

**Workshop Summary
for the
EPA Board of Scientific Counselors**

**Nanomaterial Case Studies Workshop:
Developing a Comprehensive Environmental Assessment
Research Strategy for Nanoscale Titanium Dioxide**

September 29-30, 2009

May 2010

National Center for Environmental Assessment-RTP Division
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC

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Chapter 1. Introduction

This report describes how the National Center for Environmental Assessment (NCEA) designed and carried out the “Nanomaterial Case Studies Workshop: Developing a Comprehensive Environmental Assessment Research Strategy for Nanoscale Titanium Dioxide” in September 2009. Two case studies focusing on different uses of nanoscale titanium dioxide (nano-TiO₂), for water treatment and for topical sunscreen, were developed around a framework known as comprehensive environmental assessment (CEA), which is a holistic approach to risk assessment that encompasses the product life cycle, fate and transport, exposure-dose, and both ecological and human health effects. The case studies were presented in a draft document to selected reviewers in advance of a workshop in which they served as participants in a structured process (Nominal Group Technique [NGT]) to identify and prioritize information or research needed to support a CEA of nano-TiO₂. The results of the ranking process are presented, followed by some brief observations about the process and a discussion of next steps.

1.1. Background

Engineered nanoscale materials (nanomaterials) are conventionally described as having at least one dimension between 1 and 100 nanometers (nm) and possessing unusual, if not unique, properties that arise from their small size. Like all technological developments, nanomaterials offer the potential for both benefits and risks. The assessment of such risks and benefits requires information, but given the emergent state of nanotechnology, much remains to be learned about the characteristics and effects of nanomaterials before such assessments can be completed.

In its 2007 *Nanotechnology White Paper* (2007, [090564](#)) (p. 89), the U.S. Environmental Protection Agency (EPA) included the following recommendations regarding the risk assessment of nanomaterials:

6.2.7. Recommendations to Address Overarching Risk Assessment Needs - Case Study

One way to examine how a nanomaterial assessment would fit within EPA’s overall risk assessment paradigm is to conduct a case study based on publicly available information on one or several intentionally produced nanomaterials. ... From such case studies and other information, information

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

gaps may be identified, which can then be used to map areas of research that are directly affiliated with the risk assessment process. This has been done in the past with research on airborne particulate matter.

Additionally, a series of workshops involving a substantial number of experts from several disciplines should be held to use available information and principles in identifying data gaps and research needs that will have to be met to carry out exposure, hazard and risk assessments.

In keeping with these recommendations, the National Center for Environmental Assessment (NCEA) in EPA's Office of Research and Development (ORD) conducted the "Nanomaterial Case Studies Workshop: Developing a Comprehensive Environmental Assessment Research Strategy for Nanoscale Titanium Dioxide" on September 29-30, 2009, in Durham, North Carolina. The *Nanomaterial Case Studies: Nanoscale Titanium Dioxide in Water Treatment and in Topical Sunscreen [External Review Draft]* (<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=210206>) was used as a starting point for the workshop, which was conceived as the first of a series of case study workshops to be used in developing and refining a long-term research strategy for assessing potential human health and ecological risks of nanomaterials (U.S. EPA, 2009, [225004](#)). A key feature of the case studies is the comprehensive environmental assessment (CEA) framework, which takes a holistic view of specific applications of selected nanomaterials beginning with the product life cycle and encompassing environmental fate and transport, exposure, and ecological as well as human health implications. The specific objectives of the workshop were to identify and prioritize research or information needed to conduct a CEA of nanoscale titanium dioxide (nano-TiO₂). The present report describes the approach used in developing the case studies and in designing and conducting the workshop, as well as some of the more salient outcomes of the workshop.

The Nanomaterial Case Studies Workshop was conducted under the auspices of the EPA Board of Scientific Counselors (BOSC), an advisory committee of independent scientists and engineers established by EPA to provide advice, information, and recommendations concerning practices and programs of the Office of Research and Development, including ORD's research planning process. In compliance with the Federal Advisory Committee Act (FACA) (5 U.S.C. App. 2 <http://www.archives.gov/federal-register/laws/fed-advisory-committee>) and related regulations, the BOSC announces its meetings in the Federal Register, opens its meetings to the public, and provides opportunities for public comment on issues before the Board. This summary document is meant to serve as an aid to the BOSC in its development of a report that will, among other things, provide technical feedback and guidance to EPA on the design, implementation, and outcomes of the workshop.

It is important to note that the Nanomaterial Case Studies document and workshop were not intended to be ends in themselves, even though they may have value or be of interest in their own right. They were primarily conceived as initial steps in the development and refinement of a long-range research strategy to support the comprehensive environmental assessment of selected nanomaterials. Such a strategy will require the examination of other nanomaterial case studies and is expected to develop in an evolutionary process reflecting adjustments and modifications as additional nanomaterials are considered and new information becomes available.

Chapter 2. Approach

Scientific research is a primary means of obtaining information needed for assessing the potential ecological and human health risks related to nanomaterials, although other types of information (e.g., production volumes, monitoring data) may also be needed. Determining which specific information needs are most critical to support assessment efforts can be a complex and difficult endeavor. The case study workshop approach described here reflects several choices and assumptions, some of which were based on prior experience with other environmental issues (Davis, 2007, [089803](#)).

Section 2.1 describes the development of the nano-TiO₂ case studies document. Section 2.2 discusses the objectives and design of the workshop. Section 2.3 describes the procedure used to rank research needs. Section 2.4 highlights the main outcomes of the ranking process.

2.1. Case Studies Document

This section provides background information about EPA's nano-TiO₂ case studies document that served as a starting point for the workshop discussions. The section explains the rationale for using a case study approach and process for selecting the case studies and the CEA approach and also summarizes the contents of the case studies document and the process of its preparation.

2.1.1. Rationale and Selection Process for the Case Studies

The complex properties of various nanomaterials make evaluating nanomaterials in the abstract or with generalizations difficult if not impossible. Thus, EPA decided to use a “bottom-up” rather than a “top-down” approach and initially focus on specific nanomaterial applications.

The process for selecting the nanomaterials for the case study involved an EPA workgroup composed of members from the Office of Research and Development, the Office of Prevention, Pesticides and Toxic Substances, the Office of Air and Radiation, the Office of Solid Waste and Emergency Response, the Office of Water, the Office of Environmental Information, and Regional Offices 3 and 9. The workgroup grew rapidly in size from around 20 persons initially to the approximately 60 members listed in Section C.1.3 and in the front matter of the *Nanomaterial Case Studies: Nanoscale Titanium Dioxide in Water Treatment and in Topical Sunscreen [External Review Draft]* (U.S. EPA, 2009, [225004](#)).

In addition to titanium dioxide, several other candidate nanomaterials were considered and discussed by the workgroup, especially single-wall and multi-wall carbon nanotubes, fullerenes, metals (e.g., zero valent iron, silver), and metal oxides (e.g., cerium oxide). Several selection criteria

were used in deciding which materials to examine as case studies: (1) “nano-ness,” i.e., one or more properties that distinguish the engineered nanoscale form from its conventional form; (2) potential exposure for human populations and biota; (3) ecological as well as human health relevance; (4) data availability; (5) relevance to EPA programs. Limited summaries of information bearing on these points were provided for the workgroup to consider, but the evidence pertaining to most of the selection criteria would be better characterized as “preliminary” rather than “demonstrated.”

After multiple conference calls and email exchanges over a period of a couple of months, the workgroup members were asked to vote for one carbon nanomaterial and one metal/metal oxide nanomaterial. Although the EPA program offices varied in the number of members on the workgroup, the top ranked choices were single-wall carbon nanotubes (SWCNTs) and nano-TiO₂, regardless of whether votes were counted on the basis of individual members (34 voted) or individual program offices (8 voted).

