be finalized and released as quickly as possible.

One reviewer stated that researchers are currently dealing with these materials in a laboratory setting and need to know what the risks are to lab personnel and what to do with the byproducts once testing is finished. EPA's unique role could be to provide these researches with a characterization framework and structure in order to predict risks. In characterizing nanomaterials it was suggested that the EPA collect biomonitoring, epidemiology, and animal *in vitro* data. It was also suggested that academic laboratories be surveyed for this type of data, since academic laboratories have been researching nanomaterials for several years. Once this information is collected, EPA might create a database to house available hazard data, which would be helpful to scientists trying to link ambient or occupational exposures to observed effects.

3.2.4 Charge Question D

Are there additional studies or other information that should be included in this document? If so, please cite or identify that information.

Reviewers found that the paper reasonably well referenced and acknowledged the growing scientific literature on environmental aspects of nanotechnology. It was also stated that some of the citations are incorrect and these have been captured in the written comments provided by the panel (Appendix F). One reviewer commented that the White Paper relies too heavily on non-peer reviewed literature and should incorporate a greater number of articles from the peer-reviewed literature. Many suggestions were made to expand and update the citations to incorporate important recent studies and conference proceedings (e.g., the February 2006 Nanotox meeting in Miami, the December 2005 OECD workshop in Washington, and the Andre Nel et al. paper in *Science*). Balancing older studies with newer studies was an important issue to some reviewers; however, many reviewers encouraged EPA to complete and publish the paper quickly. Reviewers felt that the paper may become outdated if EPA takes the time to incorporate information on all recent studies because the number of papers is increasing ever more rapidly as time passes.

The reviewers provided other suggestions to improve citations in the White Paper by including additional data from hazard, exposure, and dermal studies (e.g. penetration of ultrafine TiO_2). These studies may come from International Agency for Research on Cancer (IARC), major scientific journals, FDA, NIOSH, or other similar organizations. One reviewer also communicated that information may be obtained from standards development organizations such as the International Standards Organization (ISO) and American Society for Testing and Materials (ASTM).

Adding discussion on how EPA will go about making nanomaterials management decisions will be valuable for readers. Reviewers discussed the value of information analysis, adaptive management, and multi-criteria decision analysis tools which could provide a good foundation for both bringing together multiple information sources to assess risks and develop regulatory decisions. Reviewers commended EPA on the glossary and supported continued collaboration with other organizations like ISO and ASTM on nomenclature, which will help to encourage the use of consistent terminology

when discussing nanomaterials and nanotechnology. Several reviewers offered that it may be useful for the document to incorporate a matrix that categorizes studies currently underway, notes what material and what effects are being examined in each study, and what other agencies may be looking at, which will limit duplication of effort. Sections 1.4 and 1.5 introduce some of these issues but should be expanded and updated to better reflect the different responsibilities and capabilities of EPA and other Federal agencies. Such a matrix might also contain dollar amount allocations on each study. It was suggested that the EPA may want to use a larger portion of its budget on risk related research. One reviewer suggested that the Agency look into creating partnerships with academia and industry in order to obtain data for risk management.

3.2.5 Charge Question E

Do the identified research needs adequately address knowledge gaps about nanotechnology and the environment? Please specify any additional research gaps that you think should be identified

The scientific information needs are presented as an unstructured list of questions concerning many disparate topics without prioritization. As previously noted, many reviewers suggested that EPA prioritize and organize the listed research needs. However, some reviewers cautioned that if prioritizing the research needs would delay the release of the paper, then this step could be left to be incorporated into a subsequent strategic plan. Doing so will help to highlight major areas that need further study to enable EPA's research program to develop the tools needed by the Agency for risk management of nanomaterials. Reviewers reiterated that development of a framework for characterization of nanomaterials would be one of the most worthwhile endeavors. This could include research for traditional risk assessment parameters which include population-level ecological effects (e.g., growth and reproduction of select species), development of test methods, and other aspects of ecological exposure assessment. In general, all possible exposure pathways could be further examined, but funding and research efforts should be carefully prioritized given the large uncertainty characteristic of nanomaterials. For example, respiratory tract dosimetry models (e.g., ICRP) developed for radionuclides may be not adequate for nanoparticles and computational fluid dynamic modeling may be necessary. The aerosol literature may need to be reviewed for potential use in characterizing inhalation exposures to nanomaterials. One reviewer suggested that the Agency collect data through the use of personal air monitors for workers who manufacture nanomaterials. It was suggested that other particles that are monitored by the EPA could be related to nanoparticles. One reviewer noted that Section 5.4, Environmental Fate Research Needs, is unevenly balanced and the discussion of pathways for entering the body, tissue distributions, and accumulation in humans and animals should be expanded.

Reviewers encouraged EPA to focus on developing nanoparticle assessment methods and tools in basic scientific areas – measurement and characterization, fate and transport, exposure assessment, toxicology, and risk assessment. These tools can be then further be refined by other agencies and industry. One reviewer cautioned that tools such as Monte

Carlo analysis may present a problem due to large uncertainties, and it was suggested that other decision analysis tools be implemented (e.g. Multi-Criteria Decision Analysis, value of information analysis, and adaptive management).

One effort that would be helpful to risk assessors, risk managers, and regulators would be to further efforts to classify/categorize nanomaterials (including a nano periodic table) and test the hypothesis that a specific material could be "representative" of that class of compounds. The state of science on the health effects of nanoparticles is still developing, including the determination of what properties are key determinants of their toxicity, which is an important factor in selecting a representative material. It was suggested that tier I testing be conducted, which will provide certain base triggers for tier II and III testing. If standard testing methods are not adequate, then the Agency will need to develop new test methods. The Agency should develop these methods in conjunction with the National Toxicology Program (NIEHS), NIOSH, FDA, the National Cancer Institute, and other such Agencies. One reviewer suggested looking at how the biotechnology industry approached these issues and developed protocols to deal with RNA, DNA, and proteins; since these are nanomaterials that have been researched to a greater extent. Data from testing and monitoring should be collected and managed as part of EPA's strategic plan; which should include an emergency response plan. A final step should be to identify whether or not current legislation and regulations are sufficient to regulate nanomaterials.

3.2.6 Charge Question F

Is this document useful for explaining to stakeholders Agency plans for conducting scientific activities related to nanotechnology? If not, why not?

A majority of the reviewers felt that the document was a very good science document that encompasses many of the possible ecological and human health risk assessment topics of interest related to nanotechnology. However, most reviewers felt that the White Paper fails to provide a clear picture of the Agency's current and future efforts to address nanotechnology's potential risks. A major concern, as noted earlier, is that the paper's purpose statement in the introduction does not accurately portray the scope of topics that are actually covered in the body of the paper. Revising the purpose statement in the introduction and incorporating a more complete plan with priorities for research, along with the addition of appropriate policy issues, would strengthen the White Paper.

As noted earlier in the discussion on the prioritization of research needs, the White Paper fails to lay out the expertise, time, and budgetary allocations necessary to develop a strategic plan in order to assess and regulate nanomaterials, both in the short-and long-terms. As also previously noted, some reviewers suggested revising the White Paper to include more of the aspects of a strategic plan, particularly prioritizing the listed research needs. However, some reviewers cautioned that such an effort could delay the release of the White Paper, which should be published as soon as practicable.

The Agency needs to fully identify all possible stakeholders and their interactions with the Agency on nanotechnology issues. Some reviewers felt that stakeholder interactions should be described within the paper. The plan should also identify how other national and international Agencies will provide scientific knowledge which can aid EPA in the regulation of these materials. The White Paper should also list regulatory limitations in overseeing the use of nanomaterials.

3.3 Summary

Following the discussion of their general comments and specific responses to the six charge questions, the reviewers summarized their recommendations and suggestions. The first set of recommendations identified eight focus areas for EPA to consider in finalizing the White Paper. The second set provided ten key areas to help the Agency in developing a strategic plan to address nanotechnology issues. The last summary session provided the Agency with focus areas which highlight EPA's unique capabilities in the nanotechnology field, in response to the question posed by Dr. Gray during his opening remarks to help identify EPA's niche capabilities where the Agency's technical expertise could be most beneficial. Key points from the three summary sessions are provided below.

(a) Suggestions for Enhancements of the White Paper for Clarity and Focus

1. Prioritize and fine tune EPA's list of research needs and recommendations, presented in Chapters 5 and 6, and add specific timelines for implementation.
2. Rewrite the Executive Summary – The Executive Summary should be revised to report major conclusions and present an introduction to the scope and coverage of the paper, rather than presenting an overview of the structure of the document.
3. Remove redundancy and provide more even coverage of all topics.
4. Utilize a technical editor to improve consistency across the sections.
5. Reorganize the discussion of EPA's future plans and activities so that regulatory needs and authorities are clearly communicated.
6. Consider dropping Appendix C.
7. More clearly place this document in the context of EPA's overall plan to address nanomaterials, including succinctly describing the Agency's plans in the executive summary, and in more detail in a next steps section.
8. Add a dedicated Appendix that outlines current EPA efforts in nanotechnology, an organization chart showing EPA's offices and their different responsibilities in this subject area (collaboratively and otherwise), and a list of publications, reports, patents, etc.

(b) Expert-Driven Suggestions for Enhancement of the Technical Content of the White Paper and EPA's Strategic Plan for Nanotechnology

1. Determine relevance of *in vitro* assays for predicting *in vivo* effects of nanomaterials for both ecological and human health effects.

2. Outline and diagram a "roadmap" for specific statutes/authorities, and how they apply to nanomaterials, and their limitations for application to nanomaterials.
3. Complete full *in vivo* characterization of several key (1-3) nanomaterials.
4. Describe present and future collaborations at all organizational levels: intraagency, interorganizational, and international.
5. Place EPA research in context of national nanotechnology strategic plan.
6. Focus on supporting research for EPA-specific regulatory needs that other organizations and agencies would not address.
7. Discuss the use of multi-criteria decision analysis, value of information analysis, and adaptive management that supplement a risk assessment framework which can be used to prioritize nanotechnology research needs.
8. Develop and utilize a framework to methodically identify potential releases of nanomaterials and assess their associated risks through the complete product life-cycle.
9. Expand on environmentally beneficial applications of nanotechnology and integrate risk assessment approaches to ensure that nanomaterials are safe.
10. Develop a "nano periodic table" that defines a framework or a roadmap for assessing patterns and structure activity and physio-chemical properties.

(c) EPA's Technical Niche Capabilities

The reviewers provided the following suggestions for activities that EPA should consider, because of their niche capabilities and specific needs:

1. Mechanistic studies on inhaled or pulmonary exposures to nanoparticles.
2. Environmental fate and transport, and ecological studies.
3. Partnering with other agencies (NCI, NCL, NIST, FDA, NIEHS, etc.) for toxicity testing.
4. A broad look at sources, pathways for ambient exposure to humans and other organisms (e.g., linking w/FDA for pharmaceutical exposure to the environment).
5. Basic research necessary for development of models (including quantitative structure-activity relationship (QSAR), absorption, distribution, metabolism, and excretion (ADME), physiologically based pharmacokinetic (PBPK), and fate/transport models).
6. Examine how nanotechnology can be applied to control the release of pollutants, and remediate and protect the environment.
7. Develop risk assessment and policy guidance for nanotechnology that incorporates multi-criteria decision analysis tools.
8. Develop methods and tools for routine use in environmental monitoring, and determination of persistence and bioaccumulation potential.
9. Support development and application of "green" principles in all nanotechnology development.
10. Play a primary role to play in development of methods and tools that it and others can use to execute 1 through 9.

11. Use its authority through the Toxic Substances Control Act (TSCA) and other relevant statutes to call in data on use, production, releases, toxicity and other information from manufacturers and producers of nanomaterials.

4.0 OBSERVER COMMENTS

Observers provided comments twice during the two-day meeting; once during the first day following reviewer discussion on the overall document, and again at the conclusion of the meeting. This section summarizes the statements made by observers who spoke during the meeting. Written statements provided by observers during the meeting are presented in Appendix G.

4.1 First Comment Period

Mr. I. Sam Higuchi, National Aeronautics and Space Administration, stated that the Agency should look at effects of nanomaterials at the atomic level and how they might affect human cells and organelles. Since nanomaterials are on a nano scale, health physics aspects of nanomaterials might be important to biological effects to humans and the ecosystem.

Ms. Pat Casano, General Electric, thanked the Agency for its efforts and supports the reviewers' suggestion to take a holistic approach to group/categorize nanoparticles/materials based on physical properties. Ms. Casano stated that nanomaterials that are extruded from metals are less of a risk and should have a lower priority for the Agency. Ms. Casano also stated that nanomaterials are difficult to manufacture; thus limiting what is already in the market place. The Agency should focus on regulating what is in the market and then set priorities based on nanomaterial categories.

Dr. Rick Canady, Food and Drug Administration, stated that his comment was one of collaboration and noted that the National Cancer Institute's Nano Characterization Laboratory was in the process of developing standard testing methods.

4.2 Second Comment Period

Ms. Lynn Bergeson, Bergeson & Campbell, P.C., representing the American Chemistry Council (ACC) Nanotechnology Panel, stated that the ACC commends and supports EPA on its efforts. Ms. Bergeson stated that it would be premature for the EPA to prioritize research needs prior to developing a research strategy. A research strategy is essential, but EPA is one of several other federal, international, and state agencies that should be part of the strategy. The ACC is also supportive of the stewardship program and is willing to aid once a voluntary structure is put in place by EPA.

Mr. Scott Slaughter, Center for Regulatory Effectiveness, stated that the Agency should revise the White Paper to reflect the paper's impacts on the National Technology Transfer and Advancement Act of 1995, 15 CFR 287, and OMB circular A-119.

Mr. Sean Murdock, Nano Business Alliance, commended the Agency for its efforts, agrees with the reviewer's suggestions, especially on the issue of prioritization. The

Nano Business Alliance looks forward to working with the Agency on nanotechnology issues.

Mr. George Kimbrell, International Center for Technology Assessment, noted that the White Paper did not achieve its stated goal. The current White Paper is a science only document and fails to address policy issues for future and present regulations of nanomaterials, which potentially have unique and varied harm. The White Paper also fails to address the current research the Agency is conducting on nanotechnology. Mr. Kimbrell stated that the document fails to address TSCA's shortcomings in regulating nanotechnology and the shortcomings of EPA's voluntary program when dealing with nano products. The ICTA would also like more of the National Nanotechnology Initiative (NNI) budget to be devoted to health and safety, which currently is only 4% of the budget.

Mr. Jonathan Gledhill, Policy Navigation Group, stated that the Group also commends the Agency for its efforts. Mr. Gledhill noted that the EPA budget is small and that the White Paper should discuss EPA's voluntary program. Data should either be pulled from the market or from EPA funded research. Mr. Gledhill stated that the current risk assessment paradigm has been effective even in the field of radiation. He believes that the Agency should focus on human health, and fate and transport of nanotechnology.

APPENDIX A
LIST OF PEER REVIEWERS AND BIOGRAPHICAL SKETCHES

List of Peer Reviewers

Name	Organization
Pratim Biswas	Washington University in St. Louis
Richard Denison	Environmental Defense
Rebecca Klaper	University of Wisconsin-Milwaukee
Igor Linkov	Cambridge Environmental, Inc.
Andrew Maynard	Woodrow Wilson International Center
Vladimir Murashov	National Institute for Occupational Safety and Health
Stephen Olin	ILSI Research Foundation
Jennifer Sass	Natural Resources Defense Council
Donald Tomalia	Dendritic Nanotechnologies, Inc.
Nigel Walker	National Institute of Environmental Health Sciences
David Warheit	DuPont Haskell Laboratory

Biographical Sketches for
Nanotechnology White Paper Peer Review Panel

Pratim Biswas, Ph.D.
Washington University in St. Louis
St. Louis, MO

Dr. Pratim Biswas is the Stifel and Quinette Jens Professor and Director of the Environmental Engineering Science Program at Washington University in St. Louis. His research work focuses on aerosol science and engineering, air quality and pollution control, environmentally benign synthesis of novel materials, and environmental nanotechnology. He received his Ph.D. from California Institute of Technology in 1985, and his M.S. from the University of California, Los Angeles in 1981. After receiving his Ph.D., he joined the University of Cincinnati as an Assistant Professor in the Environmental Engineering Science Division in 1985. He became Full Professor in 1993. He also served as the Director of the Environmental Engineering Science Division at the University of Cincinnati for four years. In the interim, he spent a year's sabbatical at the National Institute of Standards and Technology in their Chemical Sciences and Technology Division in 1994. He joined Washington University in St. Louis in August 2000 as the Stifel and Quinette Jens Professor and Director of the Environmental Engineering Science Program. Dr. Biswas has published extensively in his field - with more than 150 refereed journal papers. He has supervised the thesis work of 20 M.S. degree students and 25 Ph.D. degree students. Several of his doctoral students are on the teaching faculty of various universities in the US and worldwide, and in research divisions in Industry and National Laboratories. He is a member of several Technical and Professional Organizations, and will become the President of the American Association for Aerosol Research in 2006. He has won several Teaching and Research Awards: was the recipient of the 1991 Kenneth Whitby Award given for outstanding contributions by the American Association for Aerosol Research; and the Neil Wandmacher Teaching Award of the College of Engineering in 1994. His current research is funded by the National Science Foundation Nanotechnology Program, Department of Energy, Department of Defense, National Institute of Health, National Institute of Environmental Health Sciences and other organizations. The focus is on nanoparticle synthesis, applications in environmental nanotechnology and nanoparticle toxicology.

Richard A. Denison, Ph.D.
Environmental Defense
Washington, DC

Dr. Richard Denison is a Senior Scientist in Environmental Defense's Environmental Health Program, working in its Washington, D.C. office. He specializes in hazard and risk assessment and management for industrial chemicals (including nanomaterials), and associated policy and regulatory issues. Dr. Denison is a member of USEPA's National

Pollution Prevention and Toxics Advisory Committee (NPPTAC), including its Workgroup on Nanotechnology, and serves on the Steering Group for Nanotechnology of the Organization for Economic Cooperation and Development (OECD).

Dr. Denison monitors and manages Environmental Defense's participation in the U.S. High Production Volume (HPV) Chemical Challenge Program, initiated by Environmental Defense, EPA 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 in proceedings of the Chemicals Committee and the Existing Chemicals Task Force of the OECD that pertain to its HPV SIDS Initiative and related matters. He has authored several papers and reports, and is active in a variety of activities pertaining to nanomaterials and chemicals regulation and policy at the federal and state levels and internationally.

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 in the Oceans and Environment Program, Office of Technology Assessment, United States Congress.

Rebecca D. Klaper, Ph.D.
Great Lakes WATER Institute
University of Wisconsin-Milwaukee
Milwaukee, WI

Dr. Rebecca Klaper received her Ph.D. in Ecology from the Institute of Ecology, University of Georgia. She is currently a Shaw Scientist at the Great Lakes WATER Institute, an organization dedicated to providing basic and applied research to inform policy decisions involving our freshwater resources. Dr. Klaper studies the potential impact of emerging contaminants, such as nanoparticles and pharmaceuticals, on aquatic organisms using traditional toxicology methods as well as investigations using genomic technologies. Dr. Klaper has served as an American Association for the Advancement of Science-Science and Technology Policy Fellow where she worked in the National Center for Environmental Assessment at the US Environmental Protection Agency. She has served as an invited scientific expert to the Organization for Economic and Cooperative Development panel on nanotechnology where she testified on the potential impact of nanoparticles on the environment. She also was involved in writing the EPA White Paper on the use of genomic technologies in risk assessment. She belongs to several scientific societies including the Ecological Society of America, The Society for Environmental Toxicology and Chemistry and the American Fisheries Society.

Igor Linkov, Ph.D.
Cambridge Environmental, Inc.
Cambridge, MA

Dr. Igor Linkov is a Senior Scientist at Cambridge Environmental Inc. in Cambridge, MA and an Adjunct Professor of Engineering and Public Policy at Carnegie Mellon University in Pittsburgh, PA. Dr. Linkov has a BS and MSc in Physics and Mathematics (Polytechnic Institute, Russia) and a Ph.D. in Environmental, Occupational and Radiation Health (University of Pittsburgh). He completed his postdoctoral training in Biostatistics, Toxicology and Risk Assessment at Harvard University. Dr. Linkov's research in the area of emergent materials and technologies, ecological and human health risk assessment, and decision analysis has been supported by the U.S. Department of Defense, NOAA, DOE, and EPA, as well as by multiple private clients. For DOD, Dr. Linkov is organizing a workshop that focuses on recent advances in nanotechnology that may have environmental implications, both beneficial and detrimental. Dr. Linkov is developing decision support tools to prioritize resource allocation and technology gaps in several military programs. He conducts ecological and human health risk assessments for both government and industry. Many of his projects implement advanced modeling techniques such as probabilistic assessment and spatially explicit analysis. Dr. Linkov has organized more than dozen national and international conferences and continuing education workshops. He has published widely on environmental policy, environmental modeling, and risk analysis, including seven books and over 80 peer-reviewed papers and book chapters. Dr. Linkov serves as a Scientific Advisor to the Toxic Use Reduction Institute, a position that requires nomination by the Governor of Massachusetts. Dr. Linkov is the Founding Chair of the SRA Decision Analysis and Risk Specialty Group. Dr. Linkov is Past President for the Society for Risk Analysis-New England. He is also Past Chair of the SRA Ecological Risk Assessment Specialty Group and participates in several SRA and Society of Environmental Toxicology and Chemistry (SETAC) Committees. Dr. Linkov is the recipient of the prestigious 2005 SRA Chauncey Starr Award for exceptional contribution to Risk Analysis. Dr. Linkov has served on many review and advisory panels for U.S. and international agencies.

Andrew D. Maynard, Ph.D.
Project on Emerging Nanotechnologies,
Woodrow Wilson International Center for Scholars
Washington, DC

Dr. Andrew Maynard is the Chief Science Advisor to the Project on Emerging Nanotechnologies, at the Woodrow Wilson International Center for Scholars. He received his Ph.D. in ultrafine aerosol analysis at the University of Cambridge in the United Kingdom (UK), and has since led research into the potential health risks of nanometer-scale particles in the UK (working for the Health and Safety Executive) and the US (with the National Institute for Occupational Safety and Health), where he was instrumental in developing NIOSH's nanotechnology research program. Dr. Maynard was a member of the U.S. government's Nanomaterial Science, Engineering and

Technology subcommittee of the National Science and Technology Council (NSET), and co-chaired the Nanotechnology Health and Environment Implications (NEHI) working group of NSET. He has also chaired the ISO working group addressing occupational aerosol characterization, and has been responsible for organizing a number of international meetings and conferences addressing nanosized particles and health impact. Dr. Maynard has published over 40 papers on various aspects of aerosol characterization and health impact, holds honorary positions at the University of Cincinnati and University of Aberdeen (UK), and is a regular international speaker on nanotechnology. His current work is focused on enabling sustainable nanotechnology through addressing potential risks at an early stage.

Vladimir Murashov, Ph.D.
National Institute for Occupational Safety and Health
Washington, DC

Dr. Vladimir Murashov is a Special Assistant to the Director of the National Institute for Occupational Safety and Health (NIOSH) in the U.S. Department of Health and Human Services (HHS) providing scientific expertise in the area of nanotechnology and other emerging technologies to the Office of the Director. Prior to his appointment as Special Assistant on Nanotechnology, Dr. Murashov served as a Senior Scientist in the Office of the Director, NIOSH from 2003-2005. Dr. Murashov received his Ph.D. in Chemistry from Dalhousie University in Halifax, Canada in 1998. His scientific work encompasses broad range of experimental and computational studies on complex functional materials. He joined NIOSH as a Senior Service Fellow to conduct computational chemistry studies of molecular dynamics and reactions on mineral surfaces in 2001. Dr. Murashov became an active member of the Nanoscale Science, Engineering and Technology Subcommittee of the National Science and Technology Council's (NSTC) Committee on Technology and Nanotechnology, Environmental and Health Implication working group representing NIOSH in 2004. He also represents NIOSH in the Toxics and Risk Subcommittee of the NSTC's Committee on Environment and Natural Resources. He is a member of the U.S. Technical Advisory Group to the International Organization for Standardization (ISO) Technical Committee on Nanotechnology.

Stephen S. Olin, Ph.D.
ILSI Research Foundation
Washington, DC

Dr. Stephen Olin is Deputy Director of the International Life Sciences Institute (ILSI) Research Foundation. Since 1990 he has worked in the ILSI Research Foundation's Risk Science Institute (RSI) to advance and improve the scientific basis and methods of risk assessment.

At ILSI Dr. Olin has organized and convened many expert panels, working groups, workshops, and conferences and has prepared or edited the proceedings and related

publications. Topics have included the assessment of children's health risks, cancer risk assessment, exposure assessment, and risks from exposure to fibers and particulates. He organized the ILSI RF/RSI workshop that produced the report, "The Relevance of the Rat Lung Response to Particle Overload for Human Risk Assessment" (*Inhalation Toxicology* 12(1-2):1-148 (2000)). He also participated in the ILSI RF/RSI Nanomaterial Toxicity Screening Working Group that produced "Principles for characterizing the potential health effects from exposure to nanomaterials: elements of a screening strategy" (*Particle and Fibre Toxicology* 2005 2:8). He was an invited observer at the OECD Workshop on the Safety of Nanomaterials in Washington, DC, December 2005.

Dr. Olin has participated in approximately 40 expert working groups convened by the International Agency for Research on Cancer (the IARC Monograph Program) since 1984. These have included several monographs evaluating the carcinogenic potential of natural and man-made fibers and particulates. He is also a member of the Steering Committee for the International Programme on Chemical Safety's initiative on harmonization of risk assessment methodologies.

Prior to joining ILSI RF/RSI in 1990, Dr. Olin was director of health sciences and laboratories at Tracor Technology Resources, where he worked for 16 years in the fields of chemical carcinogenesis, toxicology, and environmental chemistry. He was previously on the faculty in the Department of Chemistry at the University of Maryland. Dr. Olin holds a Ph.D. in Organic Chemistry from Columbia University and a B.S. in Chemistry from Purdue University.

Jennifer Sass, Ph.D.
Natural Resources Defense Council
Washington, DC

Dr. Jennifer Sass is a Senior Scientist in NRDC's Health and Environment Program and serves as Director of the Scientific Integrity Project, which oversees U.S. government regulations of industrial chemicals and pesticides. She has published over two dozen articles in scientific journals related to scientific integrity and regulation of toxics. Over her five years with NRDC, Jennifer has provided written and oral testimony on numerous occasions to the Environmental Protection Agency and National Academies of Science, as well as served on several Federal scientific and stakeholder committees and working groups. Dr. Sass serves on several US federal scientific and stakeholder committees related to nanotechnology, including: 1) the National Toxicology Program Nanotechnology Working Group, NIEHS (2005 to present), and 2) the EPA Interim Ad-Hoc Work Group on Nanoscale Materials, National Pollution Prevention and Toxics Advisory Committee (NPPTAC) (July-October, 2005). Dr. Sass has also submitted written comments on the EPA White Paper on Nanotechnology (EPA-HQ-ORD-2005-0504 January, 2006), and the EPA Proposal to Regulate Nanomaterials Through a Voluntary Pilot Program (OPPT-2004-0122. July, 2005).

Dr. Sass has published articles on the risks of nanotechnologies, and need for regulations: 1) Sass et al, (2006) Nanotechnologies: The promise and the perils. Sustainable Development Law & Policy (SDLP) journal, 2) Sass, J (2006) No small problem: It's high time for the United States to get nanotech regulations - and it needs to get them right. Bull Atom Sci, Mar/April; 62(2): 21-22.

Donald A. Tomalia, Ph.D.
Dendritic Nanotechnologies, Inc.
Central Michigan University
Mt. Pleasant, MI

Dr. Donald Tomalia received his B.A. in chemistry from the University of Michigan and while at The Dow Chemical Company (1962-1990) completed his Ph.D. in physical-organic chemistry from Michigan State University (1968). His discovery of the cationic polymerization of 2-oxazolines led to two international industrial research awards (R&D – 100) for creative research in 1978 and 1986. His discovery of dendrimers (dendritic architecture) in 1979 led to a third R&D –100 Award in 1991 and the Leonardo da Vinci Award (Paris, France) in 1996. He recently received the Society of Polymer Science Japan (SPSJ) Award for Outstanding Achievement in Polymer Science (2003) for discovery of the fourth major macromolecular architectural class, *dendritic polymers*.

In 1990, he joined the Michigan Molecular Institute (MMI) as Professor and Director of Nanoscale Chemistry & Architecture (1990-99). Dendritech, Inc., the first commercial producer of dendrimers, was co-founded by Tomalia in 1992 after which he was named founding President and Chief Scientist (1992-2000). He became V.P. of Technology for MMI (1998-2000) while simultaneously serving as Scientific Director for the Biologic Nanotechnology Center, University Michigan Medical School (1998-2000).

Dr. Tomalia founded Dendritic Nanotechnologies, Inc. (DNT), Mt. Pleasant, Michigan, in a joint venture with Starpharma Pooled Development (Melbourne, Australia) (2002) and presently serves as President and C.T.O. of this dendrimer-based nanotechnology company with production and laboratory facilities located at Central Michigan University, Mt. Pleasant, Michigan. Tomalia was recently appointed scientific director of the National Dendrimer & Nanotechnology Center located on the Central Michigan Campus (2004) and is the DNT Principal Investigator in the Massachusetts Institute of Technology/Institute for Soldier Nanotechnologies (MIT/ISN) (2003--). Other positions currently held by Tomalia include *Distinguished Visiting Professor* (Columbia University, Department of Chemistry) and *Distinguished Research Scientist*/*Professor* (Central Michigan University, Department of Chemistry).

Dr. Tomalia is listed as the inventor of over 110 U.S. patents and is author/coauthor of more than 210 peer reviewed publications. Over 170 papers are focused in the dendrimer/dendritic polymer field, including a monograph entitled "*Dendrimers and Other Dendritic Polymers"* (J. Wiley) co-edited with J.M.J. Fréchet (2001). Dr. Tomalia

serves on the editorial advisory board of *Bioconjugate Chemistry* (1999-) and is a founding member of the editorial advisory board for *NanoLetters* (2000-2004).

Nigel J. Walker Ph.D.
National Institute of Environmental Health Sciences
National Institutes of Health
Research Triangle Park, NC

Dr. Nigel Walker is a staff scientist in the Toxicology Operations Branch of the Environmental Toxicology Program at the National Institute of Environmental Health Sciences (NIEHS), one of the National Institutes of Health. He received his B.Sc. in Biochemistry in England from the University of Bath in 1987 and his Ph.D. in Biochemistry from the University of Liverpool in 1993. Following postdoctoral training in environmental toxicology at the Johns Hopkins School of Hygiene and Public Health in Baltimore MD, he moved to the NIEHS, where he has been since 1995. Dr Walker has over 10 years expertise in environmental molecular toxicology, quantitative dose response modeling and risk analysis, with particular emphasis on persistent organic pollutants. He has over 80 publications in this area, and has given numerous invited presentations at national and international workshops and symposia. Dr. Walker currently is the lead scientist for the U.S. Department of Health and Human Services' National Toxicology Program's (NTP) evaluation of the safety of engineered nanoscale materials. He is an adjunct assistant professor in the Curriculum in Toxicology at the University of North Carolina at Chapel Hill and is currently outgoing Past-President of the North Carolina Society of Toxicology.