The next step entailed more in-depth examination of published literature and other sources of information (e.g., web sites) to determine which specific applications of the two selected classes of nanomaterials would be suitable to serve as case studies. Two uses of nano-TiO₂ emerged: water treatment and topical sunscreen. With regard to use of nano-TiO₂ for water treatment, several published studies pointed to the effectiveness of nano-TiO₂ in removing arsenic, but eventually we discovered there was little evidence that it was in fact being routinely used by community water suppliers. Although this apparent lack of usage might be seen as contrary to the selection criterion of exposure potential, we reasoned that if nano-TiO₂ were used in the future, the potential for exposure would presumably exist at that time and that our consideration of its implications could be viewed as proactive rather than reactive. As for the use of nano-TiO₂ in topical sunscreen, there was no doubt that such products were in use by the general population, but some workgroup members questioned the relevance of these products to EPA programmatic interests, given that sunscreen products were under the purview of the Food and Drug Administration (FDA). From a CEA standpoint, however, the potential for direct and indirect effects on ecological receptors as well as human populations through multiple pathways provided a cogent reason to focus on the broad environmental implications of nano-TiO₂ in sunscreen.

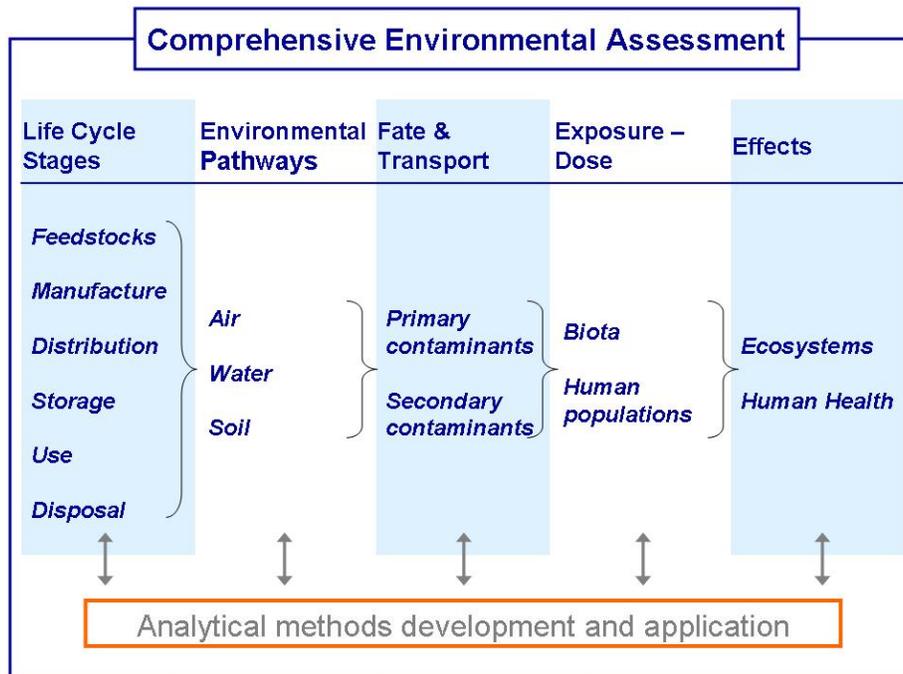
Although the literature on SWCNTs appeared to be reasonably robust, it ultimately proved to be insufficient to develop a compelling scenario for significant exposure of the general population to SWCNTs. The possibility of substituting a different nanomaterial was explored, but we finally decided in the face of various resource constraints to limit our efforts to developing the two nano-TiO₂ case studies for the first workshop.

2.1.2. Comprehensive Environmental Assessment Approach

The case studies were organized around the concept of comprehensive environmental assessment (CEA), which combines a product life cycle framework with the risk assessment paradigm. In essence, CEA expands the risk assessment paradigm by including life-cycle stages and considering both indirect and direct ramifications of the substance or stressor. Figure 2-1 illustrates the principal elements in the CEA approach. The first column lists typical stages of a product life cycle: feedstocks, manufacturing, distribution, storage, use, and disposal (including reuse or recycling, if applicable). The second column lists environmental pathways or media (air, water, soil) to which nanomaterials or associated materials (e.g., manufacturing by-products) might be released at various stages of the life cycle. Within these media, nanomaterials or associated materials can be transported and transformed, as well as interact with other substances in the environment, both natural and anthropogenic. Thus, a combination of primary and secondary contaminants can be spatially distributed in the environment (column 3).

The fourth column of Figure 2-1 (Exposure-Dose) goes beyond characterizing the occurrence of contaminants in the environment, as exposure refers to actual contact between a contaminant and organisms (i.e., biota as well as human populations). Under the CEA approach, exposure characterization can involve aggregate exposure across routes (e.g., inhalation, ingestion, dermal); cumulative exposure to multiple contaminants (both primary and secondary); and various spatiotemporal dimensions (e.g., activity patterns, diurnal and seasonal changes). Dose is the amount of a substance that actually enters an organism by crossing a biological barrier. Conceptually, dose links exposure with the last column of Figure 2-1, which refers to ecological and human health effects that can result when an effective dose reaches a target cell or organ in a receptor organism or, in an ecological context, when a stressor is at a sufficient level to cause an adverse response in a receptor. “Effects” encompass both qualitative hazards and quantitative exposure-response relationships.

In the present context of research planning and strategy development, CEA is underpinned by the development and use of analytical methods that make detection, measurement, and characterization of nanomaterials in the environment and in organisms possible. A key aspect of CEA is the use of collective judgment based on diverse technical and stakeholder perspectives, as will be described later.



Source: Modified from Davis (2007, [089803](#)) and Davis and Thomas (2006, [089638](#))

Figure 2-1. Comprehensive Environmental Assessment Diagram.

2.1.3. Contents of the Case Studies Document

The External Review Draft of *Nanomaterial Case Studies: Nanoscale Titanium Dioxide in Water Treatment and in Topical Sunscreen* (U.S. EPA, 2009, [225004](#)) comprised five chapters: an introduction, a description of the life cycle stages of both applications, a discussion of the fate and transport of TiO₂ through different environmental media, data regarding potential ecological and human exposure and dose, and information regarding the known ecological and health effects of nano-TiO₂. Although the document summarized much information relevant to a CEA of nano-TiO₂, it also pointed to many information gaps and listed several unanswered questions at the end of each chapter or certain sections of the document. These questions, listed in Appendix B of this report, served as a starting point for the workshop participants to think about the research priorities on which EPA should focus.

2.1.4. Process

The case studies were developed through a team effort involving EPA staff, contractors, and consultants, assisted by several external reviewers and internal EPA Work-group members, all of whom are listed in Appendix C. In addition to soliciting review comments on the case studies document from the workshop participants, EPA also solicited public comment. As of September 23,

2009, nine public comments had been submitted to the docket.

(<http://www.regulations.gov/search/Regs/home.html#docketDetail?R=EPA-HQ-ORD-2009-0495>)

(Note: check the “public submissions” box on the docket screen to view all nine comments). EPA plans to address comments from the workshop participants and the public in the final version of the nano-TiO₂ case studies document.

2.2. Workshop Objectives and Design

Two key features figured into our thinking about the design and objectives of the Nanomaterial Case Studies Workshop. One was the importance of going beyond simply generating another list of nanotechnology research needs. Various “research strategies” and statements of research needs related to nanotechnology risk assessment have appeared in recent years, including the *NNI Strategy for Nanotechnology-Related Environmental, Health and Safety Research* (NEHI, 2008, [598308](#)), which was criticized by a NRC review panel for, among other things, its “failure to identify important research needs [and] the lack of rationale for and discussion of research priorities...” (NRC, 2009, [597919](#)). Although the EPA Nanomaterial Case Studies Workshop was conceived before the NRC review had been started, the importance of prioritizing research needs was a primary objective from the outset in our plans for a workshop. To satisfy this objective, we felt that it was essential to use a more formal or structured decision-support process rather than a typical “free discussion” workshop discussion format. A second feature of fundamental importance was having a diverse, multi-disciplinary, and multi-stakeholder group of workshop participants to consider these issues. This also happened to be consistent with the NRC review in its call for diverse stakeholder input in developing a research strategy for nanomaterial risk assessment.

2.2.1. Choice of Prioritization Method

A number of collective judgment and decision-support methods were considered for identifying and prioritizing research or information needs. In particular, multi-criteria decision analysis (MCDA) (Linkov et al., 2008, [157531](#); Seager and Linkov, 2008, [157493](#)) and a variant of MCDA known as multi-criteria integrated resource assessment (MIRA) (Stahl et al., 2002, [041601](#)), as well as some form of expert elicitation (Cooke, 1991, [598306](#); Cooke and Goossens, 2004, [598304](#); U.S. EPA, 2009, [598301](#)), were given consideration. In the end, nominal group technique (NGT) (Delbecq and Van de Ven, 1971, [598309](#)) was selected for the 2009 workshop for various reasons, including because it seemed more appropriate given the nascent state of the science related to nanomaterial risk assessment and because it could be implemented more easily in the face of temporal and other constraints.

NGT is a structured process for a set of individuals to identify and rank a number of choices. Several individuals (nominally a group) are convened and each person is afforded an equal opportunity to offer his or her view(s) about which choices are highest priority. When a large number of choices are under consideration, they may be grouped or consolidated into a more manageable number. A multi-voting process is then used to rank the choices. More details on how NGT was applied are presented in Section 2.3.2 and in Appendix I.

Although not necessarily unique to NGT, one feature of NGT that recommended it for this project was that it allows for both independence and interaction in judging issues. For example, participants are free to introduce and argue for any issue they wish, and each participant is accorded an equal amount of time in a round-robin procedure to make their case. Independent viewpoints are thus encouraged, while at the same time participants can be exposed to and perhaps influenced by other points of view. Moreover, interaction occurs during the NGT consolidation process (Section 2.3.4) when participants discuss and decide whether their respective issues are similar to others' issues. Independence of judgment is assured in the multi-voting procedure during which all participants vote simultaneously and essentially anonymously. The outcome of the voting is a rank ordering of priorities that reflects a collective judgment of the participants acting individually.

Since 1992, the National Water Research Institute (<http://www.nwri-usa.org/>) has used NGT in numerous workshops for “identifying, prioritizing, and developing approaches to address critical local, state, and national water issues” (e.g., <http://www.nwri-usa.org/pdfs/OxygenateContaminationworkshopreportSept.2000.pdf>). We drew upon our own individual past experience with the NWRI workshops and more recent informal communications with NWRI personnel in planning the case studies workshop.

2.2.2. Identification and Selection of Participants

Several steps were involved in securing a diverse, multi-disciplinary, and multi-stakeholder group of workshop participants, and EPA retained a contractor (ICF International) to assist in organizing and facilitating the workshop. First, a list of candidate participants was developed based on suggestions from EPA, Internet searches, and other investigation. An initial inquiry was sent via email to 188 potential invitees on June 15, 2009, with a link to more information (Section D.1) and a webform through which they could provide information about their interest in participating in the workshop, their availability across six different dates in late September, the sector in which they worked (government, academic, industry, non-government organizations [NGOs], etc.), and their areas of expertise (Section D.2). On June 22, an additional 97 potential participants were contacted to ensure an adequate pool of candidates from which to select invited participants. The objective of the initial inquiry was to obtain sufficient information to select the dates for the workshop based upon potential participant availability and to enable an adequate representation and balancing across

“demographic” factors (i.e., sector affiliation and subject matter expertise). As potential participants responded to the initial inquiry using a Web-based system (MemberClicks), their information was stored in a password-protected online database.

Of the range of proposed dates for the workshop, the dates on which the most potential participants were available to attend were September 29 and 30, 2009. Those who were available to attend the workshop on these dates were then separated into subcategories, first by sector, then by subject matter expertise. Considerable attention was given to achieving, as much as possible, a balanced representation of areas of expertise and sectors (Section 2.3.2 and Tables 2-2 and 2-3).

A target number of 50 participants was set. The basis for this number is discussed in more detail in Section 2.3.2. (We also happened to have roughly 50 demographic categories, but we did not attempt to match every such category specifically with a participant.) To reduce travel expenses, preference was given to potential participants located in North America. In the event any invitees were unable to complete certain pre-workshop requirements or were unable to attend, a list of 25 alternates, distributed between sectors and subject matter expertise was generated so that substitutions could be made with minimal impact on the representation balance.

An invitation was sent to 50 potential participants starting on July 14 with a request to complete a conflict of interest disclosure and certification form. No conflict of interest concerns were identified. Generally, an agreement was executed with the non-federal government participants to reimburse them for their travel expenses and pay an honorarium of \$1,500 for their services. A legal agreement and honorarium were used to help ensure that participants would understand that a commitment of their time and attention was expected and that their services were not being offered gratis on their part.

The invitees then received a “charge to workshop participants” (Figure 2-2) with guidance for their review of the case studies. They also received instructions (Section D.3) for submitting additional or modified information/research needs and for ranking the questions listed in the draft document using a Web form in advance of the workshop (discussed further in Section 2.3.1). A small number of invitees had to decline or drop out of the process due to conflicts or emergencies. Replacements were identified and retained as time permitted, with 49 invitees ultimately attending. See Table 2-1 for the list of 49 workshop participants and Appendix E for the biosketches they submitted. In addition to the workshop participants, a few other individuals attended the workshop as observers for varying periods of time; their names and affiliations are listed in Appendix F.

Table 2-1. List of Workshop Participants

<u>NAME</u>	<u>AFFILIATION</u>
David Andrews	Environmental Working Group
Jeff Baker	TSI Incorporated
Brenda Barry	American Chemistry Council
Catherine Barton	DuPont
Eula Bingham	University of Cincinnati
Pratim Biswas	Washington University in St. Louis
Jean-Claude Bonzongo	University of Florida
Steven Brown	Intel Corporation
Mark Bunger	Lux Research, Incorporated
Carolyn Nunley Cairns	Consumers Union
Richard Canady	McKenna, Long & Aldridge LLP
Janet Carter	U.S. Occupational Safety and Health Administration
Elizabeth Casman	Carnegie Mellon University
Sylvia Chan Remillard	HydroQual
Shaun Clancy	Evonik Industries AG
Ramond David	BASF Corporation
Joan Denton	California Environmental Protection Agency
Gary Ginsberg	Connecticut Department of Public Health
Perti (Bert) Hakkinen	National Institutes of Health (NIH), National Library of Medicine
Jaydee Hanson	International Center for Technology Assessment
Patricia Holden	University of California – Santa Barbara
Paul Howard	U.S. Food and Drug Administration
Sheila Kaplan	University of California – Berkeley, Graduate School of Journalism
Fred Klaessig	Pennsylvania Bio Nano Systems, LLC
Rebecca Klapser	University of Wisconsin, Great Lakes Water Institute
Todd Kuiken	Woodrow Wilson International Center for Scholars, Project on Emerging Nanotechnologies
John LaFemina	Battelle
Thomas Lee	Minneapolis Star Tribune
Shannon Lloyd	Concurrent Technologies Corporation
Christopher Long	Gradient Corporation
Margaret MacDonell	Argonne National Laboratory
Fred J. Miller	Independent Consultant
Nancy Monteiro-Riviere	North Carolina State University
Paul Mushak	PB Associates
Srikanth Nadadur	NIH, National Institute of Environmental Health Sciences (NIEHS)
Michele Ostraat	Research Triangle Institute
Anil Patri	SAIC (at NIH, National Cancer Institute, Nanotechnology Characterization Laboratory)
Maria Victoria Peeler	Washington State Department of Ecology
Richard Pleus	Intertox, Incorporated
John Small	National Institute for Standards and Technology
Jeff Steevens	U.S. Army Corps of Engineers Research and Development Center
Geoffrey Sunahara	National Research Council – Canada, Biotechnology Research Institute
Treye Thomas	U.S. Consumer Product Safety Commission
John Veranth	University of Utah
Donald Versteeg	The Procter & Gamble Company
Nigel Walker	NIH, NIEHS, National Toxicology Program
William Warren-Hicks	EcoStat, Incorporated
Paul Westerhoff	Arizona State University
Mark Wiesner	Duke University

2.3. Research Needs Ranking Procedure

The 49 selected participants were asked to do several things as part of the process of identifying and ranking research priorities. Some of these activities were carried out prior to the workshop, but the workshop itself was the primary venue for the process of ranking research needs.