David B. Warheit, Ph.D.
DuPont Haskell Laboratory
Newark, DE

Dr. David Warheit graduated from the University of Michigan in Ann Arbor with a BA in Psychology. He received his Ph.D. in Physiology from Wayne State University School of Medicine in Detroit. Subsequently, he was awarded an NIH Postdoctoral Fellowship, and 2 years later, a Parker Francis Pulmonary Fellowship, both of which he took to NIEHS to study mechanisms of asbestos-related lung disease. In 1984, he moved to DuPont Haskell Laboratory to develop a pulmonary toxicology research laboratory. Dr. Warheit's major research interests are pulmonary toxicological mechanisms and corresponding risk related to inhaled particulates, fibers, and nanomaterials. He is the author/co-author of more than 100 publications and has been the recipient of the ILSI Kenneth Morgareidge Award (1993 - Hannover, Germany) for contributions in Toxicology by a Young Investigator, and the Robert A. Scala Award and Lectureship in Toxicology (2000). He has also attained Diplomat status of the Academy of Toxicological Sciences (2000) and the American Board of Toxicology (1988). He has served and currently serves on NIH review committees (NIH SBIR, NIH Bioengineering) and has participated on working groups at IARC, ECETOC, ILSI RSI and ILSI-HESI and

the National Academy of Sciences, as well as several journal editorial boards. (including current Associate Editor – Inhalation Toxicology and Toxicological Sciences). Currently he is the chairman of the ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) Task force on "Health and Environmental Safety of Nanomaterials", and serves on the NIOSH Board of Scientific Counselors and National Toxicology Program - Nano Working Group.

APPENDIX B
LIST OF OBSERVERS

List of Observers

Name	Organization
James Alwood	EPA/OPPT
Rochelle Araujo	EPA/ORD
Daniel Axelrad	EPA/OPEI
Ambika Bathija	EPA/OW
Raanan Bloom	FDA
Michael Brody	EPA/OCFO
Lynn L. Bergeson	Bergeson & Campbell, P.C.
Richard Canady	FDA
Pat Casano	GE Corporate Environmental Programs
Flora Chow	EPA/OPPT
Andrea DeCenzo	EPA
John DiLoreto	NanoReg
Jeremiah Duncan	EPA Science Policy Fellow
Julie Fitzpatrick	ILSI Research Foundation
Thomas Fontaine	EPA/ORD
Elisabeth Freed	EPA/OECA
Kathryn Gallagher	EPA/ORD
Hend Galal-Gorchev	EPA/OW
Jonathan Gledhill	Policy Navigation Group
Brian Gober	EPA/OAR
George Gray	EPA/ORD
Noel Guardala	NSWCCD
Tala Henry	EPA/OPPT
I. Sam Higuchi	NASA
Colette Hodes	EPA/OPPT
Chris Hornback	National Association of Clean Water Agencies
Joe Jarvis	EPA/ORD
Barb Karn	Wilson Carter/EPA
Nagu Keshava	EPA/ORD
George Kimbrell	International Center for Technology Assessment
Maria Cristina Manzoni	European Commission Delegation to the USA
Jeff Morris	EPA/ORD
Kristy Morrison	American Chemistry Council
Sean Murdock	Nano Business Alliance
Thomas Myers	U.S. Chamber of Commerce
Canice Nolan	European Commission Delegation to the USA
Onyemaechi Nweke	EPA/OPEI
Marti Otto	EPA/OSWER

Larry Pearl	Pesticide and Toxic Chemical News
Michael Peterson	Intertox, Inc.
Pat Phibbs	BNA, Inc
Scott Prothero	EPA/OPPT
Nancy Rachman	Food Products Association
Jim Rollins	Policy Navigation Group
Joshua Saltzman	CropLife America
Phil Sayre	EPA/OPPT
John Scalera	EPA/OEI
Scott Sirchio	NSWCCD
Scott Slaughter	Center for Regulatory Effectiveness
Ahson Wardak	ENVIRON International Corporation
Jim Willis	EPA/OPPT
Elizabeth Wonkovich	EPA

APPENDIX C
CHARGE QUESTIONS

Charge Questions

A. Is the paper written in a clear, concise, and readable manner? If not, please provide comments.

B. Do the issues identified adequately address the breadth of potential science and research issues related to nanotechnology. If not, please identify additional issues that you believe should be addressed.

C. Does the Nanotechnology White Paper strike an appropriate balance between its discussion of benefits and risks? If not, what would improve that balance?

D. Are there additional studies or other information that should be included in this document? If so, please cite or identify that information.

E. Do the identified research needs adequately address gaps knowledge about nanotechnology and the environment? Please specify any additional research gaps that you think should be identified.

F. Is this document useful for explaining to stakeholders Agency plans for conducting scientific activities related to nanotechnology? If not, why not?

APPENDIX D
AGENDA

United States
Environmental Protection Agency

Panel Peer Review of the "Nanotechnology White Paper External Review Draft"

Marriott at Metro Center
775 12th Street NW
Washington, DC 20005

Agenda

WEDNESDAY, APRIL 19, 2006

8:30AM	**Registration Begins**
9:00AM	**Welcome, Goals of Meeting, and Introductions** David Bottimore, Versar, Inc.
9:20AM	**Welcome** Dr. George Gray, Science Advisor to the Administrator U.S. Environmental Protection Agency
9:25AM	**Chair's Introduction and Review of Charge** Dr. Donald Tomalia, Chair
9:35AM	**Background on "Nanotechnology White Paper"** Jeff Morris and Jim Willis, Co-chairs, Nanotechnology White Paper Workgroup U.S. Environmental Protection Agency
10:00AM	**Reviewer Roundtable of Overview Comments** Dr. Donald Tomalia, Chair
10:30AM	Break
10:45AM	**Charge Question A: Is the paper written in a clear, concise, and readable manner?**
11:45AM	Lunch
1:00PM	**Charge Question B: Do the issues identified adequately address the breadth of potential science and research issues related to nanotechnology?**
2:00PM	**Charge Question C: Does the Nanotechnology White Paper strike an appropriate balance between its discussion of benefits and risks?**
3:15PM	Break
3:30PM	**Charge Question D: Are there additional studies or other information that should be included in this document?**
4:45PM	**Recap of Comments**
5:00PM	Adjourn for the Day

United States
Environmental Protection Agency

Panel Peer Review of the "Nanotechnology White Paper External Review Draft"

Marriott at Metro Center
775 12th Street NW
Washington, DC 20005

Agenda

THURSDAY, APRIL 20, 2006

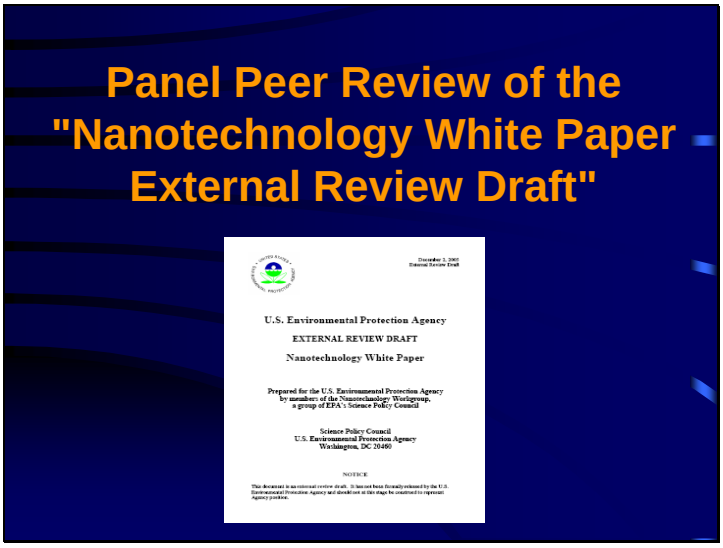
9:00AM	**Reconvene and Overview of Day Two** David Bottimore, Versar, Inc.
9:15AM	**Charge Question E: Do the identified research needs adequately address gaps in the knowledge about nanotechnology and the environment?**
10:30AM	Break
10:45AM	**Charge Question F: Is this document useful for explaining to stakeholders Agency plans for conducting scientific activities related to nanotechnology?**
11:30AM	Lunch
12:30PM	**Observer Comment Period**
3:30PM	Break
3:45PM	**Summary of Recommendations** Dr. Donald Tomalia, Chair
5:00PM	Adjourn

APPENDIX E
POWER POINT PRESENTATIONS

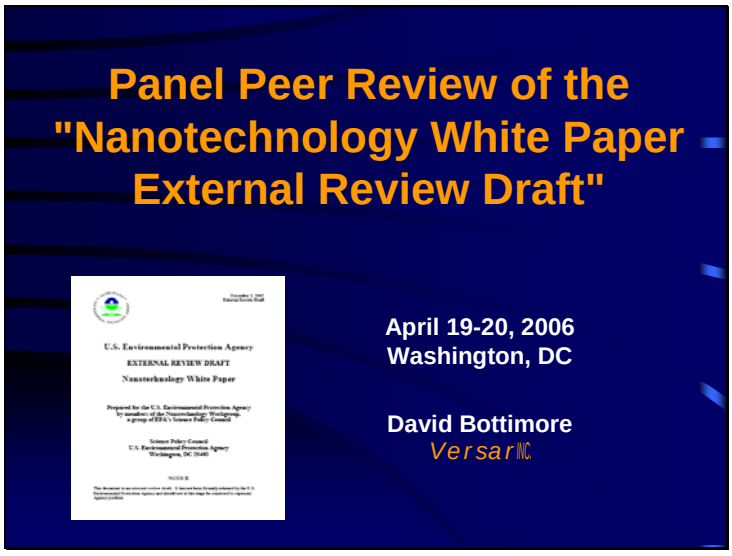
Power Point Presentations

Introduction by David Bottimore, Versar, Inc.

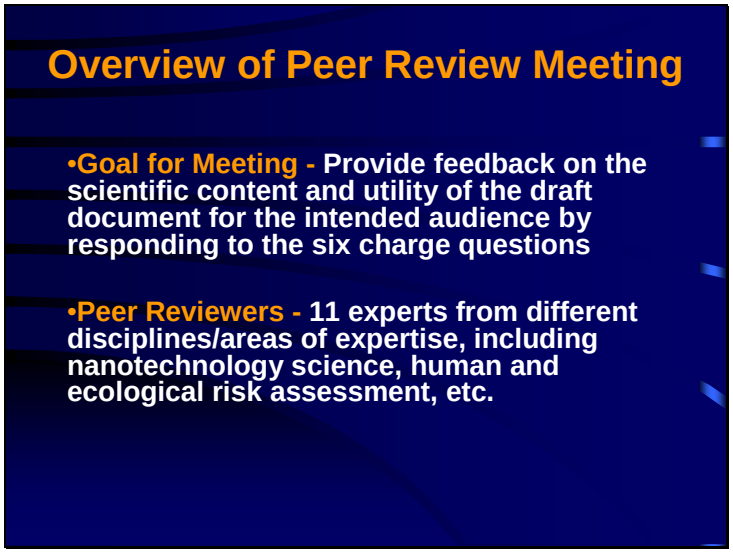
Slide 1



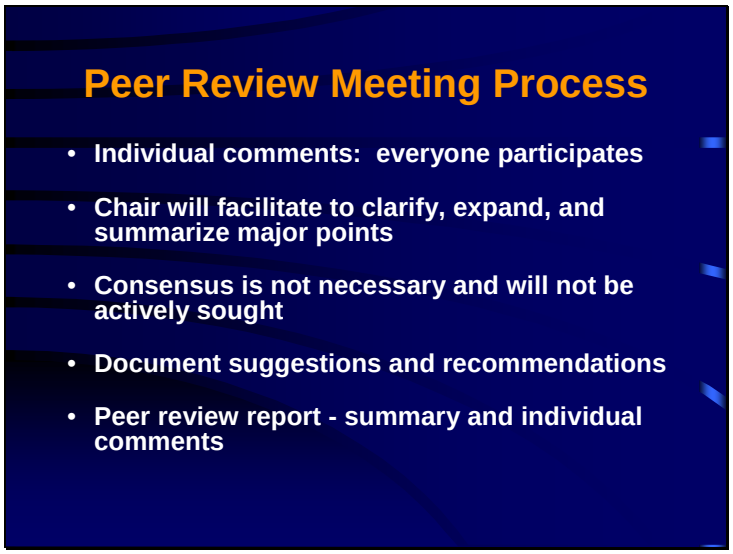
Slide 2



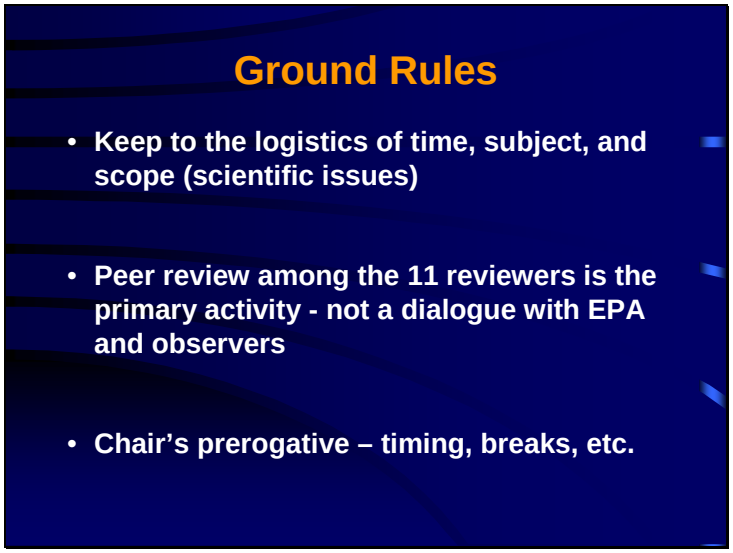
Slide 3



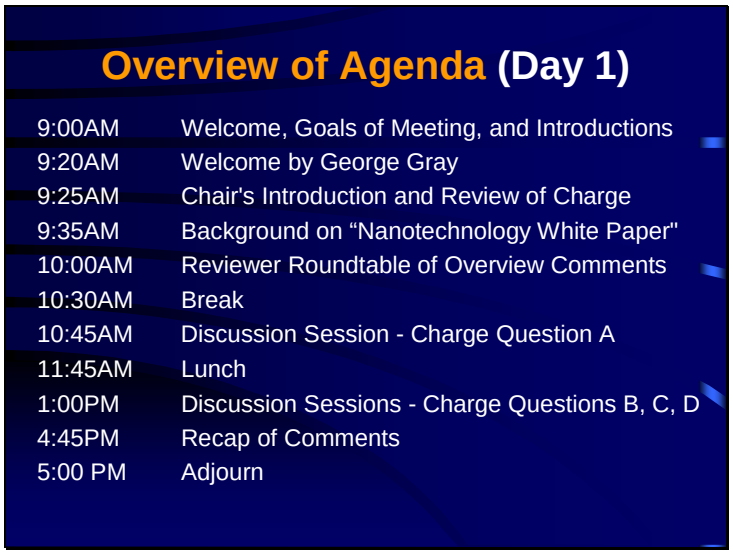
Slide 4



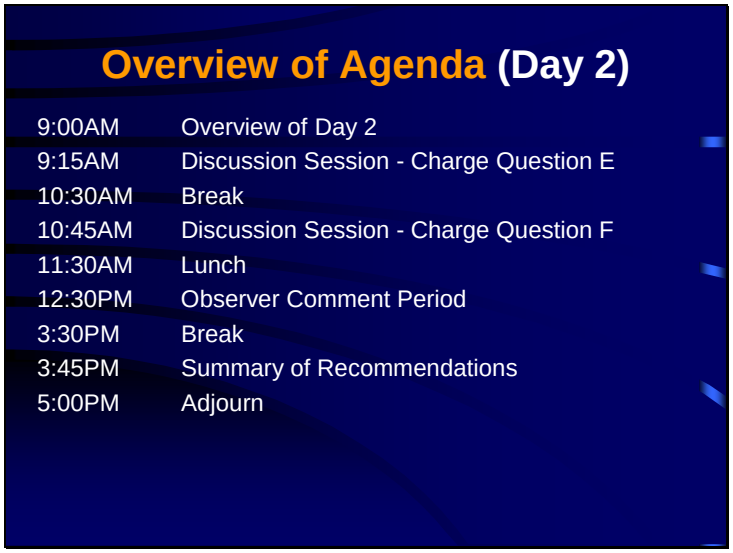
Slide 5



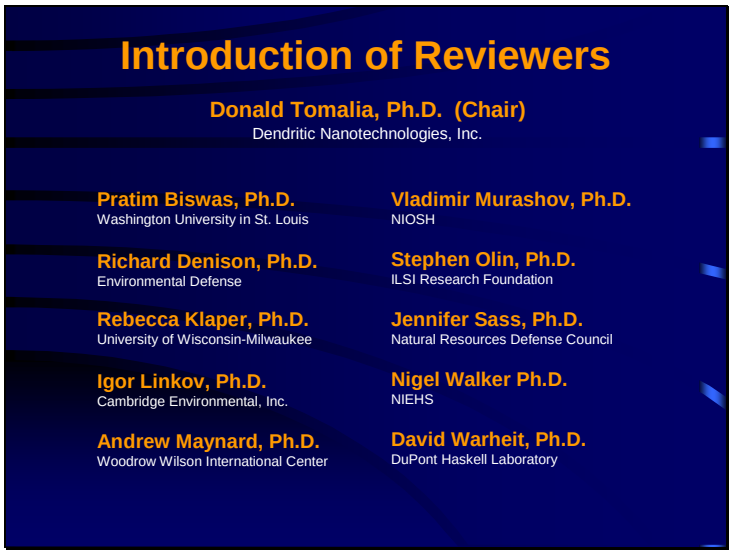
Slide 6



Slide 7

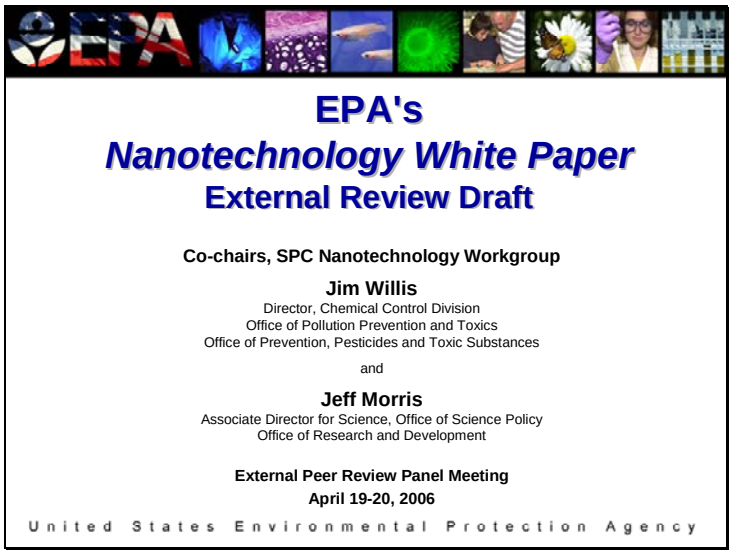


Slide 8



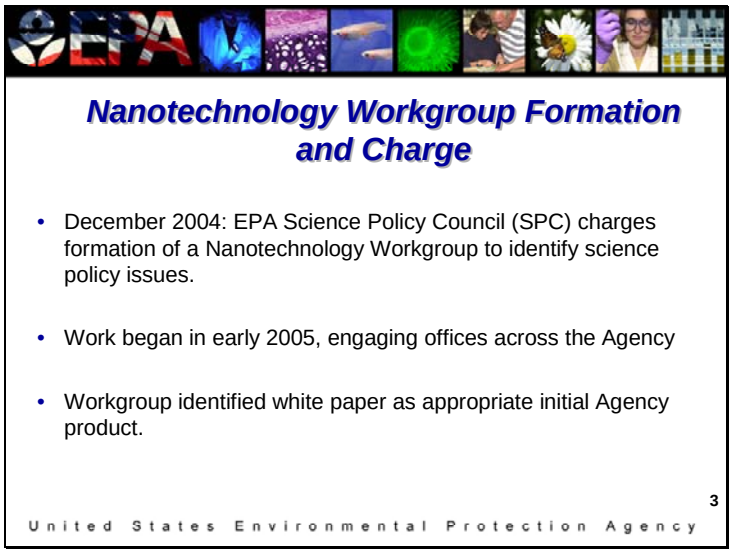
Introduction by Authors
Jim Willis, EPA OPPT, and Jeff Morris, EPA ORD

Slide 1



Slide 2

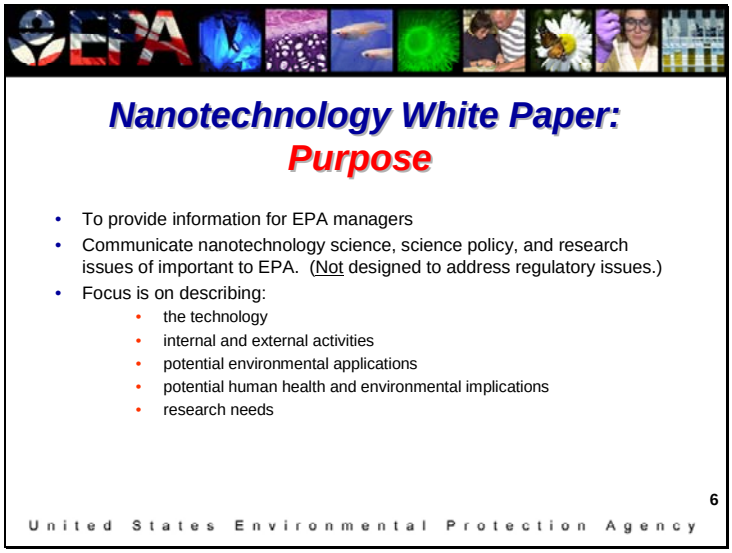
Slide 3



Slide 4

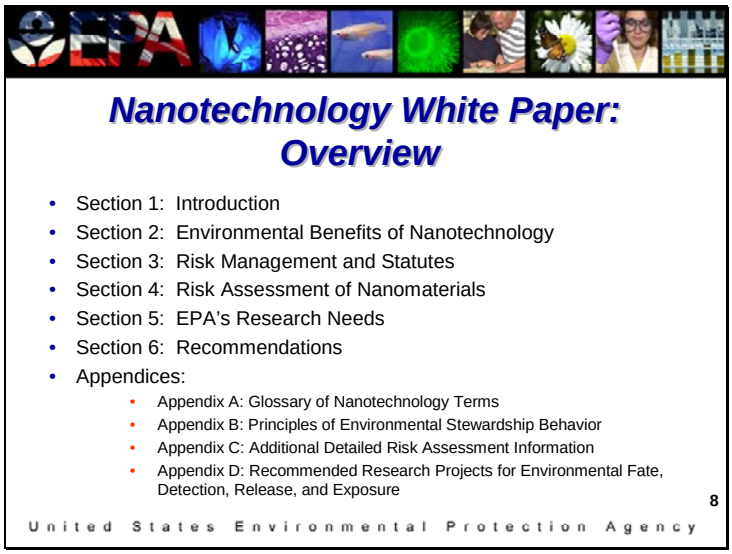
Slide 5

Slide 6



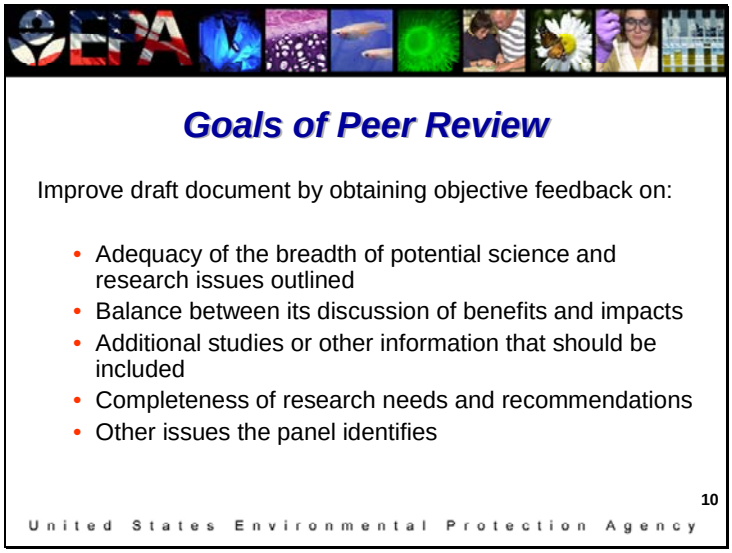
Slide 7

Slide 8



Slide 9

Slide 10



APPENDIX F
WRITTEN COMMENTS FROM REVIEWERS

Written Comments from Reviewers

Panel Peer Review of the *Nanotechnology White Paper External Review Draft*

Prepared for:
U.S. Environmental Protection Agency
Office of Research and Development (ORD)
Office of the Science Advisor
1300 Pennsylvania Avenue, N.W.
Washington, DC 20004

Prepared by:
Versar, Inc.
6850 Versar Center
Springfield, VA 22151

Contract No. C68-C02-061
Task Order 125

Reviewers:
Pratim Biswas, Ph.D.
Richard A. Denison, Ph.D.
Rebecca D. Klaper, Ph.D.
Igor Linkov, Ph.D.
Andrew D. Maynard, Ph.D.
Vladimir V. Murashov, Ph.D.
Stephen S. Olin, Ph.D.
Jennifer B. Sass, Ph.D.
Donald A. Tomalia, Ph.D.
Nigel J. Walker, Ph.D.
David B. Warheit, Ph.D

PEER REVIEWERS

Pratim Biswas, Ph.D.
Departments of Chemical and Civil Engineering
Washington University in St. Louis
St. Louis, MO

Richard A. Denison, Ph.D.
Environmental Defense
Washington, DC

Rebecca D. Klaper, Ph.D.
Great Lakes Water Institute
University of Wisconsin, Milwaukee
Milwaukee, WI

Igor Linkov, Ph.D.
Cambridge Environmental Inc.
Cambridge, MA

Andrew D. Maynard, Ph.D.
Project on Emerging Nanotechnologies
Woodrow Wilson International Center for Scholars
Washington, D.C.

Vladimir V. Murashov, Ph.D.
National Institute for Occupational Safety and Health
Washington, DC

Stephen S. Olin, Ph.D.
International Life Sciences Institute (ILSI) Research Foundation
Washington, DC

Jennifer B. Sass, Ph.D.
Natural Resources Defense Council
Washington, DC,

Donald A. Tomalia, Ph.D.
Dendritic Nanotechnologies, Inc.
Mt. Pleasant, MI

Nigel J. Walker, Ph.D.
National Institutes of Health
Department of Health and Human Services
Research Triangle Park, NC

David B. Warheit, Ph.D
DuPont Haskell Laboratory
Newark, DE

CHARGE TO THE PEER REVIEWERS

A. Is the paper written in a clear, concise, and readable manner? If not, please provide comments.

B. Do the issues identified adequately address the breadth of potential science and research issues related to nanotechnology. If not, please identify additional issues that you believe should be addressed.

C. Does the Nanotechnology White Paper strike an appropriate balance between its discussion of benefits and risks? If not, what would improve that balance?

D. Are there additional studies or other information that should be included in this document? If so, please cite or identify that information.

E. Do the identified research needs adequately address gaps knowledge about nanotechnology and the environment? Please specify any additional research gaps that you think should be identified.

F. Is this document useful for explaining to stakeholders Agency plans for conducting scientific activities related to nanotechnology? If not, why not?

GENERAL COMMENTS

Pratim Biswas

The White paper focuses on providing a review of research needs for environmental applications and implications of nanotechnology. It also provides recommendations for addressing research needs, science and policy issues. The definition of "nanotechnology" used in the report does not include unintentionally produced nanomaterials or nanosized particles that occur in the environment. Overall the report is well written, and provides a comprehensive view of a rather broad technology area. However, it would have been good to indicate who this report was directed to – presumably stakeholders (but who are they?). The report contents are presented with clarity. Some application areas and products are left out – e.g., the list of intentionally produced nanomaterials may not be the most complete. There is limited description of interaction of intentionally produced nanomaterials with unintentionally produced nanomaterials and nanoparticles. More emphasis on EPA's own efforts on nanotechnology should have been highlighted (for example, in green chemistry and work done in the sustainable technology division). Also, there should have been more emphasis on the manufacturing processes and relationship of environmental impacts to nanomaterials, so that proactive development of the field of nanotechnology could proceed. The report could have provided a somewhat greater emphasis on environmental technology applications, including nanoparticle emissions being prevented and converted to useful nanomaterials. A key shortcoming is a compiled list of potential stakeholders, and how EPA would interact with them. Interactions with industry are also not adequately highlighted. The report is not complete in outlining the efforts within EPA – an Appendix should be added that outlines nanotechnology efforts (research, policy, extramural) at USEPA; and include a level of current funding. The report is however sound on an overall basis, and the conclusions reported are adequate.

Richard A. Denison

The White Paper represents a very good effort to identify cross-agency science policy and research needs in an area that is complex and rapidly evolving. Most key aspects of the current science and the additional research needed to inform decision-making by various offices of EPA are included. EPA is to be commended for forthrightly acknowledging the major gaps in available information that need to be filled if it is to fulfill its mission, and for taking a proactive approach to identifying and seeking to address the critical needs.

While its intended audience appears primarily to be an internal one – EPA managers and staff – the paper has obvious utility to a range of interested stakeholders, and needs to be placed in this broader context as a step toward developing and implementing the Agency's overall strategies for realizing the potential beneficial environmental applications, and addressing the potential adverse consequences, of nanotechnology. In this latter regard, the paper does not do a very good job of indicating how it fits into a

larger process of informing the Agency's future actions – not only in conducting or facilitating research, but in applying its expertise and authority to assess and address potential benefits and risks. In places (see specifics below), it also overpromises, suggesting that its scope is far broader than is the case, and that it provides an actual research *strategy*, which in my view it does not. This combination of contextual flaws – describing the paper as doing more of what is needed than it actually does, and failing to preview how the paper will be used to fully address the complex and difficult issues it raises – serves to create expectations in the reader that it cannot meet, as reflected in a number of the public comments received.

I believe the current scope of the paper is appropriate and that, in finalizing it, more care needs to be taken in accurately describing a) the scope and b) how the paper relates to and informs the next steps to be taken to develop and execute not only a research strategy, but the actual Agency policies and actions needed to address nanotechnology's benefits and risks.

I identify below the need for some improvements in the paper's organization and its frequently uneven treatment of analogous topics in different sections – deficiencies that, while understandable in a draft paper no doubt written by committee, need to be remedied to make it an effective vehicle for both internally and externally communicating the Agency's direction.

Rebecca D. Klaper

The U.S. EPA Nanotechnology White Paper provides a relatively good overview of nanotechnology and the aspects of nanotechnology that will be relevant to the charge of this agency. The information is presented in a clear manner addressing research needs, how nanotechnology will be integrated into the risk assessment process for the agency, and identifying the various branches of the agency that will be involved in catalyzing research, risk assessment, and management. In addition, the document highlights the many ways in which this industry may assist in bettering the environment in the future. The benefits of this field may be great but in several fields the costs of the technology should also be considered. For example, nanotechnology may save energy consumption in the end product but the energy involved in the development and production of the nanomaterials needs to be taken into consideration in energy budget calculations and calls into question the use of the word "sustainability". Risk management for the Clean Water Act in particular needs to address that many items may end up in water systems either through pollution, runoff, or by intentional introduction for environmental cleanup. Research on the risks posed by this type of pollution appears to be addressed in the risk assessment agendas. The paper correctly identifies one of the key problems in risk management will be restructuring the current chemical classification and reporting system to include aspects relevant to nanomaterials.

It is encouraging that the agency has chosen to be forward thinking in addressing this issue relatively early in progress of the technology rather than after the fact. The White Paper does an accurate job of identifying research needs and ways in which the agency

should support the development of technologies relevant to the environment. The document appears somewhat too speculative as some references appear to be needed in places. Coordination among agencies is identified but should also include FDA as these particles are also being developed for medical purposes, and as seen with other pharmaceuticals, have the strong potential for release into aquatic and terrestrial environments via this pathway.

Igor Linkov

Rapid developments in the field of nanotechnology require immediate attention to be focused on assessing environmental and health risks associated with nanomaterials, and also on making regulatory decisions to reduce these risks. EPA's white paper provides a summary of human health and ecological risks associated with nanomaterials. The strength of EPA's approach is in placing the environmental risks associated with nanomaterials in perspective by comparing them with the environmental benefits resulting from nanomaterial use. However, even though multiple sources of information were reviewed, many relevant publications were not included, partially due to the almost untrackably rapid increase in the number of relevant publications. In general, the paper presents accurate information in a concise and structured manner. Inclusion of newer or additional papers would probably not significantly change the utility or value of the paper. More importantly, the paper can be improved by adding clear guidance on how to make decisions given the large uncertainty in understanding and characterizing even basic properties of nanomaterials, let alone toxicity, fate and transport in the environment, and other important factors necessary for risk characterization. In addition, even though the paper lists and discusses environmental statues applicable to nanomaterials, a clear roadmap for developing regulatory guidance would be helpful. Value of information analysis, adaptive management, and multi-criteria decision analysis tools could provide a good foundation for both bringing together multiple information sources to assess risks associated with nanomaterials as well as for developing justifiable and transparent regulatory decisions.

Andrew D. Maynard

This white paper sets out to develop and present the Environmental Protection Agency's response to the emerging area of nanotechnology – in terms of how the technology can be used to protect the environment, and precautions that need to be taken to avoid adverse impact from the technology. The white paper is predominantly research focused – examining what is known and not known about nanotechnology and the environment, and the research that needs to be undertaken to reduce uncertainty and develop effective applications and risk management strategies. There is very little coverage of regulatory and other oversight issues, beyond a brief description of EPA authorities. Recommendations are made on how the agency should proceed to address outstanding information gaps and questions.

This is a comprehensive paper that contains a lot of information. There is little current knowledge on nanotechnology, applications and implications in the environment that

does not appear somewhere. The document is reasonably well structured, starting with an overview of nanotechnology and EPA, and sequentially addressing benefits, risk management, risk assessment, research needs and recommendations. It represents a valiant attempt to provide a lot of information, and represent the perspectives of a lot of contributors (there are 64 people listed as participating in the internal working group). However the paper falls short of presenting a concise, coherent and accessible analysis of nanotechnology and the environment. The writing is sometimes vague, repetitive and unfocused; ideas are not developed and presented convincingly and coherently; the document weaves background information, state of knowledge review and research needs/gaps together in a confusing tapestry, making it difficult to see a logical progression from critical unknowns to research recommendations. Many sections of the paper indicate a high level of scientific expertise within the writing team. However, in places the information is presented without much care (compared to levels of expectation for a peer review journal for instance), and there are clearly some subjects – aerosol science and characterization among them - where expertise seems to have been lacking. Allied to these issues, there seems to be an overly high reliance on non peer-review reports, at the expense of using an extensive peer review literature.

The paper is also clearly aimed at developing EPA's internal position on nanotechnology. This is appropriate of course. However, it leads to the document appearing very EPA-centric, and not acknowledging leadership roles within other organizations where EPA should perhaps be partnering but not leading activities. There is a danger that, if the final document is taken out of context, the conclusions drawn may lend an inappropriate bias towards nanotechnology and risk research agendas in general. This may be addressed by emphasizing the nature of the document, the limitations of the review, the importance of partnerships and areas where others will lead, and EPA will collaborate.

Finally, while the research needs identified are extensive, they are more a re-iteration of current research questions rather than a strategic and proactive analysis of future research needs. This does not negate their usefulness, and the time and effort that must have been invested in compiling them. However, they lack the coherence, refinement and foresight necessary to underpin a strategic research agenda – which is something I would hope would emerge from this document (and which is currently not present).

In conclusion, this is an impressive document that contains most of the components of a good research policy paper, but lacks the necessary coherence and focus to give it the relevance or impact that it deserves – both issues that should be correctable as part of the review process. If used solely as an internal reference for developing appropriate research strategies, I would wholeheartedly recommend it. However, in the context of a public paper with wider impact and interpretation, I feel it needs more work.

Vladimir V. Murashov

The draft white paper provides a comprehensive overview of the scientific issues and data needs for evaluating the potential human health and environmental implications and the potential environmental applications of intentionally-produced nanoparticles. The

white paper describes the potential use of nanomaterials in environmental applications such as pollution reduction and mitigation; the statutes pertaining to the regulation of new and existing substances by the Environmental Protection Agency (EPA); and research to address the data and information needs for assessing the human and environmental implications of nanomaterials along the product life cycle.

EPA should be congratulated for this very thorough work. Recognizing that there is always room for improvement, in the rest of this section, suggestions for improvements are outlined and are intended to assist EPA in achieving its goals. The document could be more valuable if EPA were to:

1. Provide a detailed analysis of the applicability of the existing regulatory framework and specific environmental statutes to the production, use, and disposal of nanoscale materials.

2. Map the collaborations at all organizational levels: intra-agency, inter-organizations and internationally; and at all levels of program planning. Specifically, at an inter-agency level, the document needs to outline how EPA plans to collaborate with NIOSH and the Occupational Safety and Health Administration (OSHA) in conducting occupationally-relevant research and during the development of nanomaterials-related programs, guidelines, and regulations pertinent to workplace safety and health. NIOSH is a primary subject matter expert agency on occupational issues, while EPA has experience with regulating new chemicals in workplace environments. It is important for these agencies to consult closely to ensure consistency as much as possible.

3. Outline a general strategy to address the many research gaps identified in this document, and work with stakeholders to develop a unified research agenda to address research gaps.

4. Stress that this document represents a snapshot of the state of knowledge and assessment at the time of writing. The document should outline the strategy for updating the document in its role to guide EPA managers in funding decisions.

5. Outline the data requirements for evaluating the potential exposures and adverse effects of nanomaterials.

6. Outline the risk management options in the interim before the research outlined in this document is completed, and any identified gaps in the risk management statutes.

7. Address risk communication with stakeholders and the public about the state of the science and uncertainties.

Stephen S. Olin

Overall, this is a reasonably well-written introduction to nanotechnology from an EPA perspective. It is written in a straightforward, clear style that quotes the literature

sparingly, illustrates points with single examples (rather than presenting all of the evidence), has little redundancy, and has placed some more detailed text in Appendix C. Probably one-third of the main text of the document is focused on research recommendations and next steps, which is appropriate given the stated purposes of the document.

The information presented on nanomaterials seems reasonably accurate (at least within my limited range of knowledge), although in a new and rapidly advancing field like nanotechnology, sections on the current state of the science (like Chapters 2 and 4) are likely to become "dated" rather quickly. Specific comments and questions are included in Sections II and III below.

In general, the conclusions reached in the document are reasonable, based on the limited data currently available. A statement at the beginning of Section 6.2 (Research Recommendations) deserves particular note: "These recommendations should be seen as a *point of departure* [my emphasis] for further Agency discussion and the possible development of an EPA research strategy for nanotechnology." This Nanotechnology White Paper is a starting point, but not more than that. My suggestion is that EPA make whatever minor modifications are necessary in this document (not getting bogged down in the details) and carry on with its efforts to develop a focused strategy to address the critical issues.

Jennifer B. Sass

Overall, the paper is very useful as survey of existing research, and somewhat useful as an overview of research needs. The presentation is clear, generally thoughtful, and supports the conclusions well. As a survey of the current state of the science, and as a list of research needs, the document is robust, and will be useful to most readers. I find no significant fault with the document as a survey of relevant research and identification of research needs, and believe that it will be a useful tool to initiate more detailed discussions of research gaps and needs.

However, the paper promises to provide recommendations for next steps for addressing science policy issues and research needs, but these are not clearly identified. With nanomaterials are already being commercialized and used in industrial processes, the need for policy recommendations is not just academic. This document reveals a rather shameful situation in that the EPA cannot claim ignorance of the potential risks and liabilities of exposure to nanomaterials for human health and ecological integrity. Yet, the paper limits itself to fundamental scientific issues, and stops short of the promised recommendations for policy. The Executive Summary promises recommendations for addressing science policy needs, but this stops short with a lengthy, albeit thoughtful, list of research needs, no clear plan on how to accomplish this research, no clear strategy for funding this research, no clear identification of the relevant statutes and authorities to regulate nanomaterials, and thus no clear policy plan for EPA to fulfill its mandate to "protect human health and safeguard the environment" (p. 1). Maybe this is too much for

one document. However, the fact that nanomaterials are being commercialized makes these questions one of considerable urgency.

Donald A. Tomalia

The U.S. Environmental Protection Agency (EPA) has completed and presented a draft manuscript entitled: "Nanotechnology White Paper" for external review. The document consists of six major focus sections. These sections deal with (1.0) introduction to nanotechnology, (2.0) proposed environmental benefits derived from nanotechnology, (3.0 and 4.0) risk management/statutes and risk assessment of nanomaterials, (5.0) EPA research needs for nano-materials and (6.0) recommendations for important issues ranging from training, external collaborations, cross-agency work group communications, risk/benefit assessments and ultimately first opinions on rational pollution prevention/environmental stewardship.

This document is lucidly presented with rational recommendations based on extensions of traditional perspectives that have proven effective for defining appropriate risk/benefit boundaries. I am especially impressed by the breadth of involvement within the EPA agency, as well as the commitment to share/collaborate and understand more deeply the critical parameters of nanotechnology characterization/assessment (i.e., the importance of size, surface chemistry, shape, etc.). Understanding these unique/critical parameters in great detail will be essential to adequately define important risk/benefit boundaries for nanomaterials that are expected to be introduced into our environment and society.

Nigel J. Walker

In general the EPA's nanotechnology White Paper is a good attempt to lay out the breadth of issues for consideration by the USEPA in its evaluation of both the benefits of nanotechnology in addressing environmental issues as well as the potential human heath risk associated with the production and use of products generated through nanotechnology. Given the scope of the issues involved, this is a daunting task and the Agency is to be commended in taking this step in addressing these issues.

The document adequately lays out the issues that the Agency needs to consider and what its regulatory authorities are relative to these issues. This is appropriate considering this is the stated goal laid out in the Foreword. However while it is clear that this document is more of an outline of the issues it could clearly be construed by the public as a strategic plan since the document also tries to lay out essentially recommendations as to how it will go about addressing these issues. In general this is where the document falls down. With respect to this aspect, it fails to adequately lay out what are the Agencies specific priorities, how priorities will be time managed, how meeting these will be coordinated, specifics steps to address these, and how resources will be either obtained or redistributed to achieve these. If the goal of the document is also to function as a strategic plan for the Agencies activities with nanotechnology over the next 3-10 years then this area needs considerably more detail and specificity.

Many parts of the document talks about what the Agency is currently doing, but these read as being organized more around the organizational structure of the EPA rather than with any reference to specific priority or need. This may reflect simply a choice in how the materials are presented in this document but could also be construed as being a result whereby activities are currently ongoing in the absence of any overriding coordination or reference to any current Agency specific goals.

Overall if this document is to serve as an initial step towards the development of EPA's strategy as to how to deal with nanotechnology then this is a good first step. If however this is meant to serve as that strategy them additional details are clearly needed.

David B. Warheit

This is a well written and very informative document. It represents a Herculean effort and an excellent first draft. The authors should be congratulated on this effort and the outstanding coordination within all of the EPA divisions. Given the paucity of data on the topic, the document represents a well balanced description of the current information and is not overly alarmist in nature.

The document could be improved by inclusion of an expanded discussion of the hazard data, including a more complete set of paragraphs on the various inhalation toxicity studies conducted in rats with carbon black particles and ultrafine TiO_2 particles (some references are listed below in response to Charge Question B). In addition, the authors should provide background and discuss the current hypotheses (dogma) on the role of particle size and surface area in producing lung inflammation and overload related effects, particularly in the rat lung. Moreover, the authors should raise the issue of species differences and indicate that the rat is a uniquely sensitive species with regard to pulmonary inflammatory and other adverse effects – in response to low solubility particle-types.

Additional areas of discussion that have been omitted in the document include the effects of surface treatments and other physicochemical particle characteristics; as well as the relevance of in vitro studies for assessing in vivo effects. Finally, the document could be substantially improved if the authors prioritized the recommendations, including timing in Chapters 5 and 6.

RESPONSE TO CHARGE QUESTIONS

Charge Question A: *Is the paper written in a clear, concise, and readable manner? If not, please provide comments.*

Pratim Biswas

Yes.

Richard A. Denison

In the foreword (and again in the Executive Summary (page 1, lines 24-28) and in the Introduction (3:27-30[1])), the scope of the paper is described as much broader than it actually is:

> This document describes the issues that EPA must address to ensure that society benefits from advances in environmental protection that nanotechnology may offer, and to understand any potential risks from environmental exposure to nanomaterials.

In fact, the paper focuses only on "science issues," specifically science policy and research needs (this scope is accurately stated elsewhere, e.g., 1:38-39). A much broader range of issues will need to be addressed to "ensure that society benefits" in the manner described. For example, the paper does not indicate how it will actually collect or facilitate the generation of needed risk-related data, how it will assess the information, what regulatory means it will use to act when information indicates significant risk, whether it views those authorities as sufficient to address nanotechnology-specific concerns or that modifications or additional authorities may be needed – in short, the paper addresses only one of a number of issue areas that will need to be addressed. This is not a criticism of the content of the paper, which tackles a critical task, but it needs to be made clear that a) the paper's scope is limited, and b) that EPA will be taking additional steps to address the remaining issues.

In a number of places, the paper provides uneven or incomplete treatment of different or analogous aspects of a given topic. For example:

- In Chapter 3, some statutes and authorities are only cursorily discussed (e.g., the Clean Water Act, 30:17-20), while others are given more thorough treatment.
- In contrast to occupational exposure, consumer exposure to nanomaterial-containing products is given only brief consideration (46:28-36); Table 4 discusses only two of the myriad types of such products already on the market, and focuses almost exclusively on releases from the direct use of products.
- Personal protective equipment (PPE) is given a reasonably thorough discussion (p. 48), while there is almost no discussion of other engineering controls used in the workplace.

[1] Dr. Denison will use this reference convention throughout for referencing passages from the White Paper: X:Y-Z, where X is the page number, Y the starting line number and Z the ending line number.

- Environmental exposure modeling, detection and measurement receive very good and thorough treatment (sections 4.3.9 and 4.4), which raises many critical unknowns as research needs. In contrast, human exposure modeling, detection and measurement are inadequately discussed, yet many of the same or analogous concerns apply in this context and should be raised here as well. (See further detail on this under Section III below.)

I found the compilation of research needs in Chapter 5 to be poorly organized, with topics often seemingly placed in the wrong section. The bulleted list approach used for some sections contrasted with the narrative text approach used in others makes the section hard to follow. Specific comments for this section are provided in Part III below.

Rebecca D. Klaper

The paper is well organized into sections relevant to the various Agency issues from benefits of nanotechnology in various areas to issues related to risk assessment and management. It is concise and readable. There are some cases where references should be added to support inferences made in the text. These are noted below in the last section of this document.

Igor Linkov

In general, the paper is well written. Addressing the following issues could further improve the presentation flow.

Executive Summary

1. The goal of the white paper is to "examine the implication and application of nanotechnology." Even though the key recommendations are well articulated in the Executive Summary, the implications and applications of nanotechnology are not summarized. A brief description focusing on uncertainties associated with current knowledge may be useful for the reader and also provide a context for understanding the key recommendations that follows.
2. It would help to add prioritization of key recommendations (see my comments in Section D below).
3. Paragraph 4 (p. 1 lines 30-40) describes the organization of the white paper. I do not think it is necessary to have it in the Executive Summary. The same text is repeated in the Introduction (p. 3 lines 32-42).

Introduction

1. The Introduction as it currently written discusses (i) the purpose of the white paper (sect 1.1), (ii) background on nanotechnology (sect. 1.2 and 1.3), (iii) initiatives related to nanotechnology in the US and abroad (1.5.1, 1.5.2, 1.5.3), and (iv) EPA research activities and needs (1.3, 1.5.4 – 1.5.7, 1.6 and 1.7). I think it would be better to move discussion of EPA research activities to Part 5.

Environmental Benefits of Nanotechnology

1. This chapter discusses benefits of nanotechnology use, such as (i) reducing the impact of existing environmental contamination and (ii) supporting sustainable development. The current title for sub-section 2.2 may be confusing, since environmental technology applications are clearly important for sustainable development discussed in sub-section 2.3. I suggest renaming section 2.2. Also, the introduction does not need to be numbered as a sub-section.

Risk Management and Statutes

1. It would be better to call this section "Risk Management."
2. I think it is natural to discuss the environmental risks of nanotechnology after discussing the environmental benefits and only then discuss issues of risk management. Therefore, I would suggest moving this section toward the end of the document.
3. If the Risk Management section were to precede the Risk Assessment section, the Risk Assessment section should include discussion of the differences in risk assessment under the different statutes listed in the Risk Management section.
4. The first paragraph on p. 24 reads like a general introduction to the whole chapter, not just for sub-section 3.1.
5. It would be good to start with discussion of the statutes related to nanomaterials and then discuss risk management issues with a specific discussion on management actions related to each statute.
6. Discussions of individual statutes should be presented in similar formats. I would suggest removing sub-sections under individual statutes because they are very small. For example, the pesticides and RCRA sections have just one sub-section, which does not make sense.
7. Subsections 3.1.1 and 3.1.2 could be combined into one subsection.
8. In general, the Risk Management section should be expanded to include discussion of how to balance environmental benefits and risks, as well as the role of multi-criteria decision analysis and value of information analysis (see my comments below).

Risk Assessment of Nanomaterials

1. As stated above, if the Risk Management section were to precede the Risk Assessment section, the Risk Assessment section should include discussion on the differences in risk assessment under the different statutes listed in Risk Management section.
2. Consistent with other parts of the document, the introduction (section 4.1) does not need to be numbered as a sub-section and should be shortened. For example, paragraph 2 is repetitive of previous sections; paragraph 3 (lines 28-29 p. 33) can be deleted.
3. Similarly, introductions in subsections 4.6 and 4.7 do not need to be numbered.
4. It would be good to add a Table summarizing what is known about the toxicology and basic chemical and physical properties (e.g., chemical composition, geometry, industrial output, solubility, likely fate and transport mechanism, known toxic properties, etc.) of several nanomaterial classes.

EPA's Research Needs for Nanomaterials

1. Consistent with other parts of the document, the introduction (section 5.1) does not need to be numbered.
2. This section is very heterogeneous and unstructured; it reads like a random list of questions. It is not clear how EPA developed these needs or which one of them is of high importance.
3. Titles should be consistent: several subsections are called research needs in specific areas, while two have general titles (5.3 and 5.6).

Recommendations

1. Consistent with other parts of the document, the introduction (section 5.1) does not need to be numbered.
2. Recommendations are very broad and unstructured. The basis for the recommendations is not clear, nor is it clear how they relate to research needs or to the risk assessment process overall.

Appendix C: Additional Detailed Risk Assessment Information

1. I believe this Appendix can be deleted. It would be good to have a comprehensive review attached to the white paper, but most of the information presented in this Appendix is already covered in the main body of the paper. Moreover, given the fast pace of nanotechnology development and the slow review process for US Government publications, any attempts to supplement this paper with a comprehensive review will be dated by the time of document release. If EPA decides to include this section, a massive number of additional papers should be added (see the attached list).

Andrew D. Maynard

The paper seems to reflect its many authors, in that it lacks focus and coherence, and in some cases clarity. Below the overall structure, there is a lack of logical progression in how information is presented and ideas developed. It is not an easy paper to read and follow, but rather one that the reader has to invest a lot of time and effort into to extract relatively little information. There are areas where information is repeated or reiterated. Discussions on research gaps are pervasive throughout the text – separating coverage of research needs from research review would be helpful.

I would suggest that the final document is edited by a single technical writer to ensure coherence, clarity, consistency and focus.

Vladimir V. Murashov

In general, the document is written in a clear, concise and readable manner. However, in several instances it lacks specificity. For example, additional detail would be beneficial in describing next steps that EPA will take in research, regulations and collaborations with stakeholders.

Stephen S. Olin

Overall, the paper is clearly written and should be understandable to the broad scientific and regulatory community. A number of specific corrections and/or clarifications are noted in III (Specific Observations) below.

Although the White Paper attempts to contrast "applications" and "implications," the two are confused and/or intermixed at times. For example, Section 6.2.1 (Research Recommendations for Environmental Applications) should focus on research to develop, validate, and implement new environmental applications of nanotechnology. Research on the implications (potential risks) of that technology should be included, along with other nanotechnologies, in Section 6.2.2 (Research Recommendations for Environmental Implications). But 3 of the 7 "bullets" in Section 6.2.1 address implications rather than applications. Intermixing of objectives seems to be seems to be present in Section 5.2 as well.

Jennifer B. Sass

The paper is written in a clear, concise, and readable manner. The EPA Nanotechnology White Paper provides a useful overview of nanotechnology, including consideration of the benefits and applications, a toxicological review of available data, and identification of myriad research needs. The Table of Contents effectively lays out a reasonable list of topics in need of discussion by EPA and other regulatory agencies.

Donald A. Tomalia

In my opinion, this document captures remarkably well the important issues involved in this complex endeavor. In general, the information is accurate, lucidly presented with a reasonably sound conclusion. Of course, as a draft version of these critical EPA perspectives, this document does contain minor typographical, errors, etc. (see charge questions Section III) and some vagueness (i.e., priorities and timelines) in the recommendation section.

Nigel J. Walker

Yes. Given the breadth of the issue the document is not written in an overly technical language and is sufficiently short as to be concise and readable.

David B. Warheit

This is a well written document which broadly covers the major human health and ecological issues related to the potential exposures to nanomaterials. The White Paper is properly (and appropriately) superficial in scope and not overly comprehensive. This description is meant to be complimentary as there is a paucity of data in the peer-reviewed literature on exposure, mammalian health effects and ecological effects related to nanoparticulate exposure. Moreover, the authors should be applauded for NOT over

interpreting the significance nanoparticle effects by extrapolating data from the bulk particle database and from the combustion-related, ultrafine particle database. Thus, this Reviewer appreciates the careful attention paid to the relevance of other datasets for understanding the effects of exposure to nanomaterials. Therefore, it is concluded that the document provides a broad-based and relatively concise discussion of the relevant issues and points out the paucity of the database.

Charge Question B: *Do the issues identified adequately address the breadth of potential science and research issues related to nanotechnology. If not, please identify additional issues that you believe should be addressed.*

Pratim Biswas

1) There should have been a clear presentation of the fact that nanoparticles are building blocks for nanotechnology applications. Hence, the fundamental study of nanoparticles is an important aspect. Such an approach is being used to develop newer nanotechnology applications – and the same approach maybe considered in developing environmental nanotechnology applications, and/or also for studying the fundamental relationships of environmental impacts of nanomaterials.

The distinction of a nanoparticle and the form in which it is used – in a system, or a matrix should also have been elucidated. Is there any relationship of the nanoparticle and the eventual system in which it is used (e.g carbon black and tires; nanozinc oxide and cosmetics, etc).

There still is some confusion in the scientific, technical and other communities of the nomenclature. For example, on page 6, what is the basis for restricting intentionally produced nanomaterials into only 4 types? Where do ceramic oxides and doped materials fit in?

2) Beneficial environmental applications of nanotechnology are not adequately discussed. The only applications in remediation and treatment are restricted to water treatment. Several studies related to air pollution and how nanostructured sorbents are being used to minimize air and other pollutants are not discussed. More importantly, the key fundamental issues that are to be used in design of nanostructured materials for a specific environmental application should be studied.

There should have been some mention of the development of catalytic processes using nanostructured materials – many applications such as capture of mercury, reduction of nitrogen oxide emissions, etc.

Cursory mention of support of other applications that promote sustainability. The impact of nanotechnology in benign energy production is significant (see for example, reference on page 83, line 35). Refer to Biswas and Wu (2005; J. Air and Waste Mgmt. Associn., vol. 55, 708-746) paper in this section.

Certain nanostructured sorbent processes can be used to prevent emission of nanoparticles – and create byproducts that are useful nanomaterials (see Biswas P., Yang G. and Zachariah M.R"In Situ Processing of Ferroelectric Materials from Lead Waste Streams by Injection of Gas Phase Titanium Precursors: Laser Induced Fluorescence and X-Ray Diffraction Measurements", Combust. Sci. Technol., vol.134, 1-6, pp. 183-200, 1998). Use of magnetic filter based systems to remove nano-iron oxide from welding

exhausts, and the subsequent use of the captured magnetic nanomaterials in many applications, is another example.

3) Studies to establish the fundamental relationship of biological (toxicological) effects of a specific nanomaterial should be determined. What are the key variables or metrics that impact biological effects? Can this fundamental knowledge then be used to synthesis nanomaterials that are functional but do not have a negative environmental or health impact? In some sense, nanotechnology is about tailor making materials – so at least theoretically, this should be possible and the approach adopted.

4) While a somewhat detailed description of risk assessment is described in Chapter 4, there are no recommendations or concise approaches proposed to evaluate risks posed by nanomaterials. What guidance is provided to a manufacturer to assess risk to a specific nanomaterial, and what will this be based upon?

Richard A. Denison

I agree with the comments of the Institute of Steel Recycling Industries that the paper pays insufficient heed to the potential effects of nanotechnology on recycling. This is symptomatic of a more general neglect of end-of-life concerns, which receive scant mention throughout the paper.

One means of remedying this, as well as providing a much more systematic approach to assessing the potential for release of nanomaterials, would be to utilize a lifecycle framework as a means of organizing or synthesizing the discussion of risks (Chapter 4) and research needs (Chapter 5), and possibly even of statutes (Chapter 3) and recommendations (Chapter 6). While the need for a lifecycle view is mentioned a few times in the paper, what is lacking is an acknowledgment that many of the risk issues raised apply at more than one point in the lifecycle of a nanomaterial, and the associated research and information needs may in part be specific to a given lifecycle stage. For example, section 4.2 on chemical identification and characterization fails to address the fact that the characterization of a nanomaterial needed to understand the risk posed by its release during manufacturing may well be insufficient to characterize a release after the material has been further processed or introduced into a product, or once that product is discarded or recycled. Likewise, the assessment of fate of nanomaterials in water will need to be tailored to the source and nature of a specific release, which could differ significantly between a manufacturing site and a landfill.

I am suggesting that a lifecycle framework could be used to methodically identify and discuss potential releases of nanomaterials and their associated risk potentials. Use of such a framework to reorganize the current text I think could make it easier to follow. At the very least, a lifecycle-based diagram, illustration or matrix should be provided that thoroughly catalogs the activities in the various stages that could result in nanomaterial releases and identifies the settings (e.g., workplace, home, municipal sewage treatment plant) and media (e.g., groundwater, ambient air) into which such releases would occur.

Accompanying text should indicate the risk factors that may be unique to a given stage or differ from one stage to another.

The paper's discussion of RCRA (31:20-38) is very cursory, focuses almost exclusively on Subtitle C, and neglects to consider a number of RCRA-relevant topics with respect to nanomaterials:

- Their presence in consumer products that will become municipal solid waste components, disposed of in landfills or incinerators;
- non-hazardous industrial wastes that may contain nanomaterials;
- construction and demolition wastes that may contain building components made using nanomaterials (e.g., paints, insulating foams and wraps, etc.);
- the potential for wastes to exhibit hazardous waste characteristics (e.g., ignitability, reactivity, toxicity – the latter from potential leaching of heavy metals such as Pb, Cd, Se and Ag known to be used in nanomaterial forms); and
- potential effects on recycling, including:
    - the potential for releases of nanomaterials from recycling operations,
    - the potential presence of nanomaterials in wastes generated by recycling,
    - the potential for exposure from secondary uses of recovered materials, e.g., used tires ground up for use as playground surfacing, and
    - the potential for nanomaterials to affect recyclability.

Rebecca D. Klaper

The paper does a good job of addressing the various aspects of science and research issues related to nanotechnology. The paper covers a great number of issues that are important regarding benefits of the technologies, interactions with various media, toxicology and risk management issues. Items that were not necessarily mentioned include :

-Missing two sections in dealing with ecological risk assessment---namely a section corresponding to exposures (to other organisms not human), and ecological monitoring. This would correspond to equivalent sections already in the document about humans.

-With regards to energy benefits from nanotech--calculations of the costs in energy to produce the nanomaterials used in the various industries versus existing materials. The costs in waste management in order to deal with the solid and chemical wastes from these technologies versus traditional technologies.

-The potential for exposure via bioaccumulation of these materials in the food web and the potential impacts of this accumulation—uptake is discussed but bioaccumulation is only mentioned in research needs and not in the other parts of the paper related to humans and ecological risk assessment.

-How particles can change properties once in the environment due to sorption, light, temperature, charges of soils/solutions around them etc.

-Identification of proper personal protective equipment for handling these particles both for industry and academic researchers (immediate need)

-Need for identification of proper disposal procedures for academic researchers and industry using these chemicals (immediate need)

Igor Linkov

The White Paper addresses the most important science and research issues related to environmental benefits and risks associated with nanotechnology. The depth and breadth of the analysis is reflective of the state of the field in mid-2005 and, given the tremendous increase in the depth of research and the number of related publications, may be dated. Nevertheless, I believe that the white paper is an important document for presenting agency positions and thought processes concerning nanotechnology. I believe that rather than trying to update the list of important issues and to better reflect the state-of-the-science today, the white paper should be revised to include an added focus on how EPA plans to make risk management decisions given the apparent uncertainty in data requirements for risk assessment. How should risk assessment procedures be modified to deal with these information gaps? How could regulatory statutes listed in the white paper be used to regulate nanomaterials? How has the Agency planned to balance environmental benefits and risks associated with specific nanomaterials? How will environmental risks be balanced against societal (not just environmental) benefits? Addressing these issues does not require chasing an ever-changing state-of-the-science in risk assessment related to nanotechnology, but rather developing a framework for making policy decisions under uncertainty with multiple lines of incomplete information available. Developing this framework – or at least reporting the collective thoughts of the Nanotechnology Workgroup members – is important for White Paper readers. Additional issues worth considering are discussed in Section D.

Andrew D. Maynard

The paper is clearly focused on EPA's statutory remit, and the agency's internal response to nanotechnology. In this respect, there are a number of acceptable biases – such as the emphasis on environmental impact. However, as the paper will read and used outside of this context, it would be helpful if the bounds of the review, analysis and recommendations were more explicitly emphasized.

I am a little concerned that much of the paper is influenced by current research and applications, with little thought appearing to go to developing applications. Thus the use of zero valence iron nanoparticles in groundwater remediation is a strong recurring theme throughout the paper – but surely the next 5 – 10 years will see much more diverse environmental uses of nanotechnology. Similarly, the categories of nanomaterials listed on page 6 seem unnecessarily restrictive (where are the organic materials, complex materials, multifunctional materials and devices etc.) – based on where nanotechnology is now, not where it is going. For research to keep pace with nanoscience and nanotechnology, research policy needs to proactively look to the future, rather than reacting to the past and present.

Vladimir V. Murashov

The issues identified by EPA to some degree address the breadth of potential science and research issues related to nanotechnology. The document should emphasize increased

collaborations with other agencies and stakeholders. For example, on page 80, section 6.4 "Recommendations for Collaborations" the document does not suggest any extension to the existing collaborations with other governmental agencies. In order to address challenges posed by nanotechnology under funding limitations, it is imperative to closely collaborate at all organizational levels and at all levels of program planning.

Stephen S. Olin

Perhaps one of the most fundamental requirements for us to develop an understanding of the environmental and human health risks of nanomaterials is the adequate characterization of their physical and chemical nature and properties. This is discussed in the Paper, but some of the critical questions are only mentioned in passing. For example, many years' experience with the intentional production and use of ultrafine TiO_2 and carbon black has shown that these nano-scale particles form tightly bound aggregates immediately during the production process and larger more loosely bound agglomerates with time, and that exposures in the workplace are to aggregates and agglomerates and not to the primary particles. A key question with any new nanomaterial must be whether exposures are mainly to bound or primary particles.