2.3.1. Pre-Workshop Review and Rankings

In advance of the workshop, the invited participants were asked to review the case studies document and, using a Web-based form, submit their rankings of research questions by September 10, 2009. They were instructed to read the case studies and submit their top 10 questions from the document in ranked order, an additional 15 questions they felt were important but not individually ranked, and up to 10 questions they felt were the lowest priorities in laying the foundation for a CEA of nano-TiO₂ (Section D.3). Participants were also encouraged but not required to submit modifications of existing questions from the case studies and new questions that were not originally included in the document. The responses were collected through a web form. The form allowed participants to assign questions: (a) a numerical ranking from 10 down to 1 for the top 10; (b) the classification “high (not ranked)” for the next 15; (c) “low” for the bottom 10; or (d) no ranking (blank). On a separate page, participants could enter the text of new questions and indicate which chapter a question corresponded to or designate it as “multiple” chapters if it had broader relevance than a single chapter.

All newly submitted and revised questions were compiled and distributed to the workshop participants via email one week before the workshop; also, the questions were included in folders provided to the participants at the workshop. During the initial plenary session at the workshop, the facilitators presented the results of the pre-workshop ranking of the questions. The lists of new and revised questions are shown in Appendix G, and the pre-workshop ranking results and methodology used to calculate the results are shown in Appendix H. Thirty-two of the participants submitted new questions or revisions to existing questions.

Our objective in having the participants rank the questions in the draft case studies document prior to the workshop was to help ensure that they would consider and perhaps even reflect on the numerous possible questions posed in the document. The fact that several participants submitted new or modified questions may indicate that they did in fact give some thought to issues associated with a CEA of nano-TiO₂, although some “new” questions were actually redundant with questions already stated, which suggests that the submitter in those instances might not have carefully read the document. Regardless, the pre-workshop ranking exercise presumably helped focus the participants’ attention on issues raised by the document. The results of the pre-workshop ranking process and the lists of new and modified questions were provided to participants, albeit only a few days before the

workshop, with the intention of further stimulating their thinking, especially regarding issues the draft document may have failed to identify or articulate adequately.

Charge to Workshop Participants

The document you are being asked to review is one step in the development of a research strategy for the comprehensive environmental assessment of nanomaterials such as nano-TiO₂. It is a starting point for the Nanomaterial Case Studies Workshop that will be held on September 29-30, 2009. Prior to the workshop (by September 10) you should submit your review comments and ranking of Questions (research/information needs), as explained below. The preliminary ranking results will be provided at the workshop. New questions submitted by September 10 will be distributed to workshop participants approximately one week in advance of the meeting.

The document attempts to take a holistic view of selected uses of nano-TiO₂ and the potential ecological and health implications of such products across their life cycle. Although much information is presented in the document, many questions remain to be answered. Several of these questions, which can also be thought of as information or research needs, are listed throughout the document. As you review the document, please consider this overarching question:

“What research or information is most needed in order to conduct a comprehensive environmental assessment of nano-TiO₂?”

You are asked to read the entire document, not just your own areas of expertise or interest. We want reviewers to take a “big picture” view and not focus exclusively on a particular chapter or section.

The document is meant to stimulate your thinking about potential release scenarios and implications, both direct and indirect. It is a starting point for your thinking, not an end in itself.

A key aspect of your review is to identify and rank the research or information that is most needed in order to conduct a comprehensive environmental assessment of nano-TiO₂. Separate instructions for the ranking process are provided below and should be read before reviewing the document.

In your review comments, please indicate:

- Is the information presented in the document accurate, objective, and logical? Are statements properly supported by references? Note that we have by necessity had to rely on gray literature and personal communications at times. If you have better sources to cite for such information, please provide them.
- Is information clearly and concisely presented? If not, please suggest alternative wording.
- Is the information complete? Have any important points been omitted? Do you know of other information that bears directly or indirectly on the case studies? Can you provide a source (e.g., a document, Web site, person) for additional information?

Thank you for your thoughtful review and participation in this endeavor.

Figure 2-2. Charge to Workshop Participants

2.3.2. Workshop Procedures

In practice, NGT seems to be applicable to groups no larger than 25-30 persons primarily because of the amount of time required for every participant to present their views. For example, if 30 participants were each allotted 3 minutes in which to speak, a single round would take a minimum of 90 minutes. In the EPA workshop, we allowed participants more than one round and essentially continued until every individual had offered all the issues they wanted to see presented. Subsequent rounds after the first tend to go more quickly as more and more participants “pass” when all of their issues have already been raised. Nevertheless, the total period could easily exceed 3

hours, which intuitively seems too long to fully engage everyone’s attention. And if time were also included for the participants to move from their seats to a podium (although this practice was not used in the EPA workshop), the total period could be increased by a third or more. Given these considerations, we decided to limit the NGT process to 25 persons.

During the planning process, a question arose about whether one “sample” of 25 individuals would yield a substantially different outcome from another group of 25 individuals. Given this question and the fact that we had on the order of 50 demographic categories (sectors, fields of expertise), we decided to have a total of 50 participants and run two separate NGT groups of 25 each. (The actual number of participants in attendance was 49; thus, NGT Group A had 24 participants and Group B had 25.) An effort was made to achieve a rough balance in demographic characteristics between the two NGT groups (Tables 2-1 and 2-2).

Table 2-2. Participant Sector Representation in Day 1 NGT Groups and Overall

Sector	NGT Group A	NGT Group B	Total
Academia	5	5	10
Industry	4	5	9
NGO	2	1	3
Consulting	5	6	11
Government-State	2	1	3
Government-Federal	5	5	10
Government-International	0	1	1
Journalist	1	1	2
Total	24	25	49

Table 2-3. Participant Expertise Representation in Day 1 NGT Groups and Overall

Area of Expertise	NGT Group A	NGT Group B	Total
Manufacturing	3	5	8
Water Treatment	4	6	10
Fate & Transport	11	12	23
Exposure-Dose	14	16	30
Ecology	6	6	12
Health Route	12	13	25
Health Endpoint	8	10	18
Health Method	10	9	19
Evaluation	13	14	27
Risk Management	16	17	33
Other	15	11	26

A description of the NGT procedures was provided to participants in advance of the workshop so they would know what to expect (Appendix I). The workshop agenda (Appendix J) provides further detail about how the meeting was conducted. The following sections further elaborate on key activities during the course of the 2-day meeting.

2.3.3. Day 1 Activities

Early in the workshop, approximately an hour was devoted to presenting and explaining the results of the pre-workshop ranking process (Appendix H). Although the results had been provided to the participants in advance of the meeting, we wanted to provide an opportunity for group discussion and interaction as a means of further stimulating thought about the relative importance of different questions. After the workshop protocol and NGT process was briefly reviewed for all the participants, two NGT groups (Groups A and B) were assigned separate meeting rooms.

A period of approximately 20 minutes was allowed for participants to silently consider the lists of 97 questions (Appendix B) provided in the case study report and of 131 additional questions (Appendix G) submitted by the participants with their pre-workshop rankings. The round-robin procedure allowed each individual up to 3 minutes to present a single research/information need they deemed of high priority and provide the rationale for selecting that issue in relation to conducting a CEA. Participants were also given the opportunity to state a new issue in place of choosing an existing need or modify the phrasing or content of an existing research question. Each research need identified by a participant as high-priority was written on a flip-chart sheet of paper and displayed on the wall for the consideration of the group. After each participant had spoken in support of an issue, the round-robin was repeated for two additional rounds, after which the groups indicated that the research needs of highest priority had been identified. (Many of the participants did not use all of

their allotted time, which resulted in extra time for additional rounds in both groups.) Altogether, approximately 82 specific issues were identified as information needs during this stage.