Further, it already appears very likely that mass dose will not be an adequate dose metric for nanoparticles. Until the properties that determine the biological effects of nanoparticles are better understood, it is strongly recommended that dose be characterized not only by mass but also (at least) by particle size distribution and count and by surface area. The Paper appropriately suggests this as a research area, but these data should be collected routinely in toxicology and exposure assessment studies of nanomaterials. Any surface modification of the nanoparticles (coating, charge, etc.) also must be part of the characterization of the material. In addition, because these materials can be very reactive, it is important in toxicology studies to characterize the nanoparticles as administered, rather than before dose preparation. Studies are needed that carefully follow nanoparticles from their origins through exposure, intake, *in vivo* distribution, binding and transformation, and excretion, characterizing the nanoparticles and/or their transformation products at each step. Although these are not easy studies because of the unique properties of nanomaterials, they are essential for the validation and interpretation of toxicology studies and for our understanding of potential human health risks.

Section 5.7 outlines research needs for human health effects assessment, and Section 6.2.2.2 allocates responsibilities for this research to Offices within EPA (mainly ORD). Although there is a comment about collaborating with stakeholders (and Section 6.1 talks about environmental stewardship), the Paper does not fully acknowledge the important role that the nanotechnology industry must play in the study of the potential health effects of these products. Consultation and collaboration on the design and conduct of health effects studies is essential, if the wide range of identified research needs is to be credibly and effectively addressed.

Jennifer B. Sass

There is an appropriate level of detail on the toxicological research currently available, and the survey of available literature is fairly comprehensive. The paper is fairly comprehensive in identifying general and generic research needs for new materials. Section 5.0 identifies "EPA's Research Needs for Nanomaterials", and sums up these needs in Section 6.7 as the following recommendations: 1) chemical identification and characterization, ii) environmental fate, iii) environmental detection and analysis, iv) potential releases and human exposures, v) human health effects assessment, and vii) environmental technology applications. The paper also raises many thoughtful research questions, depending on the character and application of a specific nanomaterial. For example, ADME information from wildlife that is likely to be exposed (p. 71) would be very useful information for materials released to the environment.

However, the white paper falls short in the more difficult task of identifying the nano-specific scientific and research issues, so that while the risks and benefits of nanotechnologies are adequately discussed, it is not clear why this technology is any different from other technologies. It is not clear from the White Paper why nanotechnologies are deserving of special attention and consideration. For example, while there are obvious generic research needs for any new material or technology, nowhere does EPA make clear what is slowing the collection of these important data. EPA poses numerous research questions regarding chemical identification and characterization needs, such as "are current test methods adequate to evaluate hazard and exposure?" and, "do nanomaterial characteristics vary from their pure form in the laboratory to their occurrence in the environment as components of products?" (p. 64), but does not always provide responses to these questions. While it is true that there are not easy answers, without some discussion of the nano-specific issues with these research needs, the uninformed reader is left with the impression that the research needs looks like a pretty generic list, and wonders why it is not already being done.

It would be helpful for EPA to have tackled the more difficult issues that are specific to the practical collection of health and safety data on nanomaterials, to help the reader better understand where standard toxicity tests may capture nanomaterial risks, and where they may not.

The public has the right to demand that nanomaterials undergo rigorous safety testing before being commercialized and used in industrial processes where humans may be exposed or releases into the environment may occur. If this is not being done, the public needs to know why not.

Donald A. Tomalia

The white paper proposed a variety of traditional analytical methodologies that may be used for the characterization/assessment of nanomaterials. Many subtle adaptations of these methodologies have been utilized and reported in the nearly 7,000 references

published to date on the characterization of important nanostructures such as dendrimers dating back as far as 1990.

Nigel J. Walker

The document covers a significant number of the issues that the Agency needs to address. One issue not well covered is life cycle analysis and disposal/recycling issues and integration of regulatory statues with other federal agencies that may also have some jurisdiction over a given product at some stage of its life cycle.

Nanotechnology is an all-encompassing issue that is both global in nature and yet also encompasses many startup and small businesses. How the EPA will work collectively both at the international level and at "local levels" is not clearly laid out. (E.g. dealing with large scale imported bulk nanoscale materials and products incorporating nanoscale materials versus handling niche products from small startups within the domestic market.) For example are small niche startup business fully aware of EPA regulations and their responsibilities? If not, what steps is EPA planning to take to ensure that startup businesses are aware of regulations that may cover nanomaterials production.

Given the issue of size and that non- mass based metrics may be applicable for some nanoscale materials, the sections discussing regulatory authorities do not address how the current regulations can be interpreted or implemented if a different dose metric (e.g. particle surface area) were to be used. E.g. Small particles have a substantially higher surface area per unit mass than micro scale materials.

The regulatory statutes that EPA has are well laid out but not how these will be implemented and more importantly, integrated. As written it would appear that implementation and interpretation is very much distributed across different sections of the Agency and as such there could be inconsistencies. How the Agency will ensure that different areas of the organization will be coordinated needs to be discussed. In addition there are no recommendations or research needs here.

David B. Warheit

The background section of this document accurately addresses the current data base (or lack thereof) on the exposure, health effects and environmental/ecotox effects of nanotechnology – including the limited research efforts that been published thus far. This Reviewer would have preferred an expanded discussion of the results obtained with ultrafine titanium dioxide and carbon black particles, which are not combustion-related ultrafine particles, and likely would qualify as engineered nanoparticles (despite being in commerce for many decades).

Suggested inclusions include the following:

1) Health Hazard issues – include discussion on the results of studies with carbon black and ultrafine titanium dioxide. Although there is a general paucity of data on

the effects of inhaled nanoparticles – the authors have neglected to include the "relative" wealth of information on these two engineered nano/ultrafine particle-types (suggested inclusions are the Bermudez et al. ultrafine TiO_2 studies (2002; 2004). The Elder et al. study with carbon black (2005). Both of these studies also discuss the important issue of species differences.

2) It is also suggested that EPA consider the issue of parallel tracks – particularly in the recommendation section. This might suggest that EPA conduct research on mechanistic research issues related to nanoparticle- types – using "generic nanoparticles or reference materials " to evaluate (e.g.) size ranges, toxicokinetics, surface treatments and solubility, tier testing strategies. The other track would be hazard testing provided by companies attempting to register products and could conceivably consist of a base set of toxicology data.

3) The relevance of *in vitro* studies for assessing *in vivo* toxic effects should be an important issue to EPA. Most of the studies on nanoparticles are generally of the *in vitro* variety and it is unclear whether the findings have relevance as a screen for *in vivo toxic* effects – particularly because the *in vitro* studies have not been properly validated and/or conducted under systematic or uniform conditions.

4) The section on exposure assessment should be expanded to include some of the data generated by Kulbush assessing the occupational exposures in carbon black factories. The EPA should also raise the very important issue of dose metrics for assessing exposures to nanoparticles. This would include the issue of the relevance of mass vs. particle surface area or particle numbers as the appropriate dose metric.

5) The section on dermal penetration should be expanded.

6) In addition, there are some new publications which should be used to update the data base. Some of these references are listed below:

A) Oberdorster G, Maynard A, Donaldson K, Castranova V, Fitzpatrick J, Ausman K, Carter J, Karn B, Kreyling W, Lai D, Olin S, Monteiro-Riviere N, Warheit D, Yang H; ILSI Research Foundation/Risk Science Institute Nanomaterial Toxicity Screening Working Group. Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy. Part Fibre Toxicol. 2005 Oct 6;2:8.

B) Warheit DB, Webb TR, Sayes CM, Colvin VL, Reed KL. Pulmonary Instillation Studies with Nanoscale TiO2 Rods and Dots in Rats: Toxicity Is not Dependent upon Particle Size and Surface Area. Toxicol Sci. 2006 May;91(1):227-36. Epub 2006 Feb 22.

C) Sayes CM, Wahi R, Kurian PA, Liu Y, West JL, Ausman KD, Warheit DB, Colvin VL. Correlating Nanoscale Titania Structure with Toxicity: A Cytotoxicity and Inflammatory Response Study with Human Dermal Fibroblasts and Human Lung Epithelial Cells. Toxicol Sci. 2006 Apr 12; [Epub ahead of print]

D) Warheit DB, Brock WJ, Lee KP, Webb TR, Reed KL. Comparative pulmonary toxicity inhalation and instillation studies with different TiO2

particle formulations: impact of surface treatments on particle toxicity. Toxicol Sci. 2005 Dec;88(2):514-24. Epub 2005 Sep 21.

E) Elder A, Gelein R, Finkelstein JN, Driscoll KE, Harkema J, Oberdorster G. Effects of subchronically inhaled carbon black in three species. I. Retention kinetics, lung inflammation, and histopathology. Toxicol Sci. 2005 Dec;88(2):614-29. Epub 2005 Sep 21.

F) Bermudez E, Mangum JB, Wong BA, Asgharian B, Hext PM, Warheit DB, Everitt JI. Pulmonary responses of mice, rats, and hamsters to subchronic inhalation of ultrafine titanium dioxide particles.Toxicol Sci. 2004 Feb;77(2):347-57. Epub 2003 Nov 4.

G) Bermudez E, Mangum JB, Asgharian B, Wong BA, Reverdy EE, Janszen DB, Hext PM, Warheit DB, Everitt JI. Long-term pulmonary responses of three laboratory rodent species to subchronic inhalation of pigmentary titanium dioxide particles. Toxicol Sci. 2002 Nov;70(1):86-97.

Charge Question C: *Does the Nanotechnology White Paper strike an appropriate balance between its discussion of benefits and risks? If not, what would improve that balance?*

Pratim Biswas

Somewhat. There should be more discussion of the positive benefits of nanotechnology *vis a vis* environmental applications, and how one can integrate with risk assessment studies or approaches to ensure that the proposed methodology is safe.

Richard A. Denison

Overall, a good balance is struck. However, I did at times find the discussion of potential benefits in Chapter 2 to be unclear as to the actual state of development of a given application (e.g., is it research stage only, commercially promising, or in actual use?), and the potential risks of certain applications were insufficiently discussed. For example, the discussion of the use of zero-valent iron and other nanomaterials for remediation (section 2.2.1) failed to mention the potential risks of such a dispersive use, including the potential for such nanomaterials to react with unintended substances or organisms, yield toxic by-products, escape from the target zone, etc.

Section 2.3 on the potential of nanotechnology to "green" manufacturing is very important to include. However, the word "potential" should be inserted into its heading in front of "benefits," as the advantages discussed are largely yet to be realized in actual practice. This status needs to be acknowledged in the text as well. For example, page 19, lines 18-21 and Table 1 make it appear that green manufacturing and green energy based on nanotechnology are already well-ensconced in our economy. If there are examples of actual use, they should be discussed and references provided.

Section 2.3 needs a clearer caveat added to note that whether promised or claimed benefits are actually realized requires a rigorous analysis of each specific application, including a comparison to the material/use which the nanomaterial is replacing. A good example of this need is provided in Section 2.3.4, Fuel Additives, which notes (22:41-42) that cerium oxide additives may alter diesel emissions in ways that actually increase the concentrations of specific hazardous air pollutants. Similarly, when zero-valent iron reacts with chlorinated hydrocarbons, it may form toxic byproducts like benzene and biphenyl, as is discussed in Section 4.6.7 (56:30-32).

The paper should take care not to contribute to the overhyping of the benefits of nanotechnology, which only serves to generate skepticism when the inevitable delays or setbacks occur.

Rebecca D. Klaper

The White Paper provides a detailed description on the potential benefits of nanomaterials particularly relevant to environmental applications. There are calculations

included on the potential economic benefits to the technologies but missing are some of the calculations of the potential costs of the technologies. In the first section this would pertain to the actual production of the technologies themselves. Energy and supplies are required for their production that may be greater than traditional materials. Other costs would include costs for risk assessments, costs to the environment if products are released intentionally or unintentionally that cause environmental damage, costs of cleanup technologies for any products that are released prior to proper risk assessment determinations. Granted, some of these calculations are difficult at the moment but they should at the very least be mentioned. Unmentioned benefits may be a decrease in pollution due to a greater capacity for the use of renewable energy resources from these technologies. With better sensors one potential benefit could be a reduction in water treatments for contaminants or soil applications of fertilizers etc.

Igor Linkov

The white paper primarily addresses environmental risks associated with nanomaterials. Nevertheless, I believe that the major focus on risk is justifiable given the agency's mission. Even though it is important to provide a review of environmental benefits associated with nanotechnology (and I believe the White Paper addresses this well), a bigger question is, how should we balance environmental benefits with risks associated with specific nanomaterials? Moreover, how should we balance societal (not just environmental) benefits associated with nanomaterials and environmental risks? For example, how would the benefits of a hypothetical nanomaterial that revolutionized cancer treatment be balanced against the environmental and/or occupational risks associated with its life-cycle?

Andrew D. Maynard

Although the paper addresses both risk and benefits, it is dominated by risk. This is perhaps understandable for an agency responsible for managing environmental impact. However, the discussion of benefits could be extended and strengthened considerably. Only two direct applications of nanotechnology and identified – remediation and sensors – reflecting current research interests. Surely there are other nanotechnologies that may find potential application. I would like to see a review of current research that might be applicable in this area.

The section on "other applications that support sustainability" is more comprehensive, but seems to be a bit of a catch-all, and again reflects current thinking rather than extending it.

Combining these two sections into a forward-looking critical review of where nanotechnology might be applied to improving the environment in the future would strengthen the paper significantly.

Vladimir V. Murashov

The Nanotechnology White Paper strikes an appropriate balance between its discussion of benefits and risks.

Stephen S. Olin

The question implies that there should be a balance in the Paper's treatment of potential environmental risks and benefits. It's not clear to me how one could determine what "an appropriate balance" should be. The Paper only considers potential environmental benefits (i.e., applications of nanotechnology that, in some way, may improve the environment, such as environmental remediation, green manufacturing, and green energy generation technologies). It mentions very briefly other potentially beneficial uses of nanotechnology (in Sections 1.1-1.3), but the emphasis is certainly on environmental benefits and risks. EPA argues that this is necessary because the other potential benefits are outside of EPA's mandate. I would suggest that we should, therefore, not expect that the Paper will have a balanced discussion of the potential benefits and risks of nanotechnology. I would also suggest that this point be made in the Paper, and that some appropriate references/reviews be cited (perhaps in Sections 1.1-1.3) on the potential non-environmental benefits of nanomaterials (see Table 1, p.7).

Within the narrower limits of potential environmental benefits and risks, the Paper still appears to be stronger on the risk side than on benefits. But perhaps that is to be expected since even the benefits (e.g., environmental remediation technologies, new "green chemistry" processes) also have to be considered for their potential risks.

Jennifer B. Sass

The paper is fairly comprehensive in its listing of applications that are likely to be of broad social benefit, and those that have specific environmental applications (Section 2.0). This is, I think, useful for a naïve but enthusiastic reader. The discussion of potential risks (Section 4.0) is fairly comprehensive in its survey of the available literature on toxicity testing, as well as its identification of data gaps, and the relevance of related literature such as that on ultrafine air particulates. The ability to categorize nanomaterials by their properties/size/diameter/ etc. and then begin to predict their behavior, however crudely, will be essential for developing rationale toxicity testing schemes. This section provided some useful information for beginning to develop a rationale for grouping and then testing categories of nanomaterials.

Section 4.0 serves its stated purpose, "to briefly review the state of knowledge regarding the components needed to conduct a risk assessment on nanomaterials" (p. 33), including the known and predicted risks. The section on Environmental Fate (Section 4.3) was particularly detailed and thoughtful, and covered the nano-specific considerations fairly well. References to published literature and other relevant reports were very helpful to lead the reader to obtain more detail, and ably supported the extrapolation from specific research to general statements regarding predictability. For example, the discussion of

predicted airborne behavior of nanomaterials is based on diameter, using the substantial database on fine air particulate matter as a supporting source (p. 35). Sorption of some nanoparticles to suspended soil and sediment in water is predicted from some nano-specific studies (p. 37). The section on human health effects (4.6) provides a useful overview of the literature. The Paper notes the interesting finding from multiple studies that both local (port-of-entry) and systemic toxicity is seen in whole organism exposure studies (p. 54); an important observation in the design of safety studies and the development of protective regulations.

Donald A. Tomalia

In my opinion, this first draft of the "Nanotechnology White Paper" does strike a remarkably good balance in its discussion of benefits and risks.

Nigel J. Walker

While it discusses potential benefits and risks, it provides no time scale of reference. In addition the benefits section is short relative to the rest of the documents and is somewhat vague relative to specific benefits that are near term versus which benefits may simply be hyperbole.

In addition the document does not set out how the Agency will adequately evaluate the balance of risk posed from exposures to nanoscale materials in commerce now, against touted "nanotechnology will save the world" type of intangible and unrealized benefits.

Balancing what benefits are near term/long term versus risks that are near term /long term will go a long way towards helping the agency prioritize its activities. I.e. do immediate benefits outweigh the long-term risk or do the near term risks outweigh the long-term benefits.

With respect to this, public perception of risks and the EPA's activities in this area, is an important aspect not addressed at all, since a public backlash and potential lack of adoption of nanotechnology could impact upon the Agencies approach to its risk-benefit analysis.

David B. Warheit

The Nanotechnology White Paper strikes an appropriate balance between the benefits of Nanotechnology (particularly emphasizing green energy research and manufacturing, environmental remediation, environmental detection/sensors, etc. The reported beneficial impacts of nanoparticles in scavenging ultraviolet rays in products such as paints or cosmetics (sunscreens) should also be emphasized. Issues related to nanomedicine or nanoparticles in diagnostic applications are also not emphasized but may be beyond the scope of the EPA's jurisdiction.

With regard to the risks, given the substantial publicity given to the potential hazards of nanoparticles (nanotechnology), the reader might consider this issue underplayed in this White Paper. However, this Reviewer would disagree with that assertion, given that 1) there is a genuine paucity of adequate hazard information in the peer-reviewed literature; 2) the potential hazards of ultrafine particles in the rat lung (a uniquely sensitive mammalian species) has been, with regard to health risks, overinterpreted by the scientific community because most, if not all of these effects have occurred at particle overload concentrations/doses; 3) there is virtually no data currently available on nanoparticle exposures to humans; 4) many cytotoxicity studies on nanoparticles have utilized *in vitro* methods of exposure and the relevance of these findings remains to be determined. Thus, this Reviewer believes that the EPA White Paper is properly cautious about not overemphasizing the health risks (or ecorisks) and, as a consequence, the Nanotechnology White Paper strikes an appropriate balance between its discussion of benefits and risks

Charge Question D: *Are there additional studies or other information that should be included in this document? If so, please cite or identify that information.*

Pratim Biswas

1) Nanostructured sorbents for preventing combustion emissions. E.g. Biswas P. and Zachariah M.R.: "In Situ Immobilization of Lead Species in Combustion Environments by Injection of Gas Phase Silica Sorbent Precursors", Environmental Science and Technology, vol 31(9), 2455-2463, 1997. ; Lee M.H., Cho K., Shah A.P. and Biswas P., "Nanostructured sorbents for Capture of Cadmium Species in Combustion Environments", Environ. Sci. Technol., vol 39 (21), 8481-8489, 2005; and references therein.

2) Measurement and detection of nanoparticles not adequately covered. Paragraph on page 43 is not quite accurate. There are numerous papers in the aerosol science and engineering literature. See NAST report: Emerging issues in Nanoparticle Aerosol Science and Technology, June 27-28, 2003. (http://www.nano.gov/html/res/NSFAerosolParteport.pdf)

Measurement of nanoparticles in liquids and other media should also be discussed. Quantitative detection and measurement of nanoparticles is a critical aspect for a variety of reasons.

3) The entire document is very scanty in characterization methods – such as AFM, EM (SEM and TEM), BET, Mobility sizers, Spectroscopic Methods, etc. See Table 3 in Biswas and Wu (2005; J. Air and Waste Mgmt. Associn., vol. 55, 708-746), may consider preparing a similar one, or duplicating with permission of journal.

Richard A. Denison

1. Other governments have recently undertaken similar exercises, identifying knowledge gaps and research needs in the context of their consideration of approaches to identifying and addressing the potential risks of nanomaterials. These should be cited and briefly discussed. Recent reports from the United Kingdom and the European Commission are listed below.

UK Department for Environment, Food and Rural Affairs, ***Characterising the potential risks posed by engineered nanoparticles: a first UK Government research report***, 12/30/2005, available at www.defra.gov.uk/environment/nanotech/nrcg/pdf/nanoparticles-riskreport.pdf

> Additional related scoping studies on hazard and exposure data needs are available at www.defra.gov.uk/environment/nanotech/nrcg/reports/index.htm.

UK Health and Safety Executive, ***Review of the adequacy of current regulatory regimes to secure effective regulation of nanoparticles created by nanotechnology***, March 2006,

available at www.hse.gov.uk/horizons/nanotech/regulatoryreview.pdf. (focuses on occupational risks)

European Commission, Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), ***Opinion on the appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies***, 9/29/2005, available at europa.eu.int/comm/health/ph_risk/committees/04_scenihr/docs/scenihr_o_003.pdf

2. A Forum Series published in Toxicological Sciences on Research Strategies for Safety Evaluation of Nanomaterials should be cited (abstracts available at toxsci.oxfordjournals.org/cgi/search?fulltext=nanomaterials+research+strategies&x=17&y=8)

Treye Thomas, Karluss Thomas, Nakissa Sadrieh, Nora Savage, Patricia Adair, and Robert Bronaugh, "Research Strategies for Safety Evaluation of Nanomaterials, Part VII: Evaluating Consumer Exposure to Nanoscale Materials," ***Toxicol. Sci***., May 2006; 91: 14 - 19.

Kevin W. Powers, Scott C. Brown, Vijay B. Krishna, Scott C. Wasdo, Brij M. Moudgil, and Stephen M. Roberts, "Research Strategies for Safety Evaluation of Nanomaterials. Part VI. Characterization of Nanoscale Particles for Toxicological Evaluation," ***Toxicol. Sci.***, April 2006; 90: 296 - 303.

Paul Borm, Frederick C. Klaessig, Timothy D. Landry, Brij Moudgil, Jürgen Pauluhn, Karluss Thomas, Remi Trottier, and Stewart Wood, "Research Strategies for Safety Evaluation of Nanomaterials, Part V: Role of Dissolution in Biological Fate and Effects of Nanoscale Particles," ***Toxicol. Sci.***, March 2006; 90: 23 - 32.

Joyce S. Tsuji, Andrew D. Maynard, Paul C. Howard, John T. James, Chiu-wing Lam, David B. Warheit, and Annette B. Santamaria, "Research Strategies for Safety Evaluation of Nanomaterials, Part IV: Risk Assessment of Nanoparticles," ***Toxicol. Sci.***, January 2006; 89: 42 - 50.

David M. Balshaw, Martin Philbert, and William A. Suk, "Research Strategies for Safety Evaluation of Nanomaterials, Part III: Nanoscale Technologies for Assessing Risk and Improving Public Health," ***Toxicol. Sci.***, Dec 2005; 88: 298 - 306.

Michael P. Holsapple, William H. Farland, Timothy D. Landry, Nancy A. Monteiro-Riviere, Janet M. Carter, Nigel J. Walker, and Karluss V. Thomas, "Research Strategies for Safety Evaluation of Nanomaterials, Part II: Toxicological and Safety Evaluation of Nanomaterials, Current Challenges and Data Needs," ***Toxicol. Sci.***, Nov 2005; 88: 12 - 17.

Karluss Thomas and Philip Sayre, "Research Strategies for Safety Evaluation of Nanomaterials, Part I: Evaluating the Human Health Implications of Exposure to Nanoscale Materials," ***Toxicol. Sci.***, Oct 2005; 87: 316 - 321.

Michael P. Holsapple and Lois D. Lehman-McKeeman, "Forum Series: Research Strategies for Safety Evaluation of Nanomaterials," ***Toxicol. Sci.***, Oct 2005; 87: 315.

3. Recent reviews of the toxicity of carbon nanotubes and quantum dots:

Donaldson et al., "Carbon Nanotubes: a Review of Their Properties in Relation to Pulmonary Toxicology and Workplace Safety," ***Toxicol. Sci.***, 2006, abstract available at toxsci.oxfordjournals.org/cgi/content/abstract/kfj130v1.

Ron Hardman, "A Toxicologic Review of Quantum Dots: Toxicity Depends on Physicochemical and Environmental Factors," ***Environmental Health Perspectives***, February 2006, pp. 165-172, available at www.ehponline.org/members/2005/8284/8284.pdf.

4. A recent excellent review of nanotoxicity issues:

Andre Nel et al., "Toxic Potential of Materials at the Nanolevel," ***Science***, February 3, 2006, pp. 622-627.

5. A recent paper exploring the mechanistic toxicology of nanoparticles:

Iseult Lynch, Kenneth A. Dawson, and Sara Linse, "Detecting Cryptic Epitopes Created by Nanoparticles," Science STKE, pp. pe14, 21 March 2006, abstract available at stke.sciencemag.org/cgi/content/abstract/sigtrans;2006/327/pe14.

Rebecca D. Klaper

Collaborations among government agencies appear to be an important part of nanotechnology research and risk assessment. A description of these activities and particularly the role that EPA is taking in these collaborations would benefit the document, highlighting the agencies unique roles in this field. Unique roles of EPA would include supporting the development of environmental applications/technologies, ecological risk assessment, development of risk assessment strategies, and reporting and testing methods for chemicals.

Numerous studies have been published related to technologies, and potential human health impacts since this draft of the document (over 2005) that could be included with a simple literature search.

Igor Linkov

The White Paper provides detailed information on the uses of nanotechnology beneficial for the environment, the environmental fate and transport of nanomaterials, and their toxicity and risks. Since the research developments and the number of publications in this field is exploding, multiple papers published in 2005 and 2006 could be added and would clarify many issues discussed in the current draft and probably add additional research gaps. Nevertheless, I believe that adding these studies may be a tedious and time-consuming task and may be not the best use of the resources and potential of the EPA Nanotechnology Panel.

I think what is missing in the paper is a discussion of how EPA plans to use uncertain data to make regulatory decisions given the urgency of the issue. Even though EPA states that the paper "discusses what scientific information EPA will need and how it will use that information to address nanotechnology in environmental decision making… within the bounds of EPA's statutory responsibilities" (p. 4, first paragraph), neither the question of how the information will be used nor the extent of EPA's statutory responsibilities are addressed by the paper. Moreover, the scientific information needs are presented as an unstructured list of questions concerning many disparate topics without prioritization.

Adding discussion on how EPA will go about making these difficult decisions will be very valuable for readers. One of the tools that EPA widely uses in other risk assessment applications is the weight of evidence (WOE) approach. Weight of evidence considerations are required in assessing risks to ecological receptors (EPA, 1997), and EPA and other agencies use a weight-of-evidence approach in evaluating the potential carcinogenicity and toxicity of environmental contaminants (EPA, 2005). Elucidation of nanomaterial toxicity requires multiple sets of information due to both the complexity of nanomaterials and the limited database of relevant experimental studies. Traditionally, assessors weigh various lines of evidence and apply professional judgment and/or calculations to decide where the weight of evidence lies – that is, whether the various lines of evidence point to potential risk in the case of each receptor or not. Even though weight-of-evidence considerations may use some quantification, this approach often results in arbitrary weight selection and thus in risk estimates that include an unquantified degree of uncertainty and potential bias.

Weight-of-evidence approaches may be useful for assessing the toxicity of nanomaterials, but a limited knowledge base and high uncertainty and variability in their basic properties requires coupling traditional weight-of-evidence assessments with multi-criteria decision analysis (MCDA) to support both toxicity assessment and regulatory decision making. MCDA provides tools for integrating heterogeneous information (technical, social, and political), as well as for explicitly incorporating decision makers' and stakeholders' value judgments (Linkov et al., 2004; Kiker et al., 2005, Linkov et al., 2006a). MCDA is a structured decision-making process (Figueira et al., 2005) that begins with defining a hierarchy of criteria and measures by which alternatives are judged. For toxicity assessment of nanomaterials, the goal may be to decide which nanomaterial is more toxic

given multiple experimental test data and chemical and biological properties. For broader policy decisions, MCDA can be used to balance societal benefits and health risks resulting from the life-cycles of several nanomaterials and selecting one that is more advantageous and benign. MCDA provides a framework for deciding what criteria to use to judge the alternatives against one another, to determine the relative importance of each of the criteria, and to compare the scores to identify the best alternative. The advantages of using MCDA techniques over other less structured decision-making methods are numerous: MCDA provides a clear and transparent way of making decisions and also provides a formal way for combining information from disparate sources. These qualities make decisions made through MCDA more defensible than decisions made through less structured methods.

Developing a management strategy for nanotechnology presents risk managers with the challenge of incorporating a flux of new information. As I mentioned earlier, the White Paper is already dated due to all the developments in the field over the past year. Adaptive management would provide a systematic tool for the dynamic linkage of environmental management with new information on nanotechnology science or social and economic priorities. In an adaptive management paradigm, the uncertainty in our understanding of nanotechnology risks would be acknowledged at the outset, and strategies would be formulated to manage or reduce it. The basic adaptive management process is straightforward: one chooses a management action, monitors the effects of the action, and adjusts the action based on the monitoring results and updated social and economic factors (Linkov et al., 2006b). During the adaptive management process, in contrast to traditional management, changes are expected and discussed, learning is emphasized, and objectives can be revised based on the performance of a management alternative, changing societal values, or institutional learning. A combination of adaptive management and MCDA would provide a powerful framework for a wide range of environmental management problems, including nanotechnology. It would allow structured, clear decisions to be made and also the adjustment of those decisions based on their performance (Linkov et al, 2006b).

The prioritization of competing objectives, research priorities, and funding allocation options may require multi-criteria decision analysis to be combined with value of information (VOI) assessment. VOI analysis allows the evaluation of the benefit of collecting additional information to reduce or eliminate uncertainty in a scientific or management context. VOI analysis explicitly quantifies expected potential losses from errors in decision making due to uncertainty and identifies the most beneficial information collection strategy (Yokota and Thompson, 2004).

Finally, the ability to measure the utility of nanotechnology research is an important task that EPA could address. Performance standards and performance measurement have been taking on a more prominent role in government since the Government Performance Results Act of 1993. Several general kinds of indicators have been used to measure performance in governmental programs: input indicators, which measure the level of resources used; output indicators, which report the units produced or services provided; and efficiency indicators, which measure the cost per unit of output or outcome (Seager

et al., 2006). In recent years, agencies have also begun to recognize their responsibility to take into consideration the full range of potential benefits and costs in making planning and project development decisions. While a fair amount of work has been done on the development of cost-based performance measures and standards, applications of environmental and health performance metrics are less widespread. Individual technical indices are sometimes used, albeit without formal consideration of stakeholder values. Developing performance metrics that are associated with EPA recommendations listed in Section 6 of the White Paper not only will help EPA to justify funding requests but also help in communicating with stakeholders.

In summary, I believe that the value of information analysis, adaptive management, and multi-criteria decision analysis tools could provide a good foundation for both bringing together multiple information sources to assess risks associated with nanomaterials as well as for developing justifiable and transparent regulatory decisions.

Andrew D. Maynard

The paper seems to rely over-much on non peer-review reports, while not using the peer review literature as much as it could. In addition, there are a number of papers and information sources that have become available since the draft paper was released – new information should be reviewed and included where appropriate.

Specific additional sources include:

Consumer products based on nanotechnology: The WWICS Project on Emerging Nanotechnologies has released the most comprehensive inventory on nano-consumer products (www.nanotechproject.org/consumerproducts)

Inventory of current nanotechnology ESH implications research. Maynard, A. D. (2005). Inventory of Research on the Environmental, Health and Safety Implications of Nanotechnology, Washington DC, Woodrow Wilson International Center for Scholars, Project on Emerging Nanotechnologies. (www.nanotechproject.org)

Oberdörster, G., A. Maynard, K. Donaldson, V. Castranova, J. Fitzpatrick, K. Ausman, J. Carter, B. Karn, W. Kreyling, D. Lai, S. Olin, N. Monteiro-Riviere, D. Warheit and H. Yang (2005). Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy. Part. Fiber Toxicol. 2(8): doi:10.1186/1743-8977-2-8.
(replaces the ILSI (2005) reference)

Roberts, S. M. (2005). Developing experimental approaches for the evaluation of toxicological interactions of nanoscale materials. Developing experimental approaches for the evaluation of toxicological interactions of nanoscale materials. November 3 - 4 2004, Gainsville, Fl.
(referred to, but not cited)

Maynard, A. D. and E. D. Kuempel (2005). Airborne nanostructured particles and occupational health. Journal Of Nanoparticle Research 7(6): 587-614.
(comprehensive review)

Maynard, A. D. and L. M. Brown (2000). Overview of methods for analyzing single ultrafine particles. Philosophical Transactions of the Royal Society of London Series a-Mathematical Physical and Engineering Sciences 358(1775): 2593-2609.
(Comprehensive review of single particle analysis methods)

Tsuji, J. S., A. D. Maynard, P. C. Howard, J. T. James, C. W. Lam, D. B. Warheit and A. B. Santamaria (2006). Research strategies for safety evaluation of nanomaterials, part IV: Risk assessment of nanoparticles. Toxicological Sciences 89(1): 42-50.
(Comprehensive review)

Ryman-Rasmussen, J. P., J. E. Riviere and N. A. Monteiro-Riviere (2006). Penetration of Intact Skin by Quantum Dots with Diverse Physicochemical Properties. Tox. Sci. doi:10.1093/toxsci/kfj122.
(New information on dermal penetration)

Davies, J. C. (2006). Managing the effects of nanotechnology, 2006-1 Washington DC, USA, Woodrow Wilson International Center for Scholars, Project on Emerging Nanotechnologies.
(examining regulation. Not directly research related, but should be considered as a source)

Zhao, X., A. Striolo and P. T. Cummings (2005). C_{60} Binds to and Deforms Nucleotides. Biophysical J. 89: 3856-3862.
(New information on possible interaction)

Warheit, D. B., T. R. Webb, C. M. Sayes, V. L. Colvin and K. L. Reed (2006). Pulmonary Instillation Studies with Nanoscale TiO_2 Rods and Dots in Rats: Toxicity is not Dependent Upon Particle Size and Surface Area. Toxicol. Science: doi:10.1093/toxsci/kfj140.
(New information on hazard)

Nel, A., T. Xia, L. Madler and N. Li (2006). Toxic potential of materials at the nanolevel. Science 311(5761): 622-627.

NIOSH (2005). Strategic plan for NIOSH nanotechnology research. Draft, September 28 2005, NIOSH.

These are just some of the more recent key papers and sources. There are extensive literature reviews in a number of these papers, and the white paper authors should re-examine these to ensure that they are drawing on a broad literature base in their review. In addition, the activities of and reports from other government agencies should be more thoroughly documented (for instance, see the NIOSH strategic plan document above).

Vladimir V. Murashov

Due to the rapidly evolving nature of nanotechnology field, there will always be new important developments by the time a document is ready for public release. However, the following recent activities and studies should be included:

1. Standardization activities in nomenclature, metrology and ES&H occurring through a number of international mechanisms, such as ASTM (E56), ISO (TC229).

2. Most recent NIOSH publications in nanotechnology area such as "Approaches to Safe Nanotechnology: an Information Exchange with NIOSH" (NIOSH 2005a), "Nanoparticles Information Library" (NIOSH 2005b), "Strategic Plan for NIOSH Nanotechnology Research Program" (NIOSH 2005c), and the "Draft Current Intelligence Bulletin on TiO_2" (NIOSH 2005d).

3. New toxicology data presented at the 1st Nanotoxicology Conference in Miami, Fl, in February, 2006.

4. On page 59, in the description of the toxicity of fullerenes it would be beneficial to include the most recent studies (Gharbi et al. 2005) showing that the toxicity of fullerenes depends strongly on the mode of fullerene dissolution.

5. On page 60, work by Yang and Watts is cited. Please add a reference to Murashov 2006, which details some important limitations of the paper.

Stephen S. Olin

The Glossary of Nanotechnology Terms (Appendix A) is not only very helpful but essential in a document like this. The document comments on EPA's participation in ongoing efforts to develop standardized nomenclature for nanomaterials (Section 4.2), but it is not clear if the definitions in the Glossary and in Section 1.2 are harmonized with those being developed in these other efforts. (Also, the International Organization for Standards [ISO], a key player in the nomenclature harmonization work, is mentioned in Section 4.2, but should also be included in the list of international activities in Section 1.5.3.) Some other terms that are used to describe particles in the nano-range and above are aggregate, agglomerate, and ultrafine. These are terms that have been in the literature for many years but have not always been used in a consistent and internationally harmonized manner; adding them to the Glossary would be helpful. The critical importance of developing internationally harmonized nomenclature for nanomaterials should be stressed in Section 1.2 or 4.2.

The fact that this field (environmental applications and implications of nanotechnology) is extremely active means that the Paper is necessarily somewhat out of date already. The question that is not addressed in the Paper is, how does EPA propose to keep this guidance current? The research strategy presented in the Paper is very broad now, but as

data are generated, there should be a process for incorporating new knowledge and focusing the strategy on critical issues that emerge.

Jennifer B. Sass

The paper is not meant to be a detailed scientific treatise. The Paper has been adequately comprehensive in its survey of available scientific studies and information, and in its brief but useful discussion of these data. However, in the Executive Summary the Paper states that, "to help EPA focus on priorities for the near term, the paper concludes with recommendations on next steps for addressing science policy issues and research needs" (p. 1). Maybe this was too much promise for one paper; the policy issues failed to get equal attention in this paper. In the Summary of Recommendations section (6.7), the only "policy" recommendations are limited to developing case studies for future risk assessment needs, increasing collaborations, establishing a cross-Agency group for information sharing, and expand training activities for EPA scientists and managers (p. 82).

Numerous public comments noted that the Paper failed to adequately address the gaps in current relevant regulatory statutes, failed to discuss other agencies that have jurisdiction over nanotechnology environment, health and safety issues, failed to describe management and implementation strategies for an effective governance structure, and failed to identify immediate regulatory action to protect workers and the public from immediate exposures (Caruthers; Sass; Ravanesi; Kimbrell; Rossi; Schettler; Wright; Curtis; Hind; Reeves; Burrows; Lim; Weber; Phelps; Harrington; Courdes; Burns; Powell; Kupferman; Hawes). Comments from the American Chemistry Council also identified the need for, "timely and responsible development and regulation of nanomaterials in an open and transparent process" (Gulledge). The US Chamber of Commerce identified the need for EPA to clarify its statutory authority with regards to nanomaterials, and notes the need for this information to be explicitly described in a subsequent paper, with opportunity for public comment (Kovacs). One public comment recommended that EPA defer regulations until voluntary consensus standards have been established (Slaughter). In any case, the failure adequately to discuss governance and regulatory needs limits this Paper significantly. As it stands, it cannot claim to provide recommendations on next steps for addressing science policy issues.

Regarding the discussion of research needs, comments from PETA identified the need for consideration of non-animal tests in the development of toxicity testing strategies (Dozier). ISRI comments identified the need for discussion of risks specific to workers at recycling facilities, and identified a need to include recycling capacity in the product design stage of nanotechnology (Wagger). The CRN identifies the need to consider the broader long-term effects from future stages of nanotechnology development, such as widespread solar cell distributions (Phoenix). Some public commentors identified the need for discussion of R&D which is intentionally designed to eliminate risk through addressing safety in either the synthesis or final use of the material, as a way to provide primary protection of workers and community members (Burns; Powell; Kupferman;

Hawes). The paper discusses the need for pollution prevention approaches in several papers, including in the recommendations (p. 73)

I suggest that EPA consider all of these suggestions from public comments in any papers or positions that it develops in the future. All public commentors took time and effort to develop a cogent response to the EPA White Paper, and their perspective and expertise will be useful for EPA in its next steps.

Donald A. Tomalia

I believe this document is well referenced with many recent open literature citations and the contributors should be commended. It might be of interest, however, to mention certain "cutting edge" activity going on in the Nanotechnology Characterization Laboratory (NCL) (NCI at Frederick) and NIST which are focused on the development of new/traditional analytical methodologies and actual characterization of "intentionally synthesized" nanomaterials (contact: Scott McNeil, Ph.D., Director, e-mail: mcneils@ncifcrf.gov).

Nigel J. Walker

An organizational structure of EPA focused around where specific nanotechnology responsibilities lie and lines of accountability would be useful. In particular Chapter 6 details, which areas of EPA ought to take the lead in specific areas, but without a clear organizational picture of EPA it is hard to assess the feasibility to which coordination, can occur.

The recommendations section of the document needs to provide clearer guidance regarding timing and priorities. Given the number and breadth of recommendations it is hard to see what the Agency should do next. Attempts to provide some framework would be useful in guiding the subsequent discussions that will take place as a clear cross-agency strategy develops.

Under the statutes section it would be helpful to outline specifically for each if there are nanotechnology specific issue. E.g. Page 27 Would a change in "size" or Nano encapsulation constitute a change in composition of a pesticide under FIFRA?

David B. Warheit

As discussed above, the White Paper could add a more expanded perspective to the limited database on pulmonary hazards of nanoparticles – see below reference #1 for an example. (wherein the "conventional wisdom on nanoparticle is discussed – based on limited numbers of pulmonary toxicity studies with ultrafine titanium dioxide and carbon black particles).

In addition, there are some recently published manuscripts which add perspective to the current background literature. These 3 publications were either published in December,

2005 or currently are in press – thus the authors of the White Paper would not have had the opportunity to assess the impacts of these publications. The abstracts of these publications are listed below as References 2, 3, and 4.

Suggested inclusions include the following

1) Health Hazard issues – include discussion on the results of studies with carbon black and ultrafine titanium dioxide. Although there is a general paucity of data on the effects of inhaled nanoparticles – the authors have neglected to include the "relative" wealth of information on these two engineered nano/ultrafineparticle-types (suggested inclusions are the Bermudez et al. ultrafine TiO_2 studies (2002; 2004). The Elder et al. study with carbon black (2005). Both of these studies also discuss the important issue of species differences.
2) It is also suggested that EPA consider the issue of parallel tracks – particularly in the recommendation section. This might suggest that EPA conduct research on mechanistic research issues related to nanoparticle- types – using "generic nanoparticles or reference materials " to evaluate (e.g.) size ranges, toxicokinetics, surface treatments and solubility, tier testing strategies. The other track would be hazard testing provided by companies attempting to register products and could conceivably consist of a base set of toxicology data.
3) The relevance of *in vitro* studies for assessing *in vivo* toxic effects should be an important issue to EPA. Most of the studies on nanoparticles are generally of the *in vitro* variety and it is unclear whether the findings have relevance as a screen for *in vivo toxic* effects – particularly because the *in vitro* studies have not been properly validated and/or conducted under systematic or uniform conditions.
4) The section on exposure assessment should be expanded to include some of the data generated by Kulbush assessing the occupational exposures in carbon black factories. The EPA should also raise the very important issue of dose metrics for assessing exposures to nanoparticles. This would include the issue of the relevance of mass vs. particle surface area or particle numbers as the appropriate dose metric.
5) The section on dermal penetration should be expanded.
6) In addition, there are some new publications which should be used to update the nanotxicology data base. Some of these references are listed below:

A) Oberdorster G, Maynard A, Donaldson K, Castranova V, Fitzpatrick J, Ausman K, Carter J, Karn B, Kreyling W, Lai D, Olin S, Monteiro-Riviere N, Warheit D, Yang H; ILSI Research Foundation/Risk Science Institute Nanomaterial Toxicity Screening Working Group.Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy. Part Fibre Toxicol. 2005 Oct 6;2:8.

B) Warheit DB, Webb TR, Sayes CM, Colvin VL, Reed KL.Pulmonary Instillation Studies with Nanoscale TiO2 Rods and Dots in Rats: Toxicity Is not Dependent upon Particle Size and Surface Area.Toxicol Sci. 2006 May;91(1):227-36. Epub 2006 Feb 22.

C) Sayes CM, Wahi R, Kurian PA, Liu Y, West JL, Ausman KD, Warheit DB, Colvin VL. Correlating Nanoscale Titania Structure with Toxicity: A Cytotoxicity and Inflammatory Response Study with Human Dermal Fibroblasts and Human LungEpithelial Cells.Toxicol Sci. 2006 Apr 12; [Epub ahead of print]

D) Warheit DB, Brock WJ, Lee KP, Webb TR, Reed KL. Comparative pulmonary toxicity inhalation and instillation studies with different TiO2 particle formulations: impact of surface treatments on particle toxicity. Toxicol Sci. 2005 Dec;88(2):514-24. Epub 2005 Sep 21.

E) Elder A, Gelein R, Finkelstein JN, Driscoll KE, Harkema J, Oberdorster G. Effects of subchronically inhaled carbon black in three species. I. Retention kinetics, lung inflammation, and histopathology. Toxicol Sci. 2005 Dec;88(2):614-29. Epub 2005 Sep 21.

F) Bermudez E, Mangum JB, Wong BA, Asgharian B, Hext PM, Warheit DB, Everitt JI. Pulmonary responses of mice, rats, and hamsters to subchronic inhalation of ultrafine titanium dioxide particles.Toxicol Sci. 2004 Feb;77(2):347-57. Epub 2003 Nov 4.

G) Bermudez E, Mangum JB, Asgharian B, Wong BA, Reverdy EE, Janszen DB, Hext PM, Warheit DB, Everitt JI. Long-term pulmonary responses of three laboratory rodent species to subchronic inhalation of pigmentary titanium dioxide particles. Toxicol Sci. 2002 Nov;70(1):86-97.

Charge Question E: *Do the identified research needs adequately address gaps knowledge about nanotechnology and the environment? Please specify any additional research gaps that you think should be identified.*

Pratim Biswas

Page 74 – line 9: identify specific categories of emissions. For example, toxic species, fine particles emissions, others. What are the key systems: such as combustion, and others.

Page 74 – support basic science for development of nanotechnology applications for emission control, and environmental remediation.

Page 75 – line 11: Is focus on zero valent iron too narrow? A fundamental question – what is zero valent iron, and does it indeed remain zero valent in the environment.

Page 75 – With respect to fate and treatment – has EPA evaluated certain industrial sectors or collaborated with them – that have been producing nanomaterials for many decades. Two examples of industrially produced nanomaterials are carbon black and fumed silica. Have people been effected by these materials?

Page 76 – Focus on nanoparticle measurement methods. Can personal monitors be developed to monitor exposure?

Richard A. Denison

There are a number of additional critical knowledge gaps needing research that are not identified in the paper:

1. The paper argues that testing should be conducted on "representative" particles drawn from each major class of nanomaterial (62:15-19). It also poses the question of how chemical and physical characteristics vary *among different types* of nanomaterials (64:9-11). While that question is legitimate, any assumption that nanomaterials *within the same class* are likely to behave similarly – and hence that we can select a "representative" one – is at best hypothetical, and a research/testing approach that focuses on one or even a few members of each class may well fail to address critical issues. Considerable data already exist to demonstrate that even very subtle variations of a nanomaterial – or the process used to produce it – can significantly alter its chemical, physical and biological properties.

Considerable data will be needed to test any class or category hypothesis, i.e., assess the actual extent of similarity, or the regularity and predictability of trends, among category members, with respect to both hazard and exposure characteristics. Hence, another paramount research need is to generate comparative data across variants within a category, to determine how such variations in manufacturing process, subsequent processing, use of surface modifications, etc., affect hazard and exposure characteristics.

2. a) Sections 5.4.1 and 5.4.2 identify appropriate research needs with respect to the potential for nanomaterials to be transported and transformed in the environment. However, virtually no discussion of the need to understand the fate and transport of nanomaterials *within biological systems* – including humans – is included. How do such materials enter various organisms? How, to what extent, and at what rate are they absorbed, metabolized, distributed or eliminated? Do they persist or accumulate in the organisms? What are the byproducts of any transformations that take place? These important issues are reduced to a single bullet each in the environmental effects section (71:35-38) and the human health effects section (70:27-28).

b) Missing from the discussion of transformation are the more mundane but equally important questions of how, in what amounts and in what forms nanoparticles may be *released* from materials that contain them as a result of environmental forces, e.g., rain, snow/ice, wind, sun exposure, as well as mechanical forces, e.g., friction, wear and tear, etc.

3. The potential for nanomaterials entering water to accumulate in sediments needs much more attention as a research need. The fact that many filter-feeding sediment organisms consume particles in the nano range routinely as food, and that such organisms are at the base of many food chains, elevate the importance and nano-relevance of this issue (these facts are cited elsewhere in the paper, 39:2-4).

4. While the interactions of nanomaterials with naturally-occurring microbes is mentioned (71:40-42), the bactericidal and antibiotic properties of some nanomaterials warrants greater discussion and specific exploration in research conducted on this topic.

5. The research needs identified with respect to "highly dispersive nanotechnologies" (69, 35+) are appropriate. However, the restriction of such questions only to site remediation, monitoring and pollution control applications is unwarranted, for two reasons. First, other applications of nanomaterials may well be intentionally dispersive in nature. Second, unintended dispersal of nanomaterials could well be a feature of many other applications, not necessarily or only during use but in later stages of their lifecycles as well. For example, nanomaterials incorporated into products such as paints and tires are almost certain to be released in some form as those materials age or are subject to erosive forces, resulting in significant dispersal. The dismantling of discarded electronics equipment (which occurs principally in developing countries, where some 50-80% of U.S. "e-waste" collected for recycling ends up) and the subsequent chemical extraction of precious metals from the components (see Chemical & Engineering News, January 2, 2006, pp. 18–21), represent potentially highly dispersive "end-of-life" activities that will increasingly involve nanomaterials as they are incorporated into such products.

This broader approach to defining dispersive uses of nanomaterials needs to be applied throughout the document, including in the several places where it is suggested that applications should be prioritized based on their likelihood of release or exposure (see, e.g., 71:10-15). Such "likelihoods" need to reflect the full lifecycle of the materials.

6. Section 5.6 on releases and human exposures fails to encompass the full lifecycle of nanomaterials and products containing them. The list of potential sources of human exposure (67:22-27) stops at the point of the use of products, omitting any discussion of end-of-life or recycling activities as potential sources. Section 5.4 on environmental fate is largely silent as to what activities across the lifecycle may result in releases. In addition to the need to explicitly include such considerations in the delineation of research needs, this omission underscores the need more broadly to adopt a lifecycle framework for considering the potential risks of nanomaterials (see my earlier comment under Question IIB above).

7. Section 5.6.3 discusses research needed to assess the efficacy of exposure reduction and mitigation measures and technologies, an important area for research. An additional dimension of these questions that should be added is whether we currently have the capability – e.g., detection, measurement and monitoring methods and instrumentation – to adequately assess the efficacy of such controls (logically, this set of questions may belong in Section 5.6.2).

8. Under Section 5.9, Risk Assessment Research Needs, the paper offers two suggested overall approaches. The first – *use of case studies* (72:14-25) – I strongly support, with the caveat that their selection needs to take into account the caution I raised earlier (see point 1 above) about assuming that the learnings from a case study on one material can necessarily be directly extrapolated to another material, even a seemingly closely related one.

The second suggested approach – *reliance on tiered testing* (72:11-12, 17-21) – poses some serious concerns especially if considered in a research context for materials about which little is known. EPA needs to expeditiously generate or facilitate the generation of a robust body of knowledge if it is to effectively assess nanomaterials' potential hazards and risks. Any role for tiering in a research context should be viewed very differently from employing tiering in more routine settings, such as in conventional chemical regulatory programs. Too narrow a scope of testing, driven by over-reliance on tiering, will directly limit the ability of EPA to gain a much-needed "deep" understanding of key properties of nanomaterials.

The need here goes beyond testing needed to determine the level of concern warranted by a specific material in a specific application. Given the dearth of knowledge available at this point, research and data development need to be regarded as an investment:

- To pave the way for the development of predictive approaches as alternatives to direct testing (e.g., SAR models, in vitro tests), a broad and deep foundation of data must be generated and compiled as expeditiously as possible.
- Likewise, building such a foundation of data will serve regulatory needs, such as facilitating EPA's ability to conduct expeditious and credible risk reviews of "new" nanomaterials.

- In these regards, negative results are just as useful to generate as positive ones, as is derivation of quantitative values even for materials and endpoints that are "low-hazard."

Finally, an over-reliance on screening-level hazard test results or on exposure-based triggers to decide how much additional research or testing to conduct may work against the longer-term needs just identified. Triggers that are based on the nature of application or other factors thought to be predictive of exposure are fraught with uncertainty: At this early stage, one company's currently anticipated range of applications for a given nanomaterial may not even hold for that company, let alone for other companies' applications of the same or similar materials. It will be an exceedingly rare case when all reasonably anticipated applications of a nanomaterial for the foreseeable future can reliably be characterized as resulting in low releases and exposures (assuming there is a sound basis, of course, for defining what "low" is for nanomaterials!) – especially when considering the full lifecycles of those materials.

Rebecca D. Klaper

-Since ecological relevance determined by populations----need to determine not only toxicity but population relevant effects such as impact on growth and reproduction

-Need for identification of most sensitive species—with a combination of information on risk for exposure and effects. Some organisms may be at higher risk due to their behaviors, feeding rates, media.

-Properties that make certain nanomaterials bioaccumulate would be important to inform risk assessment and to make comparisions with known pollutants

-For environmental stewardship the Agency and OPPT should also develop appropriate testing methods for nanomaterials and in conjunction with offices of Water, Air and NCEA as well as regional offices develop and implement human health and ecological monitoring strategies.

-Need for research on the behavior of particles in different media with different properties (pH, temperature, velocity, water content, organic properties), how nanomaterial properties are maintained or change.

Igor Linkov

The complexity and novelty of the field of nanotechnology results in knowledge gaps and calls for research needs in all aspects of materials characterization and toxicity. The white paper presents research needs in an unstructured manner as dozens and dozens of research questions. Even though these questions cover a wide range of issues, I am sure everyone on this panel will add a few of his/her favorite ones! What is really missing from the list is a structured approach for developing research priorities that would satisfy risk assessment needs.

A recent OMB Risk Bulletin (OMB, 2006) and Circular A4 (OMB, 2003) set standards for influential risk assessments, clearly the case for nanotechnology. From my perspective, the starting point for listing knowledge gaps is developing a framework for risk assessment that will drive prioritization of other research needs. I agree that the general NAS approach to risk assessment should be valid for nanomaterials, but the way we apply risk assessment to regulate chemicals and pesticides is not going to work for nanoparticles. I believe that a risk assessment and risk management framework utilizing multi-criteria decision analysis and adaptive management should be developed, and this would be the top research priority on my list. Given uncertainty in all aspects related to nanomaterials, the structured, transparent, and justifiable tools offered by MCDA for quantifying both scientific and decision-maker values and views are consistent with OMB requirements for influential risk assessments as well as for developing a system of performance metrics required by the Government Performance and Results Act. The development of such a framework will make clear what information should be collected to support decisions. MCDA or other tools could be then used to develop research needs and prioritize them. Value of information analysis could be then conducted to refine priorities and to devise action plans.

Short of developing a risk assessment framework and prioritization as discussed above, it may be premature to discuss key knowledge gaps. Nevertheless, one of the knowledge gaps that I would like to mention relates specifically to modeling. Traditional fate and transport models may not be appropriate for characterizing occupational exposure to nanoparticles, since exposure occurs near an emission source, resulting in complex gradients and flow patterns. Moreover, the ICRP lung models used to assess retention and distribution of aerosol particles may also be not applicable, given their calibration using radionuclides exhibiting other biological and chemical properties and often larger particle sizes. Computational fluid dynamics (CFD) modeling has been demonstrated to be a capable and powerful tool for estimating the dispersion of contaminant emissions generated by typical industrial operations, both within the immediate area of the release (~2 ft) and at other locations in the near vicinity where others may work (prompting concerns over incidental exposure). CFD modeling was recently used to predict nanoparticle deposition in human airways (Wang and Lai, 2006). Coupling CFD modeling with toxicity studies could be a powerful tool in assessing exposure and toxicity for nanoparticles.

Another knowledge gap relates to a significant amount of $PM_{2.5}$ toxicity work that is not discussed in the White Paper. The White Paper correctly recognizes diesel particles as a potentially relevant category of nanoparticles. However, there are many other environmental nanoparticles besides diesel exhaust – for example, any metal fume starts as nanoparticles, and cigarette smoke likely contains them as well. EPA already regulates nanoparticles as part of $PM_{2.5}$ and PM_{10} within the Clean Air Act; as such, EPA is conducting and/or reviewing a considerable body of information potentially related to nanoparticles. The support work conducted to support particulate matter standards should be recognized in the White Paper, and to the extent possible, more completely characterized. In this way, the White Paper should integrate relevant work from studying

$PM_{2.5}$ toxicity and discuss how nanoparticles might be integrated within the existing framework of the Clean Air Act.

Andrew D. Maynard

The research needs identified are wide ranging, but seen to lack an overall coherence. They give the impression of being developed from the bottom up (a compilation of individual researchers' ideas) rather than from the top down (as would be expected in a strategic research needs analysis). They would be clearer and easier to implement if revised and placed into a more coherent framework. There is some attempt at prioritization, but it does not seem to be consistent across research needs categories, nor is it clear what the implications are to a strategic research plan.

The research needs are weak in a number of areas addressing human health impact. Where identified research needs overlap with the mission of other agencies (such as NIOSH, NIH and possibly FDA), it should be made very clear that this document isn't necessarily authoritative in addressing these areas.

In general, the identified research needs seem to reflect a response to current research, rather than using current knowledge to anticipate future challenges. They are not sufficiently focused and synthesized to provide a basis for a strategic research plan, in their current form.

Finally, it would seem that most pertinent research needs have been addressed to some extent within the white paper, but the presentation does not encourage a logical evaluation of what is covered, and what is not. From my reading, there are 7 areas which might benefit from greater emphasis within this complex matrix:

- Potential routes of entry into the body
- Health outcomes (including epidemiology)
- Potential material release routes (beyond intentional release)
- Process/material based control approaches
- New and revised risk assessment and management models
- Emergency response needs
- Terminology standards
- Risk of physical harm
- Informatics

Vladimir V. Murashov

The identified research needs address most of the currently recognized key knowledge gaps that need to be filled to support informed decision making about nanotechnology and the environment. The following additional research gaps should be included:

1. On page 77, bullet 6 (lines 13-14) should be expanded to include "to evaluate suitability of control banding techniques where additional information is needed; and

evaluate the effectiveness of alternative materials; to identify current work practices that do not provide adequate worker protection; and recommend alternative work practices to eliminate workplace hazards."

2. On page 74, section 6.2.1 "Research Recommendations for Environmental Applications" should also include applications of nanotechnology for exposure reduction, e.g. nano-enabled advanced personal protective equipment, respirators, End-of-Service-Life sensors etc.

Stephen S. Olin

The only Risk Assessment recommendation carried forward to the Executive Summary is that of case studies. Case studies could be valuable and should be part of a strategy for identifying critical issues and data gaps, but the examples should be chosen carefully. A case study on a nanomaterial for which there is little data will identify a lot of data gaps but won't be very informative regarding critical issues for risk assessment. Until nanomaterials are available with richer data sets, an alternative strategy might be to do a risk assessment scoping exercise, rather than attempting a full risk assessment, for several nanomaterials with different physicochemical properties and potential exposure scenarios.

On a related point, the Introduction to Section 5 suggests that specific nanomaterials should be selected for testing/evaluation as representatives of each of the broader classes (carbon-based, metal-based, dendrimers, or composites). The problem, of course, is that we don't know how representative any member of a class will be, because we aren't sure yet what properties of nanomaterials are going to be the key determinants of their toxicity. This is even more of a problem with nanomaterials at present than it is with other particles or chemicals. Studies need to be designed to compare the members of a class so that the assumption that a specific member is "representative" can be tested.

Jennifer B. Sass

The identified research needs are fairly thorough in addressing the key knowledge gaps, although some discussion of the limitations of current toxicity testing strategies as applied to nanomaterials would be helpful. Without such a discussion, it's not evident why EPA is not already demanding standard toxicity testing for all nanomaterials that are commercialized. Is the problem a lack of regulatory authority? Is the problem a lack of relevant testing regimes? Because workers and citizens are already being exposed to nanomaterials in consumer products and industrial processes, this is a valid question left unanswered in this Paper.

Donald A. Tomalia

As a first draft, major research needs have generally been addressed. Many well known protocols are available for characterizing/appraising precisely defined natural occurring nanostructures such as proteins, DNA/RNA and viruses in the life science field (i.e.,

electrophoresis, MALDI-TOF, light scattering, etc). In some instances, they have been used effectively for characterizing intrinsic populations of intentionally made synthetic nanostructures found in many commercial polymers. On the other hand, the absence of a definitive nomenclature and more importantly an appropriate physico/chemical roadmap remain as major knowledge voids for defining, categorizing and characterizing new, intentionally made nanomaterials (e.g., bottom-up synthesized vs. top-down engineered nanomaterials). Appropriate training, collaborations, information exchange and sponsored research (i.e., intra/inter-agency, academia and industry) will be required to fulfill these needs.

Nigel J. Walker

The research needs outlined are quite comprehensive and do address the majority of issues where there is still limiting knowledge. One aspect that did not seem to be addressed sufficiently was in the quantitative aspects of predictive models. It is clears that the breadth of nanomaterials and diversity of physiochemical properties poses a potentially daunting task if the expectation is that every material for which a risk assessment is to be made will need to be fully assessed in well accepted harmonized test paradigms such as those of OECD. It is logical to conclude that some form of benchmarking or comparative/relative toxicity approach with larger groups of materials may be used together to well conducted evaluations of a limited number of materials may have to be employed at some point. Research needs in how to potentially group materials in classes, how to deal with relative potencies of toxicity of different types and nanoscale materials and how to quantitatively link different levels of data (e.g. ex vivo, in vitro in vivo, in silico) should be included.

David B. Warheit

The identified research needs in the White Paper adequately address the key knowledge gaps that need to be filled. However, this is a bit problematic because there is a paucity of data in the peer-reviewed literature concomitant with a multitude of research needs. Accordingly, the White Paper needs to be more selective regarding the prioritization of research needs. In this regard, this Reviewer would like to see a prioritized specific list (but not necessarily in this order) – under the headings of:

1) nanomaterial characterization;
2) selection of representative nanomaterials to be evaluated;
3) development of a parallel tracks – research questions dealing with representative "generic or reference" nanomaterials along with hazard testing of specific nanomaterial-types (which types of tests would be most appropriate)
4) development of exposure methodologies;
5) assessments of which studies should be conducted to test the efficacy of personal protective equipment
6) development of health hazard data – pulmonary, dermal, oral, ocular etc. – which tests? – which tiered approach?
7) relevance of *in vitro* assays as predictive *in vivo* screens

8) environmental fate studies – which studies are recommended?
9) aquatic toxicity studies– which studies are recommended?
10) genotoxicity assay screens
11) ADME – toxicokinetic studies – how should they be conducted
12) all of the Tier 2 and Tier 3 issues – such as neurotoxicity, reproductive/ developmental, sensitive populations, chronic effects, etc.

Charge Question F: *Is this document useful for explaining to stakeholders Agency plans for conducting scientific activities related to nanotechnology? If not, why not?*

Pratim Biswas

Yes, the document is a useful compilation. However, more collaboration with other organizations should be proposed. Organizations and technical communities such as the American Association for Aerosol Research should be approached to work with USEPA on developing focused white papers, via workshops. Industry should be a key partner also in these workshops. This should be a recommendation.

While there are many tables in the document, if it is to be used for the general public (important stakeholder), it may be good to include some key figures or illustrations. For example, a table listing all the stakeholders; figures in general should be more illustrative.

Richard A. Denison

(Also see my first comment under question E.2.a. above.)

While the paper lays out a list of programmatic considerations (Chapters 3 and 4) and research needs (Chapter 5), the recommendations in Chapter 6 do little more than "assign" the tasks to relevant offices within the Agency. The recommendations themselves are generally appropriate, and the assignments of responsibility appear logical, but the paper says little about how the work is to be carried out, what resources and time it will take, which areas are the greatest priorities or need to be done first to allow other tasks to be conducted, or how the outcomes will contribute to an overall Agency strategy for nanomaterials. The articulation of an Agency *strategy* is still needed; the paper contributes toward that end, but needs to explicitly discuss how and when such a strategy will be assembled.