The second part of the NGT process involved consolidating similar or overlapping research needs into related research topic areas. Participants were given the opportunity to propose to their respective group consolidation of two or more research needs, after which those participants who had nominated the research needs were consulted on whether they agreed that the ideas should be grouped into a research area. If any one of the participants that had chosen one of the research needs under consideration for grouping did not agree that the research needs could be consolidated into one, then the issues were not grouped and each need was considered as an independent research priority. Where the participants all agreed that certain research needs should be grouped, the resulting combination was treated as a single research area, although records were kept of the individual issues that fed into the consolidated topic area. After completing the consolidation procedure, Group A had 24 research topic areas and Group B had 26 areas to be ranked.

The third part of the NGT involved a multi-voting exercise to develop a ranking of the consolidated research needs in terms of their importance for conducting a CEA. Each participant was given 10 “sticky notes” and instructed to label them 1 to 10 and include their name on each note. The participants were then asked to rank their top ten research priorities by giving 10 points to the research need they deemed most important for conducting the CEA, 9 points to their next highest priority, and so on, down to 1 point. Only 10 research topics could be ranked by each individual, and each topic could receive only one ranking per individual. After the voting process, the results were tallied and the top research priorities for each group were identified.

Originally, as described in the pre-workshop NGT handout, our plan was to have the full group consider the top 10 research priorities from each of the two subgroups, but it became evident that 10 was an arbitrary cut point and that it would be better to base the number of top priorities on breaks in the distribution of scores in the vicinity of the 10th item. For example, as shown in Table 2-3 (and in greater detail in Appendix K), a gap in the scores from Group A occurred between the 13th- and 14th-ranked items. Therefore, the top 13 research topics from Group A and the top 12 topics from Group B were brought forward to a plenary session on Day 2 (Section 2.3.4) for the entire group of 49 participants to consolidate.

Table 2-4. Tally Groupings (by Total Points) of Top-, Middle-, and Bottom-Ranked Research Needs for Separate NGT Groups

NGT Group A		NGT Group B	
Rank	Range of Points ¹	Rank	Range of Points ¹
1–4	182–123	1–6	155–101
5–13	76–49	7–12	70–55
14–24	33–0	13–26	38–0

¹Maximum possible number of points, assuming all participants in the group assigned 10 points to a single research need:
 NGT Group A: maximum = 240 points
 NGT Group B: maximum = 250 points

2.3.4. Day 2 Activities

To identify the top research priorities collectively among all the participants, each participant was given the ranked list of top research priorities from both NGT groups (Appendix K) at the start of day 2. The priorities from each group were labeled according to the group from which they originated and their ranked order (e.g., question “A.1” had the most votes from Group A). The workshop facilitators asked the participants to review the ranked priorities from each group and to consider whether any of the research priorities ranked by the two groups were similar or overlapping.

A consolidation process similar to the one used in the separate NGT groups on Day 1 was conducted with the plenary group. Participants had the opportunity to nominate research priorities from either list for consolidation either because the ideas were similar or because one idea was a component of another. The facilitators then asked the entire group to vote by a show of hands if they agreed that the two research priorities could be combined. If the majority of the group agreed, the priorities were then consolidated. In response to concerns voiced by some participants, the facilitators emphasized that by consolidating two research priorities, the original questions that made up those priorities were not lost, but were instead possibly strengthened by adding more detail and possibly a more refined description. During the consolidation process, no questions were altered.

Following consolidation of similar priorities, the plan was to have multi-voting for the top priorities by the plenary group using a commercial “audience response” system consisting of individual remote keypads and a computerized receiver to tally each participant’s weighted vote. Due to technical problems, however, the facilitators had each person in the plenary group list his/her top 10 priorities on a sheet of paper, numbering in descending order from 10 down to 1 assigning 10 points to the top priority. The scoring sheets were collected and tallied. During this process, it was discovered that a few of the participants had not voted correctly. For example, some participants assigned points to an item more than once or assigned points to a priority that was not among the set

of top NGT group priorities (e.g., voting for group A’s 15th ranked item). If a participant voted for an issue twice, the lower vote was deleted. Points assigned to non-eligible items were ignored.

Using the point tallies, the overall top research priorities were identified and then presented to the group. Rather than limiting consideration to an arbitrary top 10 priorities, the facilitators, with consensus from the group, chose to rely on break points in the voting results. Table 2-5 shows the groupings, and Appendix L lists the priorities in ranked order and also indicates which priorities from the NGT groups were consolidated prior to the final vote. Given the gap between items 8 and 9, the focus for the remainder of the workshop was on the top 8 priorities.

Table 2-5. Top-, Middle-, and Bottom-Ranked Research Needs for Plenary Group

Plenary	
Rank	Range of Points ¹
1–5	337–237
6–8	185–152
9–18	66–0

¹Maximum possible number of points, assuming all participants in the group assigned 10 points to a single research need was 480; one participant left early and did not vote.
Note: Tally Groupings by Total Points

2.3.4.1. Day 2 Breakout Groups

Eight breakout groups corresponding to the top eight research topics were formed by participants volunteering to work on an issue of their choice (with guidance to limit group sizes to no more than 7 and no fewer than 5). The groups were given around 3 hours (including lunch) to develop a short report fleshing out descriptions of the research topic areas, using an MS Word document template (Appendix M). The written reports are presented in full in Section 3 of this report. Near the end of Day 2 of the workshop, a spokesperson from each breakout group gave a 5-minute presentation to the plenary group, using a provided PowerPoint template (Appendix N). These presentations were meant to briefly summarize each breakout group’s written report, with particular emphasis on the topic’s connections to other priority areas. Some time was allowed for the plenary group to respond to these presentations, especially for the purpose of pointing out additional connections or relationships between research topic areas.

2.4. Nominal Group Technique Process Outcomes

As explained in Section 2.3.3, on Day 1 Groups A and B considered a set of more than 230 proposed research needs, identified approximately 82 issues as priorities through the round-robin

procedure, and then consolidated these issues into 24 and 26 high-priority research areas, respectively. These consolidated research needs were then ranked by the two groups using a multi-voting process. This resulted in the selection of 13 and 12 highest priority research needs by Groups A and B, respectively (Appendix K). In a plenary session on Day 2, these 25 research needs were discussed and consolidated, when possible, resulting in a total of 18 high-priority research areas on which the plenary group voted to determine the final ranking. The end result of the two-day process was a set of eight top research priorities (Appendix L).

The following list of eight priorities contains each of the constituent questions that were consolidated into the topic areas. Descriptors for the topic areas were developed by the breakout groups for their written reports, which are presented in Section 3.

Priority 1: Are current EPA standard testing protocols adequate to determine nano-TiO₂ ecotoxicity? If not, what modifications or special considerations, if any, should be made in current ecological tests? For example, what are the differences in characterization of testing material (as raw material, in media, and in organisms), dispersion methods, and realistic exposure routes between testing conventional materials and nanomaterials (commercial use)? Are the current EPA harmonized health test guidelines for assessing toxicity adequate to determine the health effects/toxicity of nano-TiO₂? What criteria, especially associated with an inert colloid particle, should the EPA use when evaluating harmonized test protocols? What set of widely shared reference samples of nano- and conventional TiO₂ would be most useful for integrating the results of different investigators regarding particle characterization and particle toxicology?

Priority 2: How do TiO₂ properties change from the manufacturing stage, upon its incorporation into products, during its use, during storage, upon release to the environment, upon environmental aging, and in different compartments? How do various manufacturing processes for nano-TiO₂ affect their physicochemical properties? How do specific physicochemical properties, including particle surface treatments and aggregation/agglomeration, affect the fate and transport of nano-TiO₂ in various environmental media? Do we have sufficient information to differentiate decision-critical characteristics across the various nano-TiO₂ sunscreens or water-formulations? Have the life cycle flows (intentional and unintentional) and properties of nano-TiO₂ in different applications been adequately characterized?

Priority 3: Are available methods adequate to characterize nano-TiO₂ exposure via air, water, and food? What properties of nano-TiO₂ should be included in such exposure characterizations? Do adequate methods exist to characterize nano-TiO₂ in relevant environmental matrices such as soil, sediment, or biofilms and living organisms?

Priority 4: How do surface coatings and physical and chemical properties affect environmental chemistry and toxicity? Do wastewater treatment plant processes affect surface coatings? What natural particle coatings are added in the environment (e.g., humic and fulvic acids) and how do these natural coatings influence environmental fate, chemistry, and toxicity? How do specific physicochemical properties, including particle surface treatments and aggregation/agglomeration affect the fate and transport of nano-TiO₂ in various environmental media? How can species be described as they move from source to sink? What effect, if any, do coatings, dopings, carriers, dispersants, and emulsion types have on biopersistence and bioaccumulation? What factors determine whether and to what extent aggregation or agglomeration of nano-TiO₂ occurs? Emphasize the importance of chemical and physical characterization at a number of stages in addressing possible toxicity of nanomaterials. What makes one type of nanoparticle more active or toxic than another?

Priority 5: Which sources, pathways, and routes pose the greatest exposure potential to nano-TiO₂ for biota and for humans (including children)? At what concentrations? Do particular species of biota and populations of humans have greater exposure potential (e.g., high-end exposures due to unusual conditions or atypical consumption)? In particular, do children get a higher exposure and/or dose? What are the relative contributions of different stages of life cycles of water treatment, sunscreen, and other applications and products to environmental levels of nano-TiO₂ and associated contaminants in air, water, and soil?

Priority 6: What is the global environmental content of nano-TiO₂ now and in the future? Ecologically is TiO₂ a point source or regional exposure problem? If a regional distribution issue, what are concentration gradients in key media? By region and environmental segment (soil, water, etc.), what is known about the background concentration and characteristics of nano-TiO₂ due to natural or non anthropogenic processes? Where does nano-TiO₂ accumulate in the environment and in humans? What is the current background level in humans? Does nano-TiO₂ bioaccumulate in humans?

Priority 7: What might be the primary mechanism(s) of action and dose causing toxic effects in different species or in different materials? Do nano- and conventional TiO₂ have different toxicological mechanisms of action or do the two materials simply have a surface-area or surface-coating dependent difference in potency? Is the available biological effects evidence adequate to support ecological risk assessment for nano-TiO₂? If not, what is needed? What are the fundamental

biological responses of nano-TiO₂ interactions at the cellular level (as dictated by its physical and chemical characteristics) (Are there dose interactions)?

Priority 8: What are the effects of long-term exposures in relevant human and ecological populations for specific nano-mixtures of concern (e.g., neurological, reproductive, integument [skin])? Need to develop comprehensive health data. How do you prioritize to get specific health effects data on specific TiO₂s of concern, based on levels in the environment or based on short-term effect data (as with PCBs)? What are the chronic, long-term effects of nano-TiO₂ (ecological and human effects)?

2.4.1. Comparison of Results for Groups A and B

A question that arose during the design and planning of the workshop concerned whether the results from the two NGT groups would be substantially similar or different. Table L-1 (Appendix L) lists the ranked priority issues for the plenary group and includes a column (Consolidated NGT Priorities) that indicates the source of the issues that went into the consolidated priority. For example, Priority 1 in Table L-1 indicates that the top-ranked issue by Group A (i.e., A.1) was linked with the third-ranked issue for Group B (i.e., B.3). Similarly, Priority 2 comprised issues A.2 and B.10. The results are summarized in Table 2-6, examination of which suggests a high correspondence between the groups in their top 5 priorities but some divergence in rankings thereafter.

Table 2-6. Correspondence between top-ranked consolidated issues for Groups A and B

	A.1	A.2	A.3	A.4	A.5	A.6	A.7	A.8	A.9a	A.9b	A.11	A.12	A.13
B.1		X											
B.2			X										
B.3	X												
B.4				X									
B.5													X
B.6													
B.7					X								
B.8													
B.9										X			
B.10													
B.11a													
B.11b													

Chapter 3. Prioritized List of Questions/Topics to Consider in a Comprehensive Environmental Assessment Research Strategy for Nano-TiO₂

The top eight research priorities identified by the plenary group on Day 2 were further discussed and articulated in breakout groups of five to seven participants each. As noted above, the breakout groups were asked to prepare a short report using a standard format (Appendix M). The format included a section for discussion of how the topic was related to related priority areas; in this respect, participants were asked to focus only on the top 18 priority areas that had been voted upon by the full group. Related priorities are referred to by their final rank number, i.e., 1 to 18, as listed in Appendix L. The following sections present the individual breakout group reports with only minor editing.

3.1. Priority 1: Approaches and Methods for Evaluating the Ecological and Human Effects of Nano-TiO₂

3.1.1. Breakout Group Members

Elizabeth Casman, Raymond David, Carolyn Nunley Cairns, Fred J. Miller, Richard Canady, and Sheila Kaplan

3.1.2. Short Description

It is necessary to understand what makes TiO₂ a unique entity, where (if anywhere) it is found in the environment or in humans, and what effects it may have on humans and the environment. If information on effects is not garnered early in the assessment process, it may lead to characterizing aspects of substances and exposures that are not meaningful or are misclassified.

3.1.3. Why this Research/Information is Needed and of High Importance

This is crucial to ensure that tests measure effects that are relevant to actual exposures ecosystems and humans may experience from TiO₂ in sunscreens, water treatment, and elsewhere. In addition, the current problem concerning the lack of comparability among assays and across test materials needs to be solved.

3.1.4. Extended Description

- Are current EPA standard testing protocols adequate to determine nano-TiO₂ ecotoxicity? If not, what modifications or special considerations, if any, should be made in current ecological tests? For example, what are the differences in characterization of testing material (as raw material, in media, and in organisms), dispersion methods, and realistic exposure routes between testing conventional materials and nanomaterials, surficial aspects including co-transport and protein corona?
- Are the current EPA harmonized health test guidelines for assessing toxicity adequate to determine the health effects/toxicity of nano-TiO₂? Additional assays may be needed including regenerative cell proliferation, body burden distribution data, bronchoalveolar lavage (BAL) for inflammatory mediators. Other batteries of tests may be needed to evaluate other endpoints such as neurotoxicity and other possible hazards.
- This topic applies to nanomaterials across the board and is not unique to nano-TiO₂ or specific applications.
- What criteria, especially associated with an inert colloidal particle, should the EPA use when evaluating harmonized test protocols?
- What set of widely shared reference samples of nano- and conventional TiO₂ would be most useful for integrating the results of different investigators regarding particle characterization and particle toxicology?
- Is it certain that it is nano-TiO₂ (or other nanomaterials) being assessed in the experiments performed (ecological/human)?
- Does EPA have standardized research methods and terms to ensure that everyone is measuring the same thing, where that is the goal?

3.1.5. Other Related Priority Areas

This topic area is underpinned by the related topic areas in Priorities 12 and 15, relating to standard metrics and reference materials; and Priority 4, relating to characterization. It also affects Priority 8, effects of long-term exposure.

3.2. Priority 2: Physico-Chemical Characterization of Nano-TiO₂ Throughout the Life Cycle Stages, Environmental Pathways, and Fate and Transport

3.2.1. Breakout Group Members

Pratim Biswas, Jean-Claude Bonzongo, Thomas Lee, Shannon Lloyd, Anil Patri, Maria Victoria Peeler, and Sylvia Chan Remillard

3.2.2. Short Description

- Physico-chemical characterization of nano-TiO₂ throughout the life cycle stages, environmental pathways, and fate and transport.
- Nanoscale in this case refers to EPA title rather than American Society for Testing and Materials (ASTM) or International Organization for Standardization (ISO) definitions.
- Life cycle stages include those listed in the nano-TiO₂ case study, as well as reuse and recycling, and includes both intentional and unintentional aspects of the life cycle stages.