Such a strategy will need to be much more specific as to what tasks EPA is best suited to undertake, which ones are better done by other agencies within the U.S. Government, and what role the private sector can and should play in funding and/or conducting the needed research and testing. It also needs to lay out how U.S. activities will integrate with and complement efforts in other countries and international organizations. As written, the paper leaves the unrealistic impression that EPA can and should do it all!

In this regard, it would be very helpful if the paper could provide a specific summary of what research and testing are underway in other federal agencies, and the resources committed to such efforts. How EPA's research recommendations serve to complement and extend these other efforts should be discussed as well.

In many cases, clear needs exist even to initiate work in the paper's recommended areas, but these are not identified and integrated into the discussion of the recommendations. For example, moving forward in many of the identified areas for conducting research and risk assessment case studies will require that the Agency be able to collect information

from, or encourage or compel its generation by, industry, yet no clear plan is articulated for how the Agency will meet this immediate need. These activities may be seen as beyond the scope of the paper, but they need to be acknowledged as prerequisites to being able to engage the work that is within the paper's scope.

Rebecca D. Klaper

The White Paper described the relevance of nanotechnology to the U.S. EPA and introduces the ways in which the Agency anticipates its role in supporting research related to nanotechnology and evaluating the products of nanotechnology for safety to humans and the environment. The paper falls short in risk assessment needs not related to the research agenda. A greater discussion of specific needs for the risk assessors of the agency would be beneficial, including mention of a plan of progress towards including nanoproducts in risk assessment practices. The idea of a case study is excellent. Besides convening workshops or discussions there are some other obvious places to begin. These include:

-Alteration of the nomenclature and description reporting requirements for chemicals (in particular those that fall under the nanomaterial category)
-Development of testing methods that incorporate description of nanoparticles in the media of interest (e.g. TEM of particles in solution)
-Revamping of exposure calculations to reflect the qualities of nanomaterials over macromaterials (e.g. surface area exposures versus ppm or g/m of air)

Igor Linkov

The document will indeed be useful for explaining EPA regulatory actions and plans. Nevertheless, its clarity and utility for stakeholders can be improved significantly if the Agency clarifies its statutory responsibilities in the area of nanotechnology and develops a risk assessment framework for nanomaterial risk assessment. Based on this, a prioritized list of knowledge gaps and research needs would also be useful.

Andrew D. Maynard

The document is a useful starting point for explaining to stakeholders how EPA is responding to nanotechnology (and why), and identifying research needs that will address current concerns. However, it does not relate current research activities to identified research needs, it does not develop a strategic assessment of research needs or a research action plan, and it does not clearly link research needs and recommendations to environmental oversight.

The document would be significantly more useful if it is edited for clarity, coherence and focus; research needs are reviewed against current research activities; the necessity and aims of research are discussed in specific rather than general terms (including the context of oversight); the relationship between EPA and other research organizations is addressed further and a strategic research action plan is developed.

Vladimir V. Murashov

This document is useful for explaining stakeholders EPA plans for conducting scientific activities related to nanotechnology.

Stephen S. Olin

At the moment, the Recommendations section is pretty long and all-encompassing. Stakeholders may wonder what the "numbered priorities" assigned to the recommendations will mean in practical terms. Also, the Recommendations are rather EPA-centric, identifying the specific Offices that "should" take on the tasks – but has that been agreed within EPA or are these Science Policy Council recommendations that still need to be discussed within the Agency? This latter issue (of which Offices at EPA should be responsible for which Agency initiatives) is an internal EPA management decision, and I have no comment on that aspect of the Recommendations.

Jennifer B. Sass

This document doesn't lay out any Agency plans for conducting scientific activities related to nanotechnology. Several public comments identified the need for EPA to provide a detailed description of the co-ordination between federal regulatory agencies regarding nanomaterials, and to detail a timeline and funding strategy for research (Kovacs; Gulledge; Gotcher; Festa). This would be helpful for understanding what exactly the Agency plans are for conducting its scientific activities related to nanotechnology.

Donald A. Tomalia

Yes. However, as rapidly as nanotechnology activity in the scientific and commercial world appears to be growing, this document should for the short term remain a "works in progress" and be periodically updated.

Nigel J. Walker

As outlined above, the document the document provides a starting point for outlining the Agencies research strategy but does not present a time-specific, prioritized research agenda or strategic plan.

David B. Warheit

While the sections 5.0 EPA's Research Needs for Nanomaterials and 6.0 Recommendations sections – represent "excellent and substantive ideas"; the fact that these lists are very general in nature and not prioritized renders these sections somewhat ineffective. This Reviewer would suggest adding a section to – the 6.0 Recommendations section which would be listed as "top priorities for immediate

attention". In this regard, EPA should list the specific recommended activities that should commence in FY 2007. These specific activities should be derived from the listing to charge question E. Otherwise, this becomes a laundry list of recommended activities – despite the fact that all of the recommendations are well justified.

Suggest focusing on priorities and timelines.

SPECIFIC OBSERVATIONS

Pratim Biswas

Provide specific observations, corrections, or comments on the document, mentioning page, paragraph, and/or line number.

These have been included in the sections above.

Page 2 – Line 12: may should indicate: chemical, physical and biological identification and characterization
Line 30 – cross agency workshop should be extended to other prominent organizations and focused scientific societies.

Page 6 – review to see if all classes of nanomaterials are being covered.

Page 10 – section 1.4: may add that EPA is conducting its own research – e.g. the Sustainable Technology Division in NRMRL and elsewhere.

Somewhere in Chapter 1 or in the document – a list of stakeholders should be summarized in a Table.

Chapter 3 – specific reasons why this has been included as a separate chapter is not clear.

Page 33 – line 38: is chemical identification and characterization sufficient. There should be a clear mention of physical characteristics – shape (morphology), size, crystallinity, surface properties, etc.

Page 34, section 4.2 – on lines 5.6 – also mention a list of key physical properties – as listed in the comment above. Change heading/title of section 4.2 accordingly also.

Page 35 – Line 28, 29: Erroneous statement – nanoparticles do not behave as gas molecules: there is a clear distinction. The diffusion coefficient is a function of size and may be orders of magnitude different.
Lines 32 to 36 – may need tightening up also.

The entire section, 4.3.2 does not really discuss "fate of nanomaterials" in air. Please refer to the extensive aerosol literature for a proper description.

Page 36 – section 4.3.3 - need for evaluation of transport characteristics of nanoparticles in porous media need to be developed.

Page 43, paragraph starting line 18 – please refer to the NAST report pointed out earlier. There are real time nanoparticle measurement instruments that have now been commercialized. Paragraph needs to be modified to accurately reflect advances (now 10 years old), and be more factual. Paragraph starting line 42 is a feeble attempt at doing so (contradicts previous paragraph) and should refer to the nanoDMA type instruments.

Characterization methods for nanomaterials are very scanty in the document.

Page 48 – refers to personal protective equipment – but a chapter on exposure assessment should refer to personal monitoring or measurement devices.

Page 68 – section 5.6.3 – discuss efficient nanoparticle control devices –e.g. soft xray enhanced electrostatic precipitation systems (Kulkarni P., Namiki N., Otani Y. and Biswas P.: "Charging of particles in unipolar coronas irradiated by in-situ soft X-rays: Enhancement of Capture Efficiency of Ultrafine Particles", J. Aerosol Sci., vol. 33 (9), 1279-1298, 2002.). Are HEPA filters the best systems – due to their pressure drops?

A key recommendation should be to develop newer technologies for nanoparticle control? Use innovative approaches – where a nanoparticle emission is prevented, and a byproduct that has useful applications is created. Use of magnetic filter systems in welding processes (captured magnetic oxides have utility in several applications); use of nanostructured sorbents in smelter exhausts to prepare ferroelectric materials (see "In Situ Processing of Ferroelectric Materials from Lead Waste Streams by Injection of Gas Phase Titanium Precursors: Laser Induced Fluorescence and X-Ray Diffraction Measurements", Combust. Sci. Technol., vol.134, 1-6, pp. 183-200, 1998.)

Richard A. Denison

3:5-8 – The EmTech Research reference is not cited in the reference list, and appears to be well out-of-date. For example, the Woodrow Wilson Center's recently released inventory (see www.nanotechproject.org/index.php?id=44) lists over 200 consumer products purported to contain nanomaterials, and others' estimates (e.g., Small Times, Lux Research) are even higher.

4:15-17 – The second element of the definition of nanotechnology – "the creation and use of structures, devices and systems that have novel properties and functions because of their small size – has altered the NNI definition in a subtle but important way: "because of their small size" has been substituted for "because of their nanometer scale dimensions." It is increasingly recognized that nanomaterials' novel properties derive from their nanoscale *structure* as well as or more than their nanoscale size. It also accounts for the many cases where particle size may significantly exceed 100 nm but key structural and functional dimensions of the particle remain within this range. (See, e.g., Andrew D. Maynard and Eileen D. Kempis, "Airborne nanostructured particles and occupational health," Journal of Nanoparticle Research (2005) 7: 587–614.) I think the NNI language is clearer in this regard.

11:17-19 – It would be useful if the paper provided actual dollar estimates for the amount and percentage of current NNI appropriations devoted directly to understanding implications versus developing applications.

12:10-14 – If specific organizations are to be mentioned here (e.g., ACC), then additional ones merit mention, especially the NanoBusiness Alliance, which represents primarily small nanotechnology companies.

14:33-34 – The NPPTAC explicitly considered and rejected the concept of a "pilot" voluntary program, instead recommending a full-scale program.

15:14-16 – The referenced website, www.epa.gov/nano – does not work.

24:34-36 – The authority EPA has to "review nanotechnology products and processes as they are introduced" is far more limited under TSCA than under FIFRA and CAA, and even that authority hinges on decisions yet to be made by the Agency, e.g., when nanomaterials are to be considered "new" substances, when uses are considered "new," what thresholds for notification apply, etc. There are also significant differences between these statutory authorities with respect to how much and under what conditions EPA can require the manufacturers of new nanomaterials to generate risk-related data. Glossing over these differences with cursory discussions such as this one does not serve the public interest.

26:29+ -- While this discussion about TSCA is more detailed than the one just cited, it too glosses over important limitations to EPA's ability to obtain information it needs to conduct a full review of a new nanomaterial's safety. The absence of an up-front hazard data requirement, the need for EPA to make a risk-based finding to request such data in the PMN process, and the absence of reliable predictive tools and methods that EPA typically relies on to compensate for the lack of data received in most PMNs, all represent very important limitations, yet none are mentioned here.

27:4-18 -- There is insufficient discussion here of just how high the hurdles are that EPA faces for nanomaterials deemed to be "existing," with respect to collecting information, requiring its generation or acting to address risks. These severely limit the ability of EPA to develop an understanding of potential risks before they manifest themselves to a degree that triggers the TSCA Section 6 or 8 authorities. A more realistic discussion of EPA authorities should be provided.

27:40-42 / 28:1-6 – The contrast between the FIFRA authorities cited here, most of which operate without requiring a significant risk finding, and their lack of a counterpart under TSCA, which was omitted from the TSCA section, is striking and should be remedied through a discussion that provides more even treatment. Otherwise, a skewed impression is given of EPA's ability to take a proactive approach to identifying and addressing nanomaterials' potential risks.

29:1-16 – Here again, the same comment applies as just made for FIFRA.

32:13-14 – The fact that TRI substances include metals used in nanomaterials raises an number of interesting questions: Should releases of TRI chemicals in the form of nanomaterials be separately reported? What metrics for release other than or in addition to mass would be appropriate?

35:39-41 – This caveat is an important one but only comes after the discussion of what appears to be a definitive finding that particles smaller than 80 nm are always short-lived. If the discussion of agglomeration mode characteristics is more theoretical, with deviations often or sometimes occurring in practice, then this needs to be made clear. In any case, the caveat needs to be made clear up front.

This same caveat is relevant to, but is missing from the discussion of this same topic in Appendix C, 103:20-38.

36:4-5 – The statement would appear to be far more definitive and sweeping than warranted based on the very limited data cited and available; it could easily be taken out of context. It also does not reflect the appropriate qualification provided by the last sentence of this paragraph, namely that any difficulty in resuspending nanoparticles may be a temporary advantage/problem!

41:24-42 / 42:1:23 – This section, 4.3.9, makes very important points: the inability to apply to nanomaterials many or most of the current fate and exposure models EPA uses to assess fate and exposure of conventional chemicals; and the need to develop substantial amounts of empirical data on nanomaterials in order to develop new models.

However, there is no comparable discussion elsewhere in the document of the analogous shortcomings of the models EPA uses to assess other risk parameters: Section 4.6 (Human health effects) and 4.7 (Ecological effects) have no discussion of models at all, even though EPA frequently relies on such models for conventional chemicals. The same points made in Section 4.3.9 should be repeated in those sections, along with any additional factors that limit the applicability of current models to nanomaterials. In addition, these points are not raised in Sections 4.5.7.2, and it is unclear as to whether or to what extent they apply.

These important points about the inability or limitations of applying current models to nanomaterials need to be discussed in all contexts where they are relevant.

44:13-17 – Occupational exposure to products incorporating nanomaterials should be included in this list of potential human exposures. Professional products made for use by workers in a host of sectors (construction, building maintenance, etc.) often are made to contain higher concentrations of active ingredients, either for dilution or for use at higher strength. Such workers are often

exposed to higher concentrations of active ingredients and for longer periods of time than are consumers.

45:13-15 / 46:1-3 – These statements appear to be quite sweeping and over-generalized. The referenced "closed systems" certainly do not apply universally; one fresh example is provided by an article appearing on the front page of the Washington Post on April 8, 2006, which described visible dust rising from a number of production and processing operations in a manufacturing facility of a leading nanotechnology company. See www.washingtonpost.com/wp-dyn/content/article/2006/04/07/AR2006040701725.html . The reference to "appropriate filtering systems" begs the question as to what data are available to demonstrate the efficacy of such systems in preventing exposure, given the primitive state of detection, measurement and monitoring instrumentation especially for routine use.

46:8-11 – The claim here that release and exposure to nanoparticles after incorporation into a product "are expected to be low" is also quite sweeping and appear to be based on very little data. Moreover, it fails to consider the full lifecycle of such products, beyond merely the use stage.

46:14-15 – Again, this limited view of potential exposure sources fails to consider the full lifecycle of nanomaterials.

46:22-24 – On what basis is it claimed that inhalation is the most likely pathway? The statement is far too sweeping. What about nanomaterials received and handled only as slurries, where waterborne releases may predominate? This and the prior section (4.5.3.1) are characterized by too many absolute statements made with little available data to support them.

47:35 / 48:1-2 – On what basis is it claimed that ingested quantities will be small? Does the claim refer to ingestion indirectly via inhalation exposures or to all oral ingestion?

48:14-22 – The questions being debated over penetration through "healthy/intact" vs. normal or damaged skin should be mentioned. Additional studies (e.g., recent papers by Tinkle (NIOSH) and Monteiro-Riviere (UNC) should be included.

48: Section 4.5.5 – Shouldn't this section be under the occupational exposure section, 4.5.3.1?

48:24-34 – This section needs to be reconciled with the discussion herein and elsewhere (page 35) of the fate of nanoparticles in air. For example, if particles below 80 nm rapidly agglomerate to form larger particles, then the fact that high-efficiency respirators work well on particles below 100 nm may be moot.

49:8-9 – There is rather broad consensus that mass dose is insufficient to characterize exposure to nanomaterials, and I think this statement could be more definitively stated. Recent reports from ILSI/HESI and NIOSH, among others, make this point.

49:25-29 – This discussion should include mention of worker health monitoring and medical surveillance as additional forms for monitoring.

50:5-6 – Biomonitoring is equally applicable to assessing occupational exposures as it is to general population exposures.

50:15-21 – Ambient monitoring is equally applicable to assessing occupational exposures as it is to general population exposures.

50:28-29 – Why is the applicability of ambient monitoring to nanomaterials "unclear"? Is it due to the lack of tools to conduct such monitoring? Clarify.

51:19-28 – This topic – the limits of mass-based thresholds and standards – is a very important topic with respect to how to assess nanomaterial releases and exposures, and merits much more attention than it is given here, where it is largely out of place. In my view a more thorough discussion of the topic is warranted and merits its own section or subsection.

Section 4.6.3 (pp. 53-54) – The discussion of pulmonary toxicity provided here is very cursory and omits a number of key findings, including:

- the development of lung granulomas in response to CNT exposures, seen in all of the published studies;
- the use of "realistic" doses in at least some of the studies (e.g., Lam) corresponding to the exposure a worker would receive within several weeks at OSHA's current (and only applicable) standard, that for nuisance dust;
- the dose-responsiveness of the effects observed by Shvedova et al, 2005, and the fact that a fibrotic response was seen in regions of the lung far removed from the point of deposition; and last but not least,
- the seminal work of Oberdorster demonstrating olfactory transport of nanoparticles directly into the brain of rodents.

The reference here to Tinkle, 2003, as well as her later work, should also be included in Section 4.5.4.3.

56:1-2 – Adsorption should also be included here.

Section 4.7.3, Aquatic ecosystems effects (p. 58) – This section in general appears aimed at downplaying the existing studies pointing to potential impacts, and hence does not appear balanced. For example, after discussing in the second paragraph the results of the few available studies on engineered nanomaterials that quantified LC50 values, which found them to be in the 100s of ppb to low

ppm range, in the third paragraph, the assertion is made that "Limited preliminary work with engineered/manufactured nanoparticles seems to substantiate" the claim that such materials will have low aquatic toxicity, in the range of tens to thousands of ppm – levels far higher than those cited in the second paragraph. The far higher values are not for engineered nanomaterials, but for carbon black and natural clays.

60:35-28 – I strongly agree with this point, which is frequently overlooked, and believe the statement should be elevated in prominence, as it is a critical factor in deciding what types and amounts of testing out to be done in any research or regulatory settings.

67:2-5 – The claim here that numerous methods exist to detect nanoparticles appears to be contradicted by the discussion of this topic elsewhere in the paper, where it is made clear that such methods are in their infancy and that this is a critical research need. Indeed the very next bullet (line 7) raises this very question.

68:38-39 / 69:1-2 – This list should be expanded to include environmental or biological breakdown products, and product (e.g., end-of-life) as well as production waste streams.

75:29-34 – The questions should be expanded to include issues associated with the potential partitioning of nanomaterials into sewage sludge, which then must be managed through land application, incineration, disposal, etc. Especially for metals or other persistence nanomaterials, any risks associated with these materials will be transferred to sludge to the extent the materials themselves are.

108:1-12 – Have any actual studies been conducting examining bioaccumulation of nanomaterials? If not, this should be stated.

118:14-17 – In several places the word "access" needs to be replaced with "assess."

Appendix C, Section C3 – As with my comment on Section 4.6.3 (pp. 53-54) – The discussion of pulmonary toxicity provided here also omits a number of key findings, including:

- the development of lung granulomas in response to CNT exposures, seen in all of the published studies;
- the use of "realistic" doses in at least some of the studies (e.g., Lam) corresponding to the exposure a worker would receive within several weeks at OSHA's current (and only applicable) standard, that for nuisance dust;
- the dose-responsiveness of the effects observed by Shvedova et al, 2005, and the fact that a fibrotic response was seen in regions of the lung far removed from the point of deposition; and last but not least,
- the seminal work of Oberdorster demonstrating olfactory transport of nanoparticles directly into the brain of rodents.

Rebecca D. Klaper

1) -p. 20, Line 23, States some estimates are that ….. Should be Brown (2005) estimates that…..

2) -p. 22, lines 4-8 need a reference for the relationship between nanotech and hydrogen economy. Any products etc to be cited?

3) -p. 25, Line 27, EPA SHOULD continue to expand its own work within the areas of LCA

4) -p.30 – Clean Water Act – need to mention that all sorts of nanomaterials may end up in water systems via coatings washing into environment, medicines through sewage systems, pesticide applications, directly (happening right now in trials) as a water treatment process

5) -p. 34 lines 20-23 need references.

6)-p. 36 section 4.3.3 Fate of Nanomaterials in the Soil – will also depend on the soil type! Particles will move differently though different soils---sands, clays. Depends on soil charge as well as nanoparticle charge ---depends on soil humic matter as well as nanoparticle carbon

7)-p 37 lines 1-2 Nanoparticles generally will be retained in the water column…… need reference for this\

8)-p 37 lines 6-9 ---Biodegredation and photocatylytic sentences need references if possible

9)p 37 Line 12 ---nanoparticles can be stabilized……need reference

10) p 39 Line 3 Aquatic and marine filter feeders near the base of the food chain feed on ---should be small particles unless can provide a reference showing they feed on nanoparticles.

11) p. 47 – chart at top of the page should include some reference to potentially eating in food---bioaccumulation potential.

12) p. 47 Ingestion at bottom of page – ingestion also due to bioaccumulation into food as well as medicines so could be larger amount that by mere consumption of residues

13) p. 58- Lines 27-30 – major physiological differences should also include immunology-ways of dealing with the particles once exposed.

14) p. 59 line 2– Oberdorster 2004 tested Daphnia and fullerenes not the 2005 reference. LC50 estimate was not 800 but 460 ppb. Also should point out that this talk abstract

made no mention of determination of clump size of particles in this solution----so how big were the particles the Daphnia were exposed to exactly? Still nano? Can't tell as this is only an abstract from a talk not a peer reviewed published paper with data. Brings up the point that toxicity research needs to carefully describe particles in air and in solutions to determine what organisms are exposed to exactly when doing these tests. For example using TEM or other imaging to view particles or "clumps" (e.g. study by Lovern and Klaper 2006 also cited). Should be brought up in describing the need for testing strategies for toxicity

15) p. 59 Line 4 – should be Lovern and Klaper 2006

16) P. 59 Lines 4-5 should state that this was a standard EPA toxicity test using Daphnia magna. Toxicity of titanium dioxide particles and fullerenes differed by an order of magnitude with fulerene particle solutions (with particle clumps measured as 10-20 nm diameter) having an LC50 of 460 ppb and titanium dioxide (10-20 nm) with an LC50 of 5.5 ppm. Particle preparation impacted toxicity with solutions with unfiltered solutions---larger particle clumps (up to 100 nm) causing LC50 of 7.9 ppm and larger titanium dioxide clumps causing no measureable toxicity.

Lines 9-10 "the kind found in sunblock paint etc. ----should be clarified. Titanium dioxide is found in these things but the size of clumps in these products is unclear unless you have a reference…

17) p 59 Line 13 Citation for swimming and disorientation is Lovern and Klaper (2005)
Lovern S, Klaper R. 2005. Impact of nanoparticle exposure on Daphnia survival and behavior. Abstracts of the Society of Environmental Toxicology and Chemistry national meeting, Baltimore, Maryland.

18) P. 59 lines 29-30 need reference here for bactericidal agents in media

19) p. 65 lines 1-2 "Do novel materials, such as fullerenes without corresponding bulk materials, differ in their mobility from the bulk materials?" This sentence needs to be restructured. If there aren't bulk materials how do you make the comparison?

20) p. 71 Needs to include :
-since ecological relevance determined by populations----need to determine not only toxicity but population relevant effects such as impact on growth and reproduction
-identification of most sensitive species

21) P. 72 Earlier (e.g. p. 42) said that QSAR's are not applicable to nanomaterials as they have unique properties not like other chemicals. I would get rid of the QSAR language here then

22) P. 73 – Lines 18-20. For environmental stewardship the Agency and OPPT should also develop appropriate testing methods for nanomaterials and in conjunction with

offices of Water, Air and NCEA as well as regional offices develop and implement human health and ecological monitoring strategies.

23) p 79 lines 16-17: ORD should support research on the distribution…..

24) p 79 lines 32-34 see issue number 21)

25) p. 80 lines 17+ EPA should also collaborate with FDA as many of these chemicals are being designed for medical use and may have a similar danger of ending up in the environment as pharmaceutical products

26) P. 89 Lines 33 Reference should be 2006 pp. 1132-1137.

Igor Linkov

p. 3 line 6 provide citation for EmTech Research

p. 5 Great figure, but it does not look good in black-and-white; consider replacing images with graphics

p. 7 Table 1.

- The caption does not match with the Table entries (e.g., electron beam and X-ray are clearly not nanotechnology products). Suggest revising the caption as "Examples of products and processes utilizing nanotechnology" and careful review of entries in the Table.
- Consumer products is a better title for the first column;
- Resists are not capital equipment;
- Software products are written programs or procedures and can not utilize nanotechnology; the column should be deleted. It is not clear how modeling and computer aid design navigation can be example of nanotechnology product;
- It would be nice to match specific products in Table 1 with nanomaterials types listed on p. 6.

p. 13 line 6 "Lux Research 2005" is not listed in the reference list
p. 13 line 20 it is not clear which document authors mean; provide citation
p. 17 line 37 "Elliot and Zhang 2001" is not listed in the reference list
p. 17 line 39 "Quinn et al., 2005" is not listed in the reference list
p. 18 line 6 "Chen 2005" is not listed in the reference list
p. 18 line 12 "Diallo 2005" is not listed in the reference list
p. 18 line 15 "Pitoniak 2005" is not listed in the reference list
p. 18 line 17 "Kanel 2005" is not listed in the reference list
p. 18 line 19 "Mattigod 2005" is not listed in the reference list
p. 18 line 27 "Tungittiplakorn 2005" is not listed in the reference list

p. 33 line 13 Correct references are NRC, 1983, and 1994 (delete NAS)
p. 46 Table 4 It would be good to add more examples. For example, consumer products listed in Table 1 could be all added to this Table
p. 47 line 21 "Health and Safety executive 2004" is not listed in the reference list
p. 48 line 17 "Hart 2004" is not listed in the reference list
p. 48 line 33 "Royal Society" should be changed to "UK Royal Society"
p. 55 line 10 "ILSI 2005" is not listed in the reference list
p. 56 line 12 Add citation for the Florida workshop
p. 56 line 19 "US EPA 2004" there are more than one EPA document dated in 2004 in the reference list, please add letters (2004a, 2004b etc) to clarify
p. 88 line 9. reference is not dated
p. 89, lines 14. List all authors
p. 89, lines 17-21. Two references by Leconet et al, 2004. please add letters a and b
p. 89, lines 36-42. references are not in alphabetical order
p. 92 references are not in alphabetical order
p. 92 Two references by Oberdoster, 2004. please add letters a and b
p. 93, line 22. List all authors
p. 94, lines 16. List all authors
p. 95 More than one references by US EPA, 2004 and US EPA, 2005. please add letters a, b etc.
p. 97 line 28. It is not a citation, should be deleted

CITED REFERENCES

- Kiker, G., Bridges, T., Varghese, A.S., Seager, T.P., Linkov, I. (2005). Application of multi-criteria decision analysis in environmental management. *Integrated Environmental Assessment and Management* 1 v. 2 49-58.

- Linkov, I., Satterstrom, F.K., Seager, T.P., Kiker, G., Bridges, T., Belluck, D., Meyer, A. (2006a). Multi-criteria decision analysis: comprehensive decision analysis tool for risk management of contaminated sediments. *Risk Analysis* 26:1-18.

- Linkov, I., Satterstrom, F.K., Kiker, G., Bridges, T., Benjamin, S., Belluck, D. (2006b). From optimization to adaptation: shifting paradigms in environmental management and their application to remedial decisions. *Integrated Environmental Assessment and Management* 2:92-98.

- Linkov, I., Varghese, A., Jamil, S., Seager, T.P., Kiker, G., Bridges, T. (2004). Multi-criteria decision analysis: framework for applications in remedial planning for contaminated sites. In: I. Linkov and A. Ramadan, eds., *Comparative Risk Assessment and Environmental Decision Making*. Kluwer, Amsterdam.

- Morgan, K. (2005). Development of a preliminary framework for informing the risk analysis and risk management of nanoparticles. *Risk Analysis 25*(6):1621-1635.

- OMB (2006). Proposed Risk Assessment Bulletin. http://www.whitehouse.gov/omb/inforeg/proposed_risk_assessment_bulletin_010906.pdf.

- OMB (2003). Circular A-4 Regulatory Analysis. Proposed Risk Assessment Bulletin. http://www.whitehouse.gov/OMB/circulars/a004/a-4.html.

- Seager, T., Tuler, S., Kay, R., Satterstrom, F.K., Linkov, I. (2006, submitted). Environmental performance metrics for oil spill response. *Environmental Science and Technology*.

- U.S. Environmental Protection Agency (1997). Ecological Risk Assessment Guidance for Superfund: Process for Designing and Conducting Ecological Risk Assessments, Interim Final. http://www.epa.gov/oswer/riskassessment/ecorisk/ecorisk.htm.

- U.S. Environmental Protection Agency (2005). Guidelines for Carcinogen Risk Assessment. EPA Risk Assessment Forum, Publication EPA/630/P-03/001F.

- Wang, J.B., Lai, A.C.K. (2006). A new drift-flux model for particle transport and deposition in human airways. *Journal of Biomechanical Engineering* 128:97-105.

- Yokota, F., Thompson, K. (2004). Value of information analysis in environmental health risk management decisions: past, present, and future. *Risk Analysis* 24(3):635-650.

ATTACHMENT A. List of Additional Studies

Balshaw, D.M., Philbert, M., and Suk, W.A. (2005). Research strategies for safety evaluation of nanomaterials, Part III. Nanoscale technologies for assessing risk and improving public health. *Toxicological Sciences 88*(2):298-306.

Borm, P., Klaessig, F.C., Landry, T.D., Moudgil, B., Pauluhn, J., Thomas, K., Trottier, R., and Wood, S. (2006). Research strategies for safety evaluation of nanomaterials, Part V: role of dissolution in biological in biological fate and effects of nanoscale particles. *Toxicological Sciences 90*(1):23-32.

Donaldson, K., Aitken, R., Tran, L., Stone, V., Duffin, R., Forrest, G., and Alexander, A. (2006). *Carbon Nanotubes: A Review of Their Properties in Relation to Pulmonary Toxicology and Workplace Safety*. Published by Oxford University Press on behalf of Society of Toxicology.

Dreher, K.L. (2004). Health and environmental impact of nanotechnology: toxicological assistance of manufactured nanoparticles. *Toxicological Sciences 77*:3-5.

Guzman, K.A., Taylor, M.R., and Banfield, J.F. (2006). Environmental risks of nanotechnology: national nanotechnology initiative funding, 2000-2004. *Environ. Sci. Technol. 40*:1401-1407.

Hardman, R. (2006). A toxicological review of quantum dots: toxicity depends on physicochemical and environmental factors. *EHP 114:*165-172.

Holsapple, M.P., Farland, W.H., Landry, T.D., Monteiro-Riviere, N.A., Carter, J.M., Walker, N.J., and Thomas, K.V. (2005). Research strategies for safety evaluation of nanomaterials, Part II: toxicological and safety evaluation of nanomaterials, current challenges and data needs. *Toxicological Sciences 88*(1):12-17.

Kagan, V.E., Tyurina, Y.Y., Tyurin, V.A., Konduru, N.V., Potapovich, A.I., Osipov, A.N., Kisin, E.R., Schwegler-Berry, D., Mercer, R., Castranova, V., and Shvedova, A.A. (2006). Direct and indirect effects of single walled carbon nanotubes on RAW 264.7 macrophages: role of iron. *Toxicology Letters (in press)*.

Kipen, H.M. and Laskin, D.L. (2005). Smaller is not always better: nanotechnology yields nanotoxicology. *Am J Physiol Lung Cell Mol Physiol 289*:L696-L697.

Lam, C-W., James, J.T., McCluskey, R., and Hunter, R.L. (2004). Pulmonary toxicity of single-wall carbon nanotubes in mice 7 and 90 days after intratracheal instillation. *Toxicological Sciences 77*:126-134.