3.2.3. Why this Research/Information is Needed and of High Importance

- This will develop an understanding of the real world physical and chemical properties of nano-TiO₂ in the life cycle stages, environmental pathways, and fate and transport. This information will ultimately help to understand the implications on the environment and human health.
- These research goals will eventually help in developing safer nanomaterials.

3.2.4. Extended Description

- How do nano-TiO₂ properties change as a result of the various manufacturing processes, upon its incorporation into products (e.g., in sunscreens and water treatment), during its use, during storage, upon release to the environment, upon environmental aging (persistent state), and in different compartments?
- How do specific physico-chemical properties, including particle surface treatments and aggregation/agglomeration, affect the fate and transport of nano-TiO₂ in various environmental media?
- Do we have sufficient information to identify the important physico-chemical characteristics of nano-TiO₂ for the relevant stages of a CEA?

3.2.5. Other Related Priority Areas

- Priority 4 (methods) comes after Priority 2 (characterization) because characterization data is required to predict the elements in Priority 4 (methods).
- Priority 2 comes before Priority 1 (methods for testing health effects/ecotoxicity) because it is necessary to characterize and define physical chemical properties of nano-TiO₂ before exposing organisms.
- Priority 3 (methods for measuring exposure) must come before Priority 2.
- Priority 2 identifies the physical and chemical characteristics of nano-TiO₂ in Priority 5 (exposure pathways) and Priority 6 (in the environment).
- This connects to Priority 1 because thorough characterization is needed to understand the mechanisms of interaction of nano-TiO₂ with the environment (ecological/human).
- Priority 2 will provide data for Priority 10 (EPA or other curated databases).

- Priority 2 relates to Priority 12 (metrics/standards to characterize nano-TiO₂).

3.3. Priority 3: Analytical Method Evaluation, Development and Validation for Analysis of nano-TiO₂ in Relevant Matrices

3.3.1. Breakout Group Members

Jeff Baker, Steven Brown, Shaun Clancy, John LaFemina, and Paul Westerhoff

3.3.2. Short Description

Are available methods adequate to characterize nano-TiO₂ exposure via air, water, and food? What properties of nano-TiO₂ should be included in such exposure characterizations? Do adequate methods exist to characterize nano-TiO₂ in relevant environmental matrices such as soil, sediment, or biofilms and living organisms? Actions needed are to evaluate current methods, develop new methods, and set up validation protocols (with reference materials).

3.3.3. Why this Research/Information is Needed and of High Importance

Quantitative and qualitative characterization of nano-TiO₂ is critical for understanding exposure, dose, and biological and environmental effects. Standardized validated methods are a critical aspect of comprehensive environmental assessment. Nano-TiO₂ is and has been in production and commerce and released to the environment. Limited analytical methods exist and preliminary exposure assessments could be conducted for nano-TiO₂. With more sophisticated analytical methods, exposure assessment uncertainty can be reduced.

3.3.4. Extended Description

This research priority pertains to sunscreen, water treatment, and other uses of nano-TiO₂, as well as for most other metallic-based nanomaterials, and in some case other non-metallic nanomaterials. The details of methods are chemical-specific, but the need for evaluation, development, and validation is common among all nanomaterials.

- Are available methods adequate to characterize nano-TiO₂ exposure via air, water, and food?
 - Quantification and characterization needed at environmentally relevant levels.
 - Terminology needs to differentiate dosage from exposure of nano-TiO₂.
- What properties of nano-TiO₂ should be included in such exposure characterizations?
 - Examples of measurement techniques that are currently available for simple matrices (air and water) include, but are not be limited to: size and number distribution, aggregates and agglomerates, particle counts (Euro V and Euro VI for air emissions), mass concentration, relative surface area, morphology, surface chemical properties and reactivity, and surface charge.
 - Comparisons against reference nano-TiO₂ materials are necessary for method validation and inter-laboratory comparison.
 - Develop method/metric to differentiate nano-TiO₂ from other forms of TiO₂ (e.g., other sizes, aggregates of nano-TiO₂). For example, less than 60 m²/g may be used in Germany, and ASTM is developing coarse/fine/nanomaterials.
- Do adequate methods exist to characterize nano-TiO₂ in relevant environmental and biological matrices such as soil, sediment, or biofilms and living organisms?
 - Dosage needs to be included with exposure.
 - In-situ measurements are desired.
 - Food is one type of biological matrix.
 - Quantification at the organism/organ/cell/sub-cellular level.

3.3.5. Other Related Priority Areas

- Development of validated reference standards and testing protocols (Priorities 1 and 12).
- Understanding how properties of nano-TiO₂ change spatially and temporally requires valid methods (Priority 2).
- Monitoring the current occurrence and sinks of nano-TiO₂ requires valid methods (Priority 6).
- Differentiation of nano-TiO₂ to bulk (non-nano) TiO₂ requires valid methods (Priority 8).
- Relates to ALL other priority areas.

3.4. Priority 4: Nano-TiO₂ Product-Focused Physico-Chemical Characterization; Changes and Possible Effects through the Life Cycle

3.4.1. Breakout Group Members

Mark Bunger, Jaydee Hanson, Fred Klaessig, Richard Pleus, John Small, Treye Thomas, and Donald Versteeg

3.4.2. Short Description

- How do surface coatings and physical and chemical properties affect environmental chemistry and toxicity? Do wastewater treatment plant processes affect surface coatings? What natural particle coatings are added in the environment (e.g., humic and fulvic acids) and how do these natural coatings influence environmental fate, chemistry, and toxicity?
- How do specific physico-chemical properties, including particle surface treatments and aggregation/agglomeration, affect the fate and transport of nano-TiO₂ in various environmental media? How can species be described as they move from source to sink?
- What effect, if any, do coatings, dopings, carriers, dispersants, and emulsion types have on biopersistence and bioaccumulation?
- What factors determine whether and to what extent aggregation or agglomeration of nano-TiO₂ occurs?
- What product-specific knowledge is necessary to conduct a CEA (Figure 3-1)?

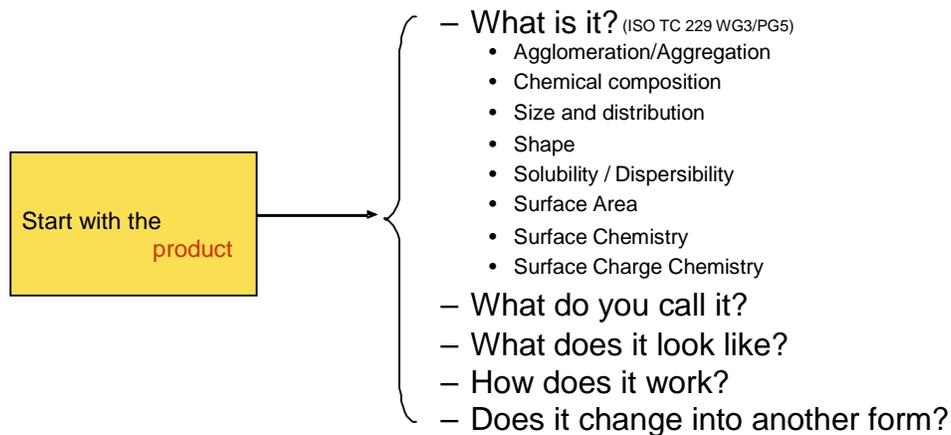


Figure 3-1. Product-Specific Knowledge Highlighted in Priority 4.

3.4.3. Why this Research/Information is Needed and of High Importance

- This work will enable the tests that cover the human and ecological endpoints to be related to the nature of the material.
- The nature of the material will be used at some point in the future to help model and therefore predict the various properties and forms of nano-TiO₂ in the life cycle.