Morgan, K. (2005). Development of a preliminary framework for informing the risk analysis and risk management of nanoparticles. *Risk Analysis 25*(6):1621-1635.

Net, A., Xia, T., Madler, L., and Li, N. (2006). Toxic potential of materials at the nanolevel. *Science 311*:622-627.

Pacheco, S., Medina, M., Valencia, F., and Tapia, J. (2006). Removal of inorganic mercury from polluted water using structured nanoparticles. *J Environmental Engineering, March*:342-349.

Robichaud, C., Tanzil, D., Weilenmann, U., and Wiesner, M.R. (2005). Relative risk analysis of several manufactured nanomaterials: an insurance industry context. *Environ. Sci. Technol. 39*:8985-8994.

Oberster, G., Maynard, A., Donaldson, K., Castranova, V., Fitzpatrick, J., Ausman, K., Carter, J., Castranova, V., Fitzpatrick, J., Ausman, K., Olin, S., Monteiro-Riviere, N., Warheit, D., Yang, H., and a report from ILSI Research Foundation/Risk Science Institute Nanomaterial Toxicity Screening Working Group (2005). Principles for

characterizing the potential human health effects from exposure to namomaterials: elements of a screening strategy. *Particle and Fibre Toxicology2:*8.

Powers, K.W., Brown, S.C., Krishna, V.B., Wasdo, S.C., Moudgil, B.M., and Roberts, S.M. (2006). Research strategies for safety evaluation of nanomaterials. Part VI. Characterization of nanoscale particles for toxicological evaluation. *Toxicological Sciences 90*(2):296-303.

Thomas, K. and Sayre, P. (2005). Research strategies for safety evaluation of nanomaterials, Part I: evaluating the human health implications of exposure to nanoscale materials. *Toxicological Sciences 87*(2):316-321.

Tsuji, J.S., Maynard, A.D., Howard, P.C., James, J.T., Lam, C-W., Warheit, D.B., and Santamaria, A.B. (2006). Research strategies for safety evaluation of nanomaterials, Part IV: risk assessment of nanoparticles. *Toxicological Sciences 89*(1):42-50.

Warheit, D.B., Webb, T.R., Sayes, C.M., Colvin, V.L., and Reed, K.L. (2006). *Pulmonary Instillation Studies with Nanoscale TIO2 Rods and Dots in Rats: Toxicity is Not Dependent Upon Particle Size and Surface Area*. Published by Oxford University Press on behalf of Society of Toxicology.

Woodrow Wilson International Center for Scholars (2005). *Informed Public Perceptions of Nanotechnology and Trust in Government*. Project on Emerging Nanotechnologies.

Andrew D. Maynard

1. P3 line7 – Cite consumer products data from www.nanotechproject.org/consumerproducts.
2. P4 line 12. The old NNI definition of nanotechnology is used – which is a little confusing. Do all three criteria have to apply for something to be nanotechnology, or just one? To what extent are macromolecules included in this definition?
3. P6 line 4 and elsewhere – Occasionally the terms "nanomaterials" and "nanoparticle" are used interchangeably. They should not be; nanoparticles are a subset of nanomaterials, and nanomaterials other than nanoparticles may present a nano-specific risk.
4. P10 line 2 – The description of inhaled nanoparticles becoming "lodged in the lung" is not accurate – they may deposit, and then may stay, may translocate or may be cleared.
5. P11 section 1.5.1 – Expand coverage of research being carried out within other federal agencies.
6. P24 line 9 – Include "exposure" explicitly in the information that informs the risk management process.
7. P33 section 4 – This section in particular would benefit from more reliance on peer review publications.

8. P33 line13 – Include an overview of the NAS risk assessment paradigm
9. P34 paragraph 1 – I may be being pedantic, but "composition" doesn't seem to appear in this list of chemical properties.
10. P34 section 4.2 – some mention of spatial composition would be useful (where chemical species occur in a nanomaterials).
11. P35 line 24 – should read "primary" rather than "process" I think.
12. P35 section 4.3.2 – here and elsewhere, coverage of aerosol behavior seems weak. Specifically, line 24 – convection is important; line 29 – it's misleading to say that nanoparticles follow the laws of "gaseous diffusion"; Line 30 - rate of diffusion is only proportional to diameter over a certain size range; Line 31 – gravitational settling is only proportional to diameter over a certain size range; Line 33 – the smallest aerosol mode is the nucleation mode, and rapid agglomeration only occurs above a threshold concentration.
13. P42 section 4.4 – This is a very general discussion of issues, with little review of current knowledge
14. P43 line 18 – Although NAAQS has been important in driving particle measurement technologies, this has not been the only driver. In fact, I would say that it has only influenced a small subset of technologies and instruments, that are specific to monitoring environmental emissions.
15. P45 table 3 – the entry for "attrition" duplicates the entry for "Colloidal".
16. P46 line 5 – Should consider including a discussion of material transport (between manufacturing site and site of use).
17. P46 line 14 – how about emissions from filter or scrubber break-through?
18. P46 table 4 – this needs to be expanded considerably (see www.nanotechproject.org/consumerproducts)
19. P47 line 11 – I would question the use of phrase "significant information" here.
20. P47 section 4.5.4.1. – Consider the influence of other phoretic mechanisms on inhalation exposure (electrophoresis, magnetophoresis etc.) For instance, generation of some nanoparticles in strong magnetic or electrostatic fields may have a significant influence on exposure patterns and characteristics
21. P48 section 4.5.5 – the aerosol science seems weak here. For instance, it is too great a generalization to say that small particles are short lived because they rapidly coagulate.
22. P49 section 4.5.6. This section seems very weak – the statements made should be backed up, and key reviews cited (e.g. Maynard and Kuempel (2005)).
23. P50 line 7 – the paragraph on personal sampling does not reflect current thinking for occupational health monitoring.
24. P50 line 9 – "administered dose" in personal sampling does not seem to make sense.

25. P51 line 8 - Most of the modeling discussion is relevant to ambient exposure, but not necessarily occupational exposure.

26. P52 line 27 – The text seems to imply that the disparity in toxicology studies between carbon nanotubes and graphite confirms an inability to extrapolate from current toxicological datasets to new nanomaterials. Surely this is rather a broad implication to draw from such a specific (and possibly unique) example.

27. P52 section 4.6. This section rushes over the state of knowledge in some areas, and at times is poorly reflective of current published information. I would recommend revisiting it to cover a more critical review of the current literature.

28. P56 line 12 – cite the proceedings from Florida workshop: Roberts, S. M. (2005). Developing experimental approaches for the evaluation of toxicological interactions of nanoscale materials. Developing experimental approaches for the evaluation of toxicological interactions of nanoscale materials. November 3 - 4 2004, Gainsville, Fl.

29. P68 section 5.7 – I thought that this presented a good overview of the state of knowledge and research needs, although it did repeat information presented earlier. I would recommend transplanting some of this text to an earlier section of the paper.

30. P72 section 5.9 – In various places throughout the white paper (and in various forms) it is stated that "The overall risk assessment approach used by EPA for conventional chemicals is thought to be generally applicable to nanomaterials". This statement needs to be justified, or removed I feel, if an impression of *a priori* assumptions on risk assessment (and management) is to be avoided.

31. P72 section 5.9 – Needs and recommendations would benefit from being separated a little more in this section.

32. P74 section 6.2 – where lists are prioritized, what was the rationale or framework for the prioritization?

33. P75 line 7 – Should this read "transport rather than "treatment"?

34. P80 section 6.3 – I found this section somewhat weak and limited. What about new risk assessment and management paradigms and approaches? For instance, in the workplace, control-based risk management is a new area of thinking – as the EPA white paper considers all human exposures, ideas like this should be addressed.

35. P99 line 28 – it worries me that in these definitions nanotechnology is driving nanosciencce - surely it should be the science driving the technology!

36. P99 line 30 – make sure the definitions of nanoscale and nanostructure are consistent.

37. P100 – there is no definition of "ultrafine" – is this intentional?

38. P103 Appendix C – There is a lot of repetition in this appendix from the main text. Some judicious editing is recommended.

Vladimir V. Murashov

Specific comments follow the italicized statements from the *Nanotechnology White Paper* below.

Page 6, lines 1-2: *There are many types of intentionally produced nanomaterials. For the purpose of this document, nanomaterials are organized into four types: ...* . The basis for categorizing nanomaterials into these four types is not clear and should be referenced here.

Page 6, line 6: It is not clear why carbon nanotubes are called "cylindrical fullerenes." In fact, it is not consistent with the definition of fullerenes given on page 98 of the Appendix A: Glossary of Nanotechnology terms.

Page 6, line 17: It is not clear whether this includes inorganic polymers.

Page 8, lines 21-26: *The Agency is committed to keeping abreast of emerging issues ...* . It would be helpful to identify general methods and strategies the Agency is considering to identify emerging issues and facilitate proactive action and planning.

Page 11, line 21: Should be National Institute *for* Occupational Safety and Health (emphasis added).

Page 12, lines 4-21: Stakeholders' and international activities should be further expanded. For example, the DuPont-led industry consortium looking at ESH issues around nanotechnology is an important program. EU Framework Programmes 6 and 7 fund research in ES&H of nanotechnology.

Page 13, lines 7-10: BSI, NIST and ANSI are not international organizations: the first is a British Standards Developing Organization (SDO), the second is a US government agency, the third is a U.S. SDO. APEC and ASTM International can be considered international organizations.

Page 13, line 20: *Specifically, the document states that the United* … Please specify, which document is referenced.

Page 14, line 21: A better link would be http://www.epa.gov/region5/sites/nease/index.htm

Page 14, lines 35-38: If available, references on the criteria and procedures that OPPT uses to review new chemical submissions for nanomaterials under TSCA could be cited here, for example, the EPA decision on carbon nanotubes reported in 2005, as it may be the first example of EPA evaluating an intentionally produced nanomaterial under TSCA. (This comment also applies to page 27, lines 4-18.)

Page 15, lines 3-5: The example cited here of a pending EPA evaluation of cerium oxide as a fuel additive may provide an opportunity to examine the data and information needs for evaluating commercial uses of nanomaterial—similar to the proposal for case studies in risk assessment (pp. 72 and 82). As noted on pp. 22-23, *Limited published research and modeling have indicated that the addition of cerium oxide to fuels may increase levels of specific organic chemicals in the exhaust, and result in emission of cerium oxide.* The criteria used to evaluate chemical substances in such situations, and the data and information gaps specific to nanomaterials compared to other chemical substances could be incorporated here.

Page 21, lines 16-29: The potential for energy savings through the use of nanomaterials is discussed, including potential applications to reduce energy loss through transmission lines using carbon nanotubes and to increase efficiency of photovoltaic cells using quantum dots and carbon nanotubes. If the applications cited in this section are realized, this would result in a substantial increase in the production and use of nanomaterials, which would also increase the potential exposures and implications for human health and the environment. Thus, it would be worthwhile to clearly state how the applications and implications research discussed in this document will be coordinated (mention here and provide detail in research needs and recommendations in Sections 5 and 6).

Page 24, lines 2-11: *Risk Management.* In this section the statutes available to EPA for risk management and the research needs to inform the risk assessment process are identified. Gaps in the current statutes that would not allow EPA to appropriately manage risks of nanomaterials should be included here.

Page 24, line 28-32: *Working in partnership with producers and users of nanotechnology to develop best practices…* EPA could also mention partnerships in this area with other government agencies.

Page 24, line 34: *EPA will review nanotechnology products and processes as they are introduced.* However, the document notes on page 8 that, "… meeting constantly changing demands will require proactive actions …" rather than reviewing processes and products "… as they are introduced." Current requirements that must be met before a nanomaterial is permitted to be introduced should be cited.

Page 24, line 39 and page 25, line 1: *EPA will use its statutory authorities, where appropriate, as the technology develops in the marketplace.* Providing the relevant reference citations would be useful.

Page 26, lines 16-18: *Until adequate nomenclature conventions are developed, it will be difficult to determine in some instances if reporting to EPA is required because the nanomaterials are not contained on the TSCA Inventory….* EPA plans to address this important issue could be discussed here.

Page 26, lines 31-33: *Nanoscale materials that are chemical substances under TSCA and which are not on the TSCA Inventory must be reported to EPA.* This statement appears to

conflict with the statement on lines 16-18 noted above. Please clarify whether or not reporting is currently required for unlisted chemical substances on the TSCA inventory and provide a reference citation for the TSCA inventory.

Page 26, lines 22-26 and lines 33-37: As stated here, existing standards need to be evaluated and possibly revised to address the novel characteristics of nanomaterials that influence their implications to humans and the environment. For example, the current regulations pertaining to the disposal or release of chemical substances in the environment could be discussed here, including any implications of mass-based or volume-based regulations for environmental release or disposal of nanomaterials, in view of the studies showing that nanoparticles are more toxic on a mass basis than larger particles of the same chemical composition (See additional comments and references for page 53, lines 41-44 and p. 120, lines 7-10).

Page 33, line 17: ... *and novel electrical and magnetic properties*. EPA may want to replace "electrical and magnetic" with "electronic" which additionally encompasses other relevant properties such as optical.

Page 33, line 28: *Occupational and environmental exposures to engineered nanomaterials have been reported ...* . This statement may imply that exposures have been reported for all nanomaterials. It can be suggested the sentence be reworded as follows: "Occupational and environmental exposures to a very limited number of engineered nanomaterials have been reported … ."

Page 35, lines 15-16: *...the potential for transformation of nanomaterials to more toxic metabolites…."* Evaluation of the potential toxicity of the parent nanomaterial should also be mentioned.

Page 35, lines 39-41 and page 36, line 1: ... *humans and other organisms may be exposed to large as well as smaller particles by inhalation.* Mention that these possible exposures may be to either freshly-generated or aged particles—a characteristic that has been shown to strongly influence reactivity and toxicity of nanoparticles [e.g., Oberdörster et al. 1995].

Page 40, lines 1-2: *It should be noted that the potential also exists for nanomaterials to effect unforeseen changes if released to the environment in large quantities.* It would be relevant to cite the provisions in the various statutes that pertain to the release of nanomaterials in the environment and specify the quantity of nanomaterials currently allowed to be released.

Page 41, lines 4-9: ... *Many groups are currently investigating the use of nanomaterials for the destruction of persistent pollutants in the environment.* In addition to these research efforts on applications of nanomaterials in pollution remediation, research on the potential environmental implications of introducing these reactive nanomaterials into the environment, including evaluations of toxicity, transport, and biopersistence should be cited. For nanomaterials that act as bacteriocides, research on the effects of these

nanomaterials on aquatic microorganisms which provide the foundation of the food chain in fresh water and marine environments should be cited, or the lack of such data indicated.

Pages 45-46: Section *4.5.3.1 Occupational Exposure.* The characterization of occupational exposure in this section is limited. In addition to exposure during synthesis, there is also the potential for exposure during research and development, during receipt of raw nanomaterials by downstream users, and in various operations in developing products for application and use. Maintenance on ventilation systems or filtration systems where nanomaterials have been captured may dislodge or resuspend nanomaterials exposing operators or maintenance workers. Exposure could also occur during product machining (e.g., cutting, drilling and grinding), repair, destruction and recycling [NIOSH 2005a].

Also, this section provides several examples of research needs and collaboration opportunities between NIOSH, EPA, and others (e.g., to assess jobs or processes with high exposure potential).

Page 46, lines 18-20: *No data have been identified quantifying the releases of nanomaterials from industrial processes or of the fate of nanomaterials after release into the environment.* It would be useful to state whether any of the existing statutes have provisions requiring the measurement and monitoring of nanomaterial releases, and if not, what are the nanomaterial-specific issues that pertain to measurement and monitoring.

Page 47, lines 4-5: *Nano-cerium oxide particles are being employed in Europe as on and off-road diesel fuel additives.* This statement should be referenced.

Page 47, lines 9-12: *Intentionally produced nanomaterials share a number of characteristics, such as size and dimensions, with other substances (e.g, ultrafine particles) for which significant information exists on how they access the human body to cause toxicity.* An additional recommendation for Section 6 is to evaluate this substantial body of existing data to determine how it may be used to provide information on potential exposures and adverse effects of intentionally-produced nanomaterials. This will be useful in the interim before complete data are available on all nanomaterials, which could be a long time given the considerable data needs for the large variety of nanomaterials at all stages of the life cycle, as described in this document. Toxicological data including chronic inhalation studies [Heinrich et al. 1995; Nikula et al. 1995] and shorter-term *in vivo* and *in vitro* studies [e.g., Donaldson et al. 1998; Brown et al. 2001] are already available on some intentionally-produced nanoparticles (e.g., ultrafine titanium dioxide, carbon black).

Page 47, lines 26-29: *This study noted that … concentrations of SWCNT… were very low (Maynard et al. 2004).* It should be clarified that the air concentrations measured in this study were relatively low *on a mass basis* (emphasis added). On a surface area basis, the concentrations would be higher compared to the same mass of larger particles. Also, it is

not known to what extent the data reported in this one study may represent conditions in other processes or uses of these nanomaterials. As noted on p. 49 (lines 8-9), *A potential issue when quantifying exposure is that mass dose…may not be an appropriate metric to characterize exposure to nanomaterials.* This issue could be specified in the research needs (e.g., page 78, lines 7-8).

Page 48: *Personal Protective Equipment.* EPA may wish to review Heim et al. [2005] for respirator filter efficiency data.

Page 48, lines 9-12: *The study noted that larger-than-respirable airborne particles of SWCNT may contribute to potential dermal exposure….* This statement is confusing because respirable particles (those capable of depositing in the gas exchange region of the lungs) have an upper limit of approximately 10 μm in humans [IARC 1994], while Tinkle et al. [2003] found that particles up to approximately 1 μm were able to penetrate human skin, but smaller particles (0.5 μm) did so to a greater extent. Thus, it is not clear how "larger-than-respirable" particles may contribute to dermal exposure, unless it is referring to irritation of the skin surface, not dermal penetration.

Page 48, lines 29-32: *As noted in the fate section above, small particles (diameters <80 nm) are short-lived because they rapidly coagulate to form larger particles. Large particles (>2000 nm) are subject to gravitational settling. Intermediate-sized particles (>80 nm and < 2000 nm) can remain suspended in air for the longest time.*

It would be useful if *rapid* were defined in this context. Relatively high nanoparticle number concentrations can exist for periods of time long enough to allow inhalation. For example, by agglomeration, a concentration of 10^6 particles/cm^3 has a half-life of approximately 30 minutes [Hinds 1999]. Furthermore, preliminary results have indicated that agglomerates held together relatively weakly (for example by Van der Waal's forces) have deagglomerated in the presence of surfactant-like substances with similar properties to those found in the human respiratory system [Maynard 2002].

Page 48, lines 36-37: *Particle filter efficiencies are typically measured at 300 nm because they are the most likely to penetrate the filters and represent a worst case.* This statement is not referenced. It can be suggested the statement be replaced with the following wording: "NIOSH certifies particulate respirators by challenging them with sodium chloride (NaCl) aerosols with a count median diameter 75 nm or dioctyl phthalate (DOP) aerosols with a count median diameter of 185 nm [42 CFR Part 84.181(g)], which have been found to be in the most penetrating particle size range [Stevens and Moyer 1989]."

Page 48, line 41: *No available data on face-seal leakage has been identified.* It can be suggested replacing this statement with the following: "Only limited data on face-seal leakage has been identified. Work done by researchers at the U.S. Army RDECOM on a headform showed that mask leakage (i.e., simulated respirator fit factor) measured using submicron aerosol challenges (0.72 μm polystyrene latex spheres) was representative of

vapor challenges such as sulfur hexafluoride (SF6) and isoamyl acetate (IAA) [Gardner, Hofacre, Richardson 2004]."

Page 50, line 7-14: It is worth mentioning the importance of personal sampling in occupational settings.

Page 50, lines 31-39 and page 51, lines 1-7: It would be helpful if reference citations were provided for the models discussed in this text.

Page 52, lines 22-25: *... the toxicity of chemically defined ultrafine particles, recently reviewed by Oberdorster et al. (2005).* An additional recent reference reviewing the toxicity of ultrafine particles is Donaldson et al. [2005].

Page 52, lines 32-34: *...graphite is not an appropriate safety reference standard for carbon nanotubes, since carbon nanotubes displayed very different mass-based dose-response relationships and lung histopathology when compared directly with graphite.* This information may be useful to EPA for future regulatory issues.

Page 53: *Figure 3. Particle Toxicity Citations.* Only the four engineered particles in the figure are labeled as "Nanomaterials," although other materials including ultrafine carbon black, ultrafine titanium dioxide, and ultrafine silica are nanomaterials according to the definition in Appendix A. These are also intentionally produced nanomaterials.

Page 53, lines 41-44 (and p. 120, lines 7-10): Three studies are cited that show ultrafines or nanoparticles are more toxic on a mass basis than are larger particles of the same chemical composition (Oberdorster et al. 1994; Li et al. 1999; and Hohr et al. 2002). Additional studies can be cited which have shown that particle surface area dose is a better predictor of the toxic and pathologic responses to inhaled particles than is particle mass dose, including: Oberdörster et al.1992; Driscoll 1996; Lison et al.1997; Donaldson et al.1998; Tran et al. 2000; Brown et al. 2001; and Duffin et al. 2002.

Page 54, lines 9-13: *Several studies have demonstrated that nanoparticle toxicity is extremely complex and multi-factorial, potentially being regulated by a variety of physicochemical properties such as size and shape, as well as surface properties such as charge, area, and reactivity.* This statement is not unique to nanoparticles, as the toxicity of larger particles and fibers is also influenced by these factors. Existing particle studies provide valuable information on the role of these properties on the toxicity, although data gaps remain even for larger-sized particles and fibers. (This comment also applies to page 69, lines 13-16).

Page 55, lines 12-27: Additional studies that provide information on the deposition and fate of inhaled nanomaterials include studies in animals: Takenaka et al. 2001; Kreyling et al. 2002 (2003 on line 15 appears to be incorrect); Oberdörster et al. 2002; and studies in humans: Brown et al. 2002; and Chalupa et al. 2004.

Page 56, lines 19-21: *Host susceptibility factors that influence the toxicity, deposition, fate and persistence of intentionally produced nanomaterials are unknown.* Chalupa et al. [2004] is a recent reference regarding the deposition of nanoparticles in the respiratory tract of asthmatics.

Page 57, lines 14-16: *Research will be needed to assess the health and environmental risks associated with environmental applications of nanotechnology.* How this implications research will be coordinated with the applications research could be added to Section 6.4, Recommendations for Collaborations (p. 80).

Page 62, lines 5-8: *The sheer variety of nanomaterials and nanoproducts adds to the difficulty of developing research needs. Since we don't have a complete understanding of how nanoparticles behave, each stage in their lifecycle, from extraction to manufacturing to use and then to ultimate disposal, will present separate research challenges.* Many of these areas are not fully understood for larger particles either.

Page 65, lines 27-28: *What are the physicochemical factors that affect the persistence of intentionally produced nanomaterials in the environment?* The physicochemical properties that influence the persistence of nanomaterials in the environment are not necessarily specific to intentionally produced nanomaterials. A related question is what data are available on the physicochemical factors that affect the persistence of unintentionally produced nanomaterials (e.g., carbon-based combustion products), which may provide information regarding intentionally produced nanomaterials of similar chemical composition and physical characteristics.

Page 68, lines 23-24: *Are current engineering controls and pollution prevention devices capable of minimizing releases and exposures to nanomaterials?* How the effectiveness of these control devices will be evaluated with regard to "minimizing releases and exposures," how exposures will be measured, and how it will be determined if the measured exposures are safe are relevant research questions that are also related to research questions in Sections 5.5 and 5.7.

Page 69, line 35-37: *Research is also needed to examine health impacts of highly dispersive nanotechnologies that are employed for site remediation, monitoring, and pollution control strategies.* This is an important data gap. Research in this area should be coordinated with research and development on potential applications involving intentionally dispersed nanomaterials. (This comment also applies to p. 74, section *6.2.1 Research Recommendations for Environmental Applications*).

Page 75: *6.2.2 Research Recommendations for Environmental Implications.* A multidisciplinary strategy, as described here, is appropriate. Section 6.2.2 is well-written, with prioritized research goals, and with consideration of how the findings would relate to other programs (e.g., p. 75, lines 38-39; p. 77, lines 4-7). Several key areas for collaboration between NIOSH and EPA are cited (e.g., p. 76, lines 9-22; p. 77, lines 9-21).

Pages 77-78: *Section 6.2.2.2 Human Health Effects Assessment Research Recommendations.* The research recommendations in this section are appropriate. Issues considered include waste byproducts associated with production (lines 30-31, p. 77) and toxicological endpoints of particular concern for nanoparticles (p. 79, lines 1-7).

Page 77, lines 9-11: Justification for OPPT to limit interactions with NIOSH on exposure scenarios for nanomaterials in manufacturing to "possible consultation" rather than to collaboration is not clear.

Page 78, lines 7-15: *Hazard Identification and Dosimetry & Fate.* The evaluation of existing particle data bases should also be considered to provide data and information that may be applicable to hazard identification, dosimetry, and fate of new nanoparticles.

Page 99, line 1: *... sized particles that may or may.* This sentence appears to be truncated or incomplete.

Page 101, Appendix B: It would be instructive to describe the history of this document and whether it has been published before.

Page 103, line 23, Appendix C: It would be instructive to indicate the half-life of coagulation mode particles.

Page 103, line 36, Appendix C: Please explain what "W" is.

Page 110, C2 *The Environmental Detection and Analysis of Nanomaterials*:
It would be useful to include both the upper and lower limit of particle size detection for each instrument discussed in this section; observed size range capabilities from laboratory and field work are important as well. Those sampling and analytical methods that provide usable measures of exposure that can be linked to adverse health outcomes and risk would benefit the effectiveness of the document.

Page 111, lines 6-8: *Cascade impactors consist of a collective series of inertia-based impactors and are limited to fractionating nanometer particles in size ranges of no less than approximately 50 nanometers (McMurry, 2000).* McMurry [2000] is a review article and is inaccurate on this point. The Electrical Low Pressure impactor (ELPI), commercially available since the early 1990s, utilizes a last impactor stage with a cutpoint of approximately 30 nm.

Page 114, line 2, Appendix C: figure A1 could not be found.

Page 114, lines 12-16: *A fast mobility particle sizer spectrometer (FMPS) (TSI, 2005B) has the ability to measure the size distribution and concentration of nanoparticles in real time. Where the SMPS is limited to a single scan every three minutes at one electrical potential, the FMPS, by using an array of electrometers as charged particle detectors, can simultaneously assess the concentration of nanoparticles in multiple size ranges within seconds.*

The ELPI (Dekati) provides a real time size distribution over a wider size range (7nm - 10µm) than the FMPS [6 to 560 nm], but uses a combination of diffusion charging and inertial separation rather than electrical mobility (utilized for the SMPS and FMPS above) to differentiate particle size [Keskinen et al. 1992; Marjamäki et al. 2000].

Considering only electrical mobility measurements, instrumentation is available offering slightly higher performance over that of the TSI FMPS, which offers a one second resolution (www.tsi.com). The Cambustion DMS50 (www.cambustion.co.uk) offers 0.1 second resolution over the 5 to 500 nm size range, and is capable of running directly from 12V DC making this instrument more amenable to field use.

Page 114, lines 18-19: *Optical particle counters (OPCs) using lasers as light sources can detect nanoparticles down to approximately 50 nanometers (McMurry, 2000).* McMurry notes that, "Lasers provide illuminating intensities several orders of magnitude higher than can be achieved with incandescent sources, thereby enabling the detection of significantly smaller particles; laser OPCs having minimum detection limits of ~ 0.05 µm are available, while white light OPCs typically cannot detect particles smaller than ~ 0.3 µm." Hinds [1999] text states that even with the use of the best light sources such as coherent (laser) light the counting efficiencies of OPCs are at 100% for particles > 100 nm. Particles claimed to be counted in the 50 to 100 nm range using OPCs are not reliable. It would be more accurate to state in this section of the white paper that OPCs operate in a usable range of 100 nm up to 5,000 nm reliably (see Hinds [1999], pages 349 and 374).

Pages 115-118, Appendix C, Subsection C2.5 "Chemical Composition": there are some new techniques developed recently for characterizing nanoscale airborne particles (e.g. Nanoaerosol Mass Spectrometer described in Wang S, et al. Chemical Characterization of Individual, Airborn Sub-10 nm Particles and Molecules. Anal. Chem. 2006, 78, 1750.)

Page 115, lines 13-17: *More recently, the development by TSI of a nanoparticle surface area monitor based upon the diffusion charging of particles followed by electrometer detection provides data that correlates with the deposition of airborne nanoparticles in human respiratory systems (TSI, 2005D). These real time analyses are capable of assessing particles in the 10 nm to 1000 nm range.* The TSI "Nanoparticle Surface Area Monitor" is a direct descendent of the TSI Electrical Aerosol detector which *"… appears not to give a useful measurement of the particle surface area. "* [Wilson et al. 2003]. A true Fuchs, or active surface area, is defined as the surface of a particle that is involved in interactions with the surrounding gas and should be proportional to particle diameter squared in the free molecular regime (approximately 80 nm or smaller) [Fuchs 1963]. The response of the TSI Electrical Aerosol Detector and the TSI "Nanoparticle surface area Monitor" is proportional to particle diameter to the power of 1.16 [Wilson et al. 2003], and, therefore, has no relevance. However, TSI does claim that the response of the nanoparticle surface area monitor is more closely related to a "deposited surface area" in the human respiratory system [www.tsi.com]. A full and critical peer reviewed

evaluation of this instrument is currently lacking and would be a useful contribution before recommending this instrument.

Two real-time surface area instruments critically evaluated recently [Ku and Maynard 2005] do show a true Fuchs or active surface area response to particle diameter in the range of 20 – 100 nm. These units are manufactured by Matter Engineering and EcoChem respectively, the latter instrument being extensively used in the workplace to monitor active particle surface area [Peters et al., in press]. NIOSH is actively conducting research in this area.

Cited References

Brown DM, Wilson MR, MacNee W, StoneV, Donaldson K [2001]. Size-dependent proinflammatory effects of ultrafine polystyrene particles: A role for surface area and oxidative stress in the enhanced activity of ultrafines. Toxicol Appl Pharmacol 175(3):191–199.

Brown JS, Zeman KL, Bennett WD [2002]. Ultrafine particle deposition and clearance in the healthy and obstructed lung. Am J Respir Crit Care Med 166:1240–1247.

Chalupa DC, Morrow PE, Oberdorster G, Utell MJ, Frampton MW [2004]. Ultrafine particle deposition in subjects with asthma. Environ Health Perspect 112(8):879–882.

Dick CAJ, Brown DM, Donaldson K, Stone V [2003]. The role of free radicals in the toxic and inflammatory effects of four different ultrafine particle types. Inhal Toxicol 15(1):39–52.

Donaldson K, Li XY, MacNee W [1998]. Ultrafine (nanometer) particle mediated lung injury. J Aerosol Sci 29(5-6):553–560.

Donaldson K, Tran L, Jimenez L, Duffin R, Newby DE, Mills N, Macnee W, Stone V [in press]. Combustion-derived nanoparticles: A review of their toxicology following inhalation exposure. Part Fibre Toxicol 2(1):10.

Driscoll KE [1996]. Role of inflammation in the development of rat lung tumors in response to chronic particle exposure. Particle overload in the rat lung and lung cancer: implications for human risk assessment. In: Mauderly JL, McCunney RJ, eds. Philadelphia, PA: Taylor & Francis, pp.139–152.

Duffin R, Tran CL, Clouter A, Brown DM, MacNee W, Stone V, Donaldson K [2002]. The importance of surface area and specific reactivity in the acute pulmonary inflammatory response to particles. Ann Occup Hyg 46:242–245.

Fuchs NA [1963]. On the stationary charge distribution on aerosol particles in a bipolar ionic atmosphere. Geofisica Pura E Applicata 56:185–193.

Gardner P, Hofacre K, Richardson A [2004]. Comparison of Simulated Respirator Fit Factors Using Aerosol and Vapor Challenges. J Occ Env Hyg 1:29-38.

Gharbi N, Pressac M, Hadchouel M, Szwarc H, Wilson SR, Moussa F [2005]. [60]Fullerene is a powerful antioxidant in vivo with no acute or subacute toxicity. Nano Lett. 5(12):2578-2585.

Heim M, Mullins BJ, Wild M, Meyer J, Kasper G [2005]. Filtration efficiency of aerosol particles below 20 nanometers. Aerosol Sci & Tech 39(8):782-789.

Hinds WC [1999]. Aerosol technology: properties, behavior, and measurement of airborne particles. 2nd ed. New York: John Wiley & Sons.

ICRP (1994). Human respiratory tract model for radiological protection. International commission on radiological protection: Publication 66. Oxford, Pergamon, Elsevier Science Ltd.

Keskinen J, Pietarinen K, Lehtimäki M [1992]. Electrical low-pressure impactor. J Aerosol Sci 23:353–360.

Ku B, Maynard A [2005]. Comparing aerosol surface-area measurements of monodisperse ultrafine silver agglomerates by mobility analysis, transmission electron microscopy and diffusion charging. J Aerosol Sci 36:1108–1124.

Lison D, Lardot C, Huaux F, Zanetti G, Fubini B [1997]. Influence of particle surface area on the toxicity of insoluble manganese dioxide dusts. Arch Toxicol 71(12):725–729.

Marjamäki M, Keskinen J, Chen D-R, Pui DYH [2000]. Performance evaluation of the electrical low-pressure impactor (ELPI). J Aerosol Sci 31:249–261.

Maynard A [2002]. Experimental determination of ultrafine TiO_2 deagglomeration in a surrogate pulmonary surfactant: Preliminary results. Ann Occup Hyg 46(1)(Suppl):197–202.

Murashov V [2006]. Letter to the Editor. Comments on "Particle surface characteristics may play an important role in phytotoxicity of alumina nanoparticles" by Yang, L., Watts, D.J., published in Toxicology Letters, 2005, 158, 122-132. Tox Lett. In press.

NIOSH [2005a]. Approaches to safe nanotechnology: An information exchange with NIOSH. http://www.cdc.gov/niosh/topics/nanotech/nano_exchange.html. Accessed on February 3, 2006.

NIOSH [2005b]. Nanoparticle information library. http://www.cdc.gov/niosh/topics/nanotech/NIL.html. Accessed on February 3, 2006.

NIOSH [2005c]. Strategic Plan for NIOSH Nanotechnology Research Program. http://www.cdc.gov/niosh/topics/nanotech/strat_plan.html. Accessed on February 3, 2006.

NIOSH [2005d]. Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide. http://www.cdc.gov/niosh/docs/preprint/tio2/. Accessed on February 3, 2006.

Oberdörster G, Ferin J, Gelein R, Soderholm SC, Finkelstein J [1992]. Role of the alveolar macrophage in lung injury–studies with ultrafine particles. Environ Health Perspect 97:193–199.

Oberdörster G, Gelein R, Ferin J, Weiss B [1995]. Association of particulate air pollution and acute mortality: involvement of ultrafine particles? Inhal Toxicol 7:111–124.

Peters T, Heitbrink W, Evans D, Slavin T, Maynard A [in press]. The mapping of fine and ultrafine particles in an engine machining and assembly facility. Ann Occup Hyg

Stevens and Moyer E [1989]. "Worst Case" Aerosol Testing Parameters: I. Sodium Chloride and Dioctyl Phthalate Aerosol Filter Efficiency as a Function of Particle Size and Flow Rate. AIHAJ 50:257 – 264.

Takenaka S, Karg E, Roth C, Shills H, Ziesenis A, Heinzmann U, Scrammed P, Heyder J [2001]. Pulmonary and systemic distribution of inhaled ultrafine silver particles in rats. Environ Health Perspect 109(4)(Suppl):547–551.

Tinkle SS, Antonini JM, Rich BA, Robert JR, Salmen R, DePree K, Adkins EJ [2003]. Skin as a route of exposure and sensitization in chronic beryllium disease. Environ Health Perspect 111(9):1202–1208.

Wilson W, Han H, Stanek J, Turner J, Pui D [2003]. The Fuchs surface area, as measured by charge acceptance of atmospheric particles, may be a useful indicator of the surface area of particles deposited in the lung. Abstracts of the European aerosol conference, Madrid, Spain. J Aerosol Sci S421–S422.

Stephen S. Olin

ACRONYMS, pp. ix-xi – "GSH" is the acronym for Glutathione. "GST" is the acronym for Glutathione-S-Transferase. Definitions are missing for OCIR, OIA, and OPA (acronyms used on pp. 73 and 80).

p. 6, line 6 – I wasn't aware that 'fullerene' is a synonym for all carbon-based nanomaterials. I thought it only referred to the 'buckyball' type structure, and not to carbon nanotubes and other carbon shapes.

p.6, line 18 – "…dendrimer has numerous…"

p.7, Table 1 – Are all of these "nanotechnology products" already in commerce? It is not clear from the text.

Section 2 – Quite a number of references cited in the text of this section do not appear in the reference list (Section 7.0). Examples include: Elliot and Zhang, 2001; Quinn et al, 2005; Dror, 2005; Diallo, 2005; Pitoniak, 2005; Kanel, 2005; Mattigod, 2003. NREL, 2005 is U.S. Department of Energy, 2005.

p.17, lines 7-10 – May be true at the level of total mass generated but is likely not true in the US for specific pollutants (e.g., lead).

pp.18-19 – The section on Sensors would benefit from a bit more detail and some references.

p.19, lines 20-21 – "…and drastically reducing waste products." This may be true, but just a cautionary note: if part of the waste from nanotech processes is the nanomaterial itself, we need to take account of the possibly 'drastically increased' activity per unit mass of nanomaterials compared with conventional waste products in our calculations.

p.21, lines 12 & 13 – Is "styrol" actually styrene (after translation from German)?

p.24, line 9 – "An understanding of the toxicity…"

p.25, line 38 – "EPA can provide…"

p.28, line 27 – "Title III of the 1990…"

p.36, line 6 – "…during the handling and use…"

p.55, line 8 – "…physicochemical…"

p.59, lines 21 & 25 – "SWCNT"

p.59, lines 29-30 – Is a reference for this information available?

p.60, lines 24-28 – It seems too optimistic to suggest that extrapolation of toxicity information from conventional substances to nanomaterials "may be based on existing structure-activity relationships (SARs), such as SARs for polycationic polymers,…" It is possible that such extrapolations may be informed by existing SARs, along with other available data.

pp.60-61 – Section 4.7.5 (Ecological Testing Requirements), although rather general, is a helpful section. A similar section has not been included for Human Health Effects Testing Requirements, but it would be helpful to have one. Section 4.6.4 (Capabilities of

Current Test Methodologies) could be renamed and expanded to incorporate such a discussion.

p.64 – Section 5.3 (Chemical Identification and Characterization) is an important research area for understanding and interpreting data on toxic effects and exposures, as noted in the text and in the response to Question II.B above. Some rephrasing of the research needs in Section 5.3 may be appropriate. For example:

> • What are the unique chemical and physical characteristics of nanomaterials? How do these characteristics vary among different classes of materials (e.g., nanotubes, fullerenes) and among the individual members of a class?
>
> • How do these properties affect the material's reactivity, toxicity and other attributes?
>
> • To what extent will it be necessary to tailor research protocols to the specific type and use pattern of each nanomaterial? Can properties and effects be extrapolated within a class of nanomaterials?
>
> • Are there adequate measurement methods/technology available to fully characterize nanomaterials, to distinguish among different types of nanomaterials, and to distinguish between intentionally produced nanomaterials and ultrafine particles or naturally occurring nano-sized particles?
>
> • Are current test methods for characterizing nanomaterials adequate for the evaluation and interpretation of hazard and exposure data?
>
> • Do nanomaterial characteristics vary from their pure form in the laboratory to their form as components of products and eventually to the form in which they occur in the environment?
>
> • What intentionally produced nanomaterials are now on the market and what new types of materials can be expected to be developed?
>
> • How will manufacturing processes, formulations, and incorporation in end products alter the characteristics of nanomaterials?

p.65, lines 1-2 – What is the meaning of, "Do novel materials, such as fullerenes without corresponding bulk materials, differ in their mobility from the bulk materials?"?

p.66, line 37 – Delete "need to".

p.70, line 27 – "…absorption, …"; see also p.78, line 11.

p.75, line 3 – "…nanomaterials at a basic level…"

p.94, lines 43-45 – The study cited here was commissioned by the UK Government. Following release of the study by the Royal Society and Royal Academy of Engineering, the UK Government published a Response (February 2005), which also should be cited here:
http://www.ost.gov.uk/policy/issues/nanotech_final.pdf.

p.99, line 1 – "…sized particles that may or may not have properties different from those of the bulk material from which they are developed."

p.99, line 10 – Delete. (Repeated on line 24.)

p.100, line 4 – Delete "and/or intermediate" – compare with p.4, lines 16-17.

Jennifer B. Sass

The discussion of regulatory statutes (p. 24-32) inadequately identifies the gaps or limitations with these statutes regarding their ability to regulate nanomaterials in such as way that the public is adequately protected. It is not clear from reading the section why nanomaterials are not being regulated already. For example, p. 24, line 34 says, "EPA will review nanotechnology products and processes as they are introduced?" How is this possible if there are already over 200 commercial products with nanomaterials, and more uses in industrial processes?

Section 1.5.1. What research is EPA actually doing? What are the other agencies doing? What materials are currently undergoing testing? What specific testing strategies are being employed, and for what materials? This section is too vague, unhelpful. Has an uncomfortable, "trust us, we're experts" flavor.

p. 14, line 1: can the SBIR program be used to drive green nano R&D that uses inherently safe design? What kinds of research are being funded under this program?
p. 8, line 24: how will EPA respond to the convergence of technologies?
p. 14, line 15, p. 75: why has EPA not initiated in-house research? Who else besides EPA is doing ecological fate and transport research? Doesn't that fall uniquely within the interests of EPA? If so, when will this be initiated?
p. 14, line 37: what new chemical submissions for nanomaterials have been submitted under TSCA, and what finding did EPA make? Did EPA require safety data? What uses will these materials have?
p. 15, line 5: who is regulation nano-cerium? what safety data was required? is there any monitoring of emissions? any monitoring of worker exposures on work sites where nano-cerium fuel is used?
p. 15, line 32, p. 73: how is EPA actively promoting green chemistry and engineering?
p. 24, line 28: how is EPA actively promoting good stewardship in workplaces? in environmental programs? how does EPA know they are working? how is EPA ensuring compliance?
p. 24, line 34: how can EPA review nanotechnology products as they are produced, when there are already over 200 in commercial products?

p. 25, line 5, p. 73: if EPA is truly committed to preventing pollution, why not regulate to prevent dispersive uses of untested or unsafe materials?
p. 26, section 3.2. this would benefit from more discussion of whether or not these statutes are effective for preventing unsafe uses and exposures to nanomaterials, and why or why not

Donald A. Tomalia

1. Section 4.6.2, page 53, line 7: Uf defines ultrafine size (<0.1 *micron* vs. nm)
2. Section 4.6.7, page 57, para. 2, line 13: .. within a variety *of* environmental….
3. Section 4.7.2, page 57,; para.1: In the dendritic polymer literature (e.g., dendrimers), there are substantial data published on size, surface chemistry, charge effects, etc. required for endocytosis or transport across cell membranes, as well as some preliminary data on excretion pathways that should be mentioned.
4. Section 5.1, page 62,: para. 1 line 8. ….of nanoparticles' *physico/chemical* vs. scientific properties.
5. Section 5.3, page 64,: I totally agree with this section. Reproducible work that articulately defines the identification/characterization of nanomaterials is critically important for determining risk/benefit boundaries. It should be part of a comprehensive roadmap, that allows one to systematically categorize new nano-entities as a function of their physico/chemical surface functionality (composition) (i.e., is it hydrophobic, amphiphilic, hydrophilic, etc.?), nano-size, shape (i.e., spheroid, rod-like, etc.), architecture, flexibility/rigidity/compressibility, thermal /hydrolytic/enzymatic stability, etc.
6. page 64, section 5.4 : line 2; …for *exposure to* humans and…
7. Section 5.7; page 69: para. 2 line 16…..size of particles *decrease*, a resulting ….
8. Section 5.6.2 ; Release and Exposure Quantitation Research Questions- In response to questions raised in this section, it should be pointed out that substantial information involving topical contact of nanostructures such as dendrimers should be available from companies such as Starpharma, Melbourne, Australia who are in Phase I clinical trials with humans based on well defined safety margins in their pre-clinical studies.
9. Prompted by the lack of systematic nanotoxicity knowledge required for risk/benefit assessment of critical importance for FDA needs/understanding, several FDA representatives (i.e., Dr. Ajaz Hussein, former Deputy Dir. CDER, now in the private sector and Dr. Nakissa Sadrieh, FDA, Assoc. Dir. For Research Policy and Implementation) have proposed a "works in progress draft white paper". This white paper is proposed to outline the systematic features offered by dendrimers to allow the establishment of toxicity, pharmacokinetic, etc. baselines for well defined/characterized nanostructures as a function of their nanoscale size, shape, surface chemistry, etc. See the following references for background: "STARBURST® Dendrimers: Molecular Level Control of Size, Shape, Surface Chemistry, Topology and Flexibility from Atoms to Macroscopic Matter," D.A. Tomalia, A.M. Naylor W.A. Goddard III, *Angew. Chem. Int. Ed. Engl.*, 29(2), 138-75 (1990); "Dendrimers – An Enabling Synthetic Science to Controlled Organic Nanostructures," D. Tomalia, R. Esfand, K. Mardel, S.A. Henderson, G.

Holan, Chapter 20 in *Handbook of Nanoscience, Engineering and Technology*, edited by W.A. Goddard III, D.W. Brenner, S.E. Lyshevski, G.J. Irafrate, CRC Press, Boca Raton, 20.1-20.34 (2002) and "Birth of a New Macromolecular Architecture: Dendrimers as Quantized Building Blocks for Nanoscale Synthetic Polymer Chemistry," D.A. Tomalia, *Prog. Polym. Sci.*, 30, 294-324 (2005).

10. Section 6.7. Summary of Recommendations. This section provides a very nice summary of recommendations; however, the priorities and timelines appear to be vague and not well defined.

Nigel J. Walker

There is often repetitive language on the same issue within the document, e.g. cerium oxide as a full additive is mentioned at least three times in the document.

Page 6 the examples section could be a lot more comprehensive and descriptions could be much more scientific. In addition the text on quantum dots is incorrect. The core of a quantum dot determines its optical properties, not its surface. Also not all quantum dots are dots. The grammar for the dendrimers section is incorrect.

The use of these categories for binning seems too simplistic and unclear as to the logic behind it. How would a dendrimer-coated quantum dot, a commercial product that is available, be categorized in this scheme? Also where would one place a functionalized fullerene/nanotube, or a silica nanorod? It is likely that as written, almost all nanomaterials would fall under composites under the present scheme.

Page 7 Section 1.2.1. This section on converging technologies would be better placed later in the document.

The referencing of specific papers for specific points is inconsistent. In some cases specific papers are cited for specific points but in other cases, citations are inadequate e.g. Section 4.3 makes many statements about nanoscale materials that are not cited at all. While it is unreasonable to expect every statement to be referenced, care should be taken to cite papers that represent new knowledge, particularly those points that are specific to nanoscale materials.

Page 14- Spelling- National Institute **of** Environmental Health Sciences

Page 17- the opening sentence is complete hyperbole. It is hard to image with a population increase of 50 % over the next 50 yrs how any technology can "shrink the human footprint on the environment"

Page 20 What is a more targeted fertilizer?

Figure 3-page 53- the number of publications seems very low given the description. More details should be given as to what this figure depicts. E.g. my own personal PubMed search of "dendrimer" yields over 800 citations so clearly some additional limits were

used to get so few publications. Also what would "toxicological" mean? There are large numbers of studies on the disposition of dendrimers in the drug delivery literature that may not fall under Toxicology.

Page 56. The report of the Florida workshop can be found at
http://ntp.niehs.nih.gov/files/NanoToxWorkshop.pdf or
http://www.nanotoxicology.ufl.edu/workshop/index.html

David B. Warheit

No Specific Comments, but four references texts are shown with abstracts of each.

Reference No. 1

Warheit DB. Nanotechnology. In the Encyclopedia of Toxicology 2e, 2005
Current Concepts on the Pulmonary Toxicity of Nanoparticulates

Abstract

Pulmonary toxicology studies in rats demonstrate that ultrafine or nanoparticles (generally defined as particles in the size range < 100 nm) administered to the lung produce an enhanced pulmonary inflammatory response when compared to larger particles of identical chemistry at equivalent mass concentrations. Particle surface area and particle number appear to play important roles in the mechanisms of nanoparticle toxicity. The terms "ultrafine" and "nano" can be used interchangeably, with the former being an older terminology and the latter representing a current nomenclature. Contributing to the effects of inflammation-promoting effects of nanoparticles is their very high size-specific deposition when inhaled as singlet particles rather than as aggregated particles. Some evidence suggests that inhaled nanoparticles, after deposition in the lung, largely escape alveolar macrophage surveillance and transmigrate through epithelial cells to the pulmonary interstitium, generally considered to be a vulnerable anatomical compartment of the respiratory system.

It is important to note that most of the published lung toxicity studies with nanoparticles have been conducted in laboratory animals at very high particle concentrations, which significantly exceed workplace or ambient exposures. These hazard-based toxicity studies are designed to assess pulmonary effects caused by particles at high concentrations and can result in the induction of lung tumors in rats following 2-year exposures. Specifically, chronic inhalation studies with nano and fine-sized TiO_2 particles (average primary particle sizes ~20 nm and ~270 nm, respectively) have shown that ultrafine particles are > 10 times more potent than fine particles in producing pulmonary fibrosis and consequent lung tumors in rats (Lee et al., 1985; Heinrich et al., 1995). Additional studies have been conducted using intratracheal instillation exposures to aggregates of ultrafine and fine carbon black, as well as to TiO_2 particles in rats (Oberdorster et al., 1998; Li et al, 1996); and results have demonstrated a significantly enhanced lung inflammatory potency of the ultrafine particles when compared to fine-sized particulates of similar composition. However, when the instilled doses were

expressed in terms of particle surface area, the responses of the ultrafine and fine TiO_2 particles fell on the same dose-response curve. This is because a given mass of ultrafine particles has a much greater surface area (and particle number) than the same mass of fine, yet respirable (3 μm) particles and therefore is more likely to cause particle overload in the lung. Thus, from a risk assessment and regulatory viewpoint, it will be important to delineate the pulmonary toxicity effects of ultrafine particles in rats at overload vs. non-overload conditions.

It may be surprising to note that the total lung toxicity database for systematic comparisons of the effects of ultrafine/nanoparticles vs. fine-sized particles in rats consists of studies on only 3 particle-types: namely titanium dioxide, carbon black and diesel exhaust particles (Lee et al., 1985; Ferin et al., 1992; Heinrich et al., 1994, 1995; Dasenbrock et al., 1996; Driscoll et al., 1996; Mauderly, 2001). Moreover, as stated above, the rat model, for which most if not all of the nano vs. fine size comparisons have been reported, is known to be an extremely sensitive species for developing adverse lung responses to particles, particularly at overload concentrations. As a consequence, long-term (2-year), high-dose, inhalation studies in rats with poorly soluble, low toxicity dusts can ultimately produce pulmonary fibrosis and lung tumors via an "overload" mechanism. The tumor-related effects are unique to rats and have not been reported in other particle-exposed, rodent species such as mice or hamsters, under similar chronic conditions (Hext, 1994; Warheit, 1999; ILSI, 2000). For the mechanistic connection, it has been postulated that the particle-overload effects in rats result in the development of "exaggerated" lung responses, characterized by increased and persistent levels of pulmonary inflammation, cellular proliferation and inflammatory-derived mutagenesis in the rat, and this ultimately results in the development of lung tumors following high dose, long-term exposures to a variety of particulate-types. In contrast to the response in rats, evidence from numerous studies demonstrate that particle-exposed mice and hamsters do not develop sustained inflammation, mesenchymal cell alterations and consequent lung tumors following high-dose, long-term exposures to low-toxicity dusts (Hext, 1994). Therefore species differences in lung responses to inhaled particles is an important consideration for assessing the health risks to nanoparticles.

To complicate further our perceptions of nanoparticle toxicity, some recent evidence suggests that, on a mass basis, not all nanoparticle-types are more toxic than fine-sized particles of similar chemical composition. As mentioned previously, the limited number of studies that have been reported suggest that ultrafine titanium dioxide particles produced greater pulmonary inflammation when compared with fine-sized TiO_2 particles. However, in contrast to the conclusions of the earlier findings, the results of recent preliminary studies comparing the effects of nano vs. fine-sized particles, have indicated that pulmonary exposures in rats to uncoated TiO_2 nanorods (200 nm lengths x 30 nm diameters) and TiO_2 nanodots (particle size < 30 nm) did not produce enhanced lung inflammation in rats when compared to fine-sized TiO_2 particles\ exposures (particle size ~ 270 nm). Other lung bioassay studies have compared the toxicity effects in rats of uncoated nanoscale quartz particles (50 nm) vs. fine-sized quartz particles (particle size ~ 1.6 μm). In pulmonary instillation studies, at equivalent mass doses, the nanoquartz particles produced less intensive and sustained pulmonary inflammatory and cytotoxic

responses when compared to the effects produced by the Min-U-Sil quartz particles (52). This result is intriguing since crystalline quartz silica particles are classified as a Category 1 human carcinogen by the International Agency for Research on Cancer (IARC) (17). In summary, the preliminary findings from these two studies suggest that particle size is only one factor in determining pulmonary toxicity.

In addition to the issues of particle size and species differences as discussed above, several additional variables are likely to play important roles in modifying the pulmonary toxicity of nanoparticles: These include the following:

1) surface coatings on particles may play an important role in influencing pulmonary effects. In this respect, using a pulmonary bioassay toxicity methodology, we recently assessed the pulmonary toxicity of a number of commercial formulations of fine-sized titanium dioxide (TiO_2) particles in rats - each formulation with different surface coatings/treatments. The results demonstrated that one of the formulations containing enhanced amounts of amorphous silica and alumina surface coatings on the TiO_2 particle produced greater pulmonary inflammation and cytotoxic effects when compared to the other formulations containing different surface treatments (51).

2) The degree to which engineered nanoparticles aggregate in the ambient aerosol and subsequently disaggregate following inhalation will strongly influence particle deposition patterns and interactions with lung cells. If the ultrafine particles disaggregate upon interaction with alveolar lung fluids, then they could behave as discrete individual nanoparticles and may stimulate enhanced inflammatory cell recruitment and/or the particles could preferentially translocate to more vulnerable compartments of the lung.

Reference No. 2

Warheit DB, Brock W, Lee KP, Webb TR, Reed KL

Comparative Pulmonary Toxicity Inhalation and Instillation Studies with Different TiO2 Particle Formulations: Impact of Surface Treatments on Particle Toxicity. Toxicol Sci. 88:514-524, 2005 Sep 21; [Epub ahead of print]

Abstract

Most pigment-grade titanium dioxide (TiO_2) samples that have been tested in pulmonary toxicity tests have been of a generic variety – i.e., generally either uncoated particles or TiO_2 particles containing slightly hydrophilic surface treatments/coatings (i.e., base TiO_2). The objectives of these studies were to assess in rats, the pulmonary toxicity of inhaled or intratracheally instilled TiO_2 particle formulations with various surface treatments, ranging from 0-6% alumina (Al_2O_3) or alumina and 0-11%

amorphous silica (SiO_2). The pulmonary effects induced by TiO_2 particles with different surface treatments were compared to reference base TiO_2 particles and controls. In the first study, groups of rats were exposed to high exposure (dose) concentrations of TiO_2 particle formulations for 4 weeks at aerosol concentrations ranging from 1130 – 1300 mg/m^3 and lung tissues were evaluated by histopathology immediately after exposure, as well as at 2 weeks and 3, 6, and 12 months postexposure. In the second study, groups of rats were intratracheally instilled with nearly identical TiO_2 particle formulations (when compared to the inhalation study) at doses of 2 and 10 mg/kg. Subsequently, the lungs of saline-instilled and TiO_2-exposed rats were assessed using both bronchoalveolar (BAL) biomarkers and by histopathology/cell proliferation assessment of lung tissues at 24 hrs, 1 week, 1 and 3 months postexposure. The results from these studies demonstrated that for both inhalation and instillation, only the TiO_2 particle formulations with the largest components of both alumina and amorphous silica surface treatments produced mildly adverse pulmonary effects when compared to the base reference control particles. In summary, two major conclusions can be drawn from these studies: 1) surface treatments can influence the toxicity of TiO_2 particles in the lung; and 2) the intratracheal instillation-derived, pulmonary bioassay studies represent an effective preliminary screening tool for inhalation studies with the identical particle-types used in this study.

Reference No. 3

Warheit DB, Webb TR, Sayes CM, Colvin VL, and Reed KL.

Pulmonary Instillation Studies with Nanoscale TiO_2 Rods and Dots in Rats: Toxicity is not dependent upon Particle Size and Surface Area. Toxicol Sci. 2006 Feb 22; [Epub ahead of print]

Abstract

Pulmonary toxicology studies in rats demonstrate that nanoparticles administered to the lung are more toxic than larger, fine-sized particles of similar chemistry at identical mass concentrations. The aim of this study was to evaluate the acute lung toxicity in rats of intratracheally instilled pigment-grade TiO_2 particles (rutile-type- particle size = ~300 nm) vs. Nanoscale TiO_2 rods (anatase – 200 nm x 35 nm) or Nanoscale TiO_2 dots (anatase - ~10 nm) compared with a positive control particle-type, quartz. Groups of rats were instilled either with doses of 1 or 5 mg/kg of the various particle- types in phosphate-buffered saline (PBS). Subsequently, the lungs of PBS and particle-exposed rats were assessed using bronchoalveolar lavage (BAL) fluid biomarkers, cell proliferation methods, and by histopathological evaluation of lung tissue at 24 hrs, 1 week, 1 month and 3 months post-instillation exposure.

Exposures to Nanoscale TiO_2 rods or Nanoscale TiO_2 dots produced transient inflammatory and cell injury effects at 24 hours postexposure (pe) and were not different from the pulmonary effects of larger-sized TiO_2 particle exposures. In contrast, pulmonary exposures to quartz particles in rats produced a dose-dependent lung inflammatory response characterized by neutrophils and foamy lipid-containing alveolar

macrophage accumulation as well as evidence of early lung tissue thickening consistent with the development of pulmonary fibrosis.

The results described herein provide the first example of nanoscale particle-types which are not more cytotoxic or inflammogenic to the lung compared to larger-sized particles of similar composition. Furthermore, these findings run counter to the postulation that surface area is a major factor associated with the pulmonary toxicity of nanoscale particle-types.

Reference No. 4

Sayes CM, Wahi R, Kurian PA, Liu Y, West JL, Ausman KD, Warheit DB, and Colvin VL.

Correlating nanoscale titania structure with toxicity: A cytotoxicity and inflammatory response study with human dermal fibroblasts and human lung epithelial cells. Toxicol Sci. 2006, in press

Abstract

Nanocrystalline titanium dioxide (nano-TiO_2) is an important material used in commerce today. When designed appropriately it can generate reactive species (RS) quite efficiently, particularly under ultraviolet illumination; this feature is exploited in applications ranging from self-cleaning glass to low cost solar cells. In this study, we characterize the toxicity of this important class of nanomaterials under ambient (e.g. no significant light illumination) conditions in cell culture. Only at relatively high concentrations (100 μg/mL) of nanoscale titania did we observe cytotoxicity and inflammation; these cellular responses exhibited classic dose-response behavior and the effects increased with time of exposure. The extent to which nanoscale titania affected cellular behavior was not dependent on sample surface area in this study; smaller nanoparticlulate materials had effects comparable to larger nanoparticle materials. What did correlate strongly to cytotoxicity, however, was the phase composition of the nanoscale titania. Anatase TiO_2, for example, was one hundred times more toxic than an equivalent sample of rutile TiO_2. The most cytotoxic nanoparticle samples were also the most effective at generating reactive oxygen species; ex vivo RS species generation under ultraviolet illumination correlated well with the observed biological response. These data suggest that nano-TiO_2 samples optimized for RS production in photocatalysis are also more likely to generate damaging RS species in cell culture. The result highlights the important role that ex vivo measures of RS production can play in developing screens for cytotoxicity.

APPENDIX G
OBSERVER COMMENTS

Observer Comments

International Center for Technology Assessment

660 Pennsylvania Ave., S.E., Suite 302, Washington, DC 20003,
(202) 547-9359 fax (202) 547-9429

My name is George Kimbrell and I am here today on behalf of the International Center for Technology Assessment (CTA). I'd like to thank the panel for their efforts to improve the EPA's Draft Nanotechnology White Paper, and the opportunity to briefly comment.

CTA is a non-profit, bi-partisan organization committed to providing the public with full assessments and analyses of technological impacts on society. CTA is devoted to fully exploring the economic, ethical, social, environmental, and political impacts that can result from the applications of technology or technological systems.

CTA submitted written comments on the White Paper with several other groups. These brief oral comments supplement and further that earlier joint statement.

This panel's charge included the question of what issues were not adequately addressed in the White Paper. CTA believes one overarching issue stands out in its absence: While the scientific summary of the White Paper is perhaps commendable, the Paper fails to deliver much-needed nanotechnology policy and regulatory recommendations, in the short term or long term. Although nanotechnology has the potential for various environmental and human health improvements, research shows that the fundamentally different properties of engineered nanoparticles create serious potential dangers to human health and the environment. Adequate regulation and oversight is needed to safeguard against these unique and varied harms.

Moreover, creating and implementing EPA agency policy and regulatory objectives for nanomaterials is not merely anticipatory; rather, nanomaterials are already on industrial and consumer markets and being dispersed into the environment and human bodies. Given the urgency of the need for agency oversight of nanomaterials, and EPA's placement as possibly the "lead" agency in nanotechnology oversight, the White Paper falls woefully short in its discussion of the many aspects of this crucial issue.

EPA's White Paper should be revised to analyze the heretofore unaddressed or inadequately addressed policy issues:

- the enactment of comprehensive, mandatory nanomaterial-specific EPA regulations to protect public health and safety and ecological systems;
- the inadequacies of the Toxic Substances Control Act (TSCA) as a regulatory vehicle for EPA's regulation of nanomaterials, without nanomaterial-specific legislative and/or adminstrative amendments;
- the inadequacies of a voluntary regulatory program, like the TSCA Voluntary Pilot Program now being developed by EPA, including the lack of any binding

oversight power for the agency and the absence of data from manufacturers not choosing not to participate;
- the conclusion that engineered nanoparticles, because of fundamentally different properties and risks, should be considered a new class of substances for environmental regulatory purposes;
- the labeling of nanomaterials, including listing engineered nanoparticles as ingredients;
- and the fostering of international coordination and cooperation in the development of nanotechnology testing and regulatory standards.

EPA should enact regulatory rule adjustments to prevent all releases of nanomaterials resulting in human or environmental exposure until and unless the safety of those materials can be demonstrated. Until products containing nanoparticles have been proven safe, CTA seeks to halt the commercialization of nanotechnology.

The urgent need of proper regulatory oversight is underscored by the recent recall of the nano-spray product by German authorities due to reported respiratory health problems. As more and more nanomaterial consumer products come to market, in greater and greater numbers, more recalls will follow. These risks to human health and the environment are exacerbated by the lack of any labeling of nanomaterials, denying the public the opportunity to make educated decisions. Rather than being pushed into regulation by human and/or environmental tragedies, as with past new technologies, EPA should proactively fulfill its statutory mandates. The White Paper as currently drafted is inadequate as a starting point for that task.

Again, thank you for the opportunity to briefly comment here today.