3.4.4. Extended Description

- This work is cross-cutting along all areas of environmental health. It is fundamental work that allows for identification of specific forms of nano-TiO₂ through characterization. This work can be useful, in the future, to model and predict potential effects.
- It pertains to all forms of nano-TiO₂, rather than to only a specific application of nano-TiO₂.
- It pertains to nanomaterials in general, including, but not limited to nano-TiO₂.
- It is necessary to examine typical fate and transport issues, such as bioaccumulation and biopersistence.

3.4.5. Other Related Priority Areas

- Validate or invalidate the protocols, if and when and where they apply to the life cycle (Priority 1).
- This work would clearly identify the material in the environment, whether point or non point source, background, natural, or anthropogenic. If shown to bioaccumulate or biopersist, this work allows for the characterization of the material. This is useful for correctly identifying the material and possibly in predictive modeling (Priority 6).
- This work allows for the characterization of forms of nano-TiO₂ in food, soil, water, and air (as well as other media). It would allow for the determination of different physico-chemical parameters that are related to the amount and behavior of forms of nano-TiO₂ (e.g., the difference between a material staying in air or depositing on the ground) (Priority 3).
- This work allows for the characterization of forms of nano-TiO₂ in various pathways of exposure for human or ecological endpoints (Priority 5).
- If measuring toxicity, then it is possible to characterize the form of nano-TiO₂. This could allow for greater understanding of the mechanism of action, modeling, or prediction of possible endpoints (Priority 7).
- Priorities 12 and 15 are essential for the validation of the characterization tests (Priority 4). There is need for consolidation of Priorities 2, 3, 5–7, 9–11, 14, and 18.
- If ecological effects are discovered, then this work can be used to characterize the forms of nano-TiO₂ (Priority 8).

3.5. Priority 5: Exposure Pathways and Life Cycle Analysis

3.5.1. Breakout Group Members

Brenda Barry, Cathie Barton, Janet Carter, Joan Denton, Bert Hakkinen, and Chris Long

3.5.2. Short Description

This research adopts a life cycle analysis approach to understanding the different sources and pathways that present the greatest current and future exposures to nano-TiO₂ for humans (including both susceptible and highly exposed populations) and biota. The approach used in this research is intended to apply to materials beyond nano-TiO₂.

3.5.3. Why this Research/Information is Needed and of High Importance

Exposure information is an equal partner with toxicology in assessing and managing potential risks of [nano-]TiO₂. This research is needed to develop epidemiology studies, environmental trend

analyses, and life cycle analyses; realize risk management opportunities; and inform hazard studies and method development (e.g., sampling, monitoring, analytical).

3.5.4. Extended Description

While the results may be application-specific, the approach is anticipated to be applicable to a variety of nanoscale materials. This research applies to specific forms of nano-TiO₂ and to those materials that have similar properties. The life cycle approach is the most holistic way to consider all potential exposures to nano-TiO₂ for a given application. This research topic includes:

- Which sources, pathways, and routes pose the greatest exposure potential to nano-TiO₂ for biota and/or humans? At what concentrations?
- Do particular species of biota and particular human populations have greater exposure potential (e.g., receptors with high-end exposures, and/or sensitive subpopulations, such as children, elderly, those with compromised health)?
- What are the relative contributions at different stages of the life cycle for applications such as water treatment, sunscreen use, etc.

3.5.5. Other Related Priority Areas

- Building databases (Priority 10).
- Setting up metrics/parameters and standardized exposure protocols (Priority 1).
- Developing methods for characterization (Priority 3) and changes in properties along the life cycle (Priority 2).
- Setting health effects research priorities (Priority 8).
- Characterizing worker exposures that are compatible with hazard information including concentrations, routes, frequencies, and durations that characterize worker exposures across life cycles and within certain stages of exposure (Priority 13).
- Evaluating coatings and dopings (Priority 4).
- Standardizing terminology and nomenclature properties for current and future use (Priority 11).

3.6. Priority 6: Spatial and Temporal Distribution and Magnitude of Anthropogenic and Non-Anthropogenic Nano-TiO₂ in the Environment

3.6.1. Breakout Group Members

David Andrews, Patricia Holden, Todd Kuiken, Michele Ostraat, and Bill Warren-Hicks

3.6.2. Short Description

This priority area regards where TiO₂ originates in the environment at manufacturing, transport, and use points and its distribution from points of origins at current and future levels of production and use. This area assumes suitable characterization methods and protocols to detect and quantify nano-TiO₂ concentrations and characteristics in a wide variety of soils, water, air, and biota.

- What is the global environmental content of nano-TiO₂ now and in the future?
- Ecologically, is TiO₂ a point-source or regional-exposure problem? If a regional-distribution issue, what are the concentration gradients in key media?
- By region and environmental segment (soil, water, etc.), what is known about the background concentration and characteristics of nano-TiO₂ due to natural (non-anthropogenic) processes?
- Does nano-TiO₂ bioaccumulate in humans?
- Where does nano-TiO₂ accumulate in the environment and in humans? What is the current background level in humans?

3.6.3. Why this Research/Information is Needed and of High Importance

This research priority area is central and foundational to any regulatory risk-based decision on nano-TiO₂ because the exposure concentrations will be compared to the human or ecological no-effects concentrations to determine the magnitude of risk. Background concentrations are critical to establishing the accountability of the anthropogenic sources and to providing insights into risk reduction strategies. Establishing future concentrations based on current use activity levels can also provide insight into potential bioaccumulation rates and extents in biota and humans.

3.6.4. Extended Description

This area does not pertain to any specific application of nano-TiO₂ but provides a general discussion nano-TiO₂ uses. These issues broadly apply to other nanomaterials. The following bullets

provide elaboration on issues associated with the implementation and methodological challenges associated with the short description provided previously.

- Background
 - Requires a sampling system in production, in formulation, in use, in service, and in disposal. Actual production levels will be used to bound the mass balance. A program for a well-designed survey is required to establish the background concentrations and characteristics of nano-TiO₂.
- Current
- Local / point
 - Establish the maximum possible amount of nano-TiO₂ in the environment based upon historical production numbers to place a floor and ceiling on the nano-TiO₂ production levels. This would require:
 - Literature searches and information gathering of historical data.
 - Establishing a national database of total production of TiO₂ and implementation of internal guidance to record relative percent of nano-TiO₂.
 - Conduct spatial sampling adjacent to production/processing sites and pristine sites for comparative analysis. This sampling requires appropriate characterization and protocols to assess nano-TiO₂ detection in soils, water, air, and biota. This will produce a geospatial concentration gradient throughout the United States.
- Regional
 - Establish a database that tabulates nano-TiO₂ uses and captures information on seasonal and regional uses.
 - Compare production, formulation, use, service, and disposal amounts to quantify point sources for further analysis. Then, extend spatially beyond point sources to capture spatial distribution for fate and transport understanding (specially focused on emissions issues or accidental release).
- Future
 - Implement a long-term monitoring program to capture point-source and regional values as well as the environmental burden in water, soils, air, and biota.
 - Utilize current information to facilitate the understanding of the long-term predictive modeling of fate and transport of nano-TiO₂ into and within the environment.
 - Project changes in production, emissions, and relative percentages in-use to highlight potential environmental hotspots and to establish procedures for areas that may require remediation.
 - Predict the future spatial and temporal concentrations of nanoTiO₂ in soil, water, air, and biota.

- Use models and monitoring data to identify potential accumulation in the environment, in biota, and up the food chain.

3.6.5. Other Related Priority Areas

- Priority 3 relates to whether or not methods are adequate to characterize exposures and are methods adequate to characterize nano-TiO₂ in relevant environmental matrices.
- Priority 4 also addresses bioaccumulation and the impact of coatings and other formulations.
- Priority 2 involves life cycle issues, a concept highly related to the proposed monitoring system discussed above.
- Priority 8 discusses ecological studies of long-term exposures that, together with the long-term monitoring, are required to estimate risk.
- Fate and transport modeling concepts for predicting and forecasting concentrations are lacking. This needs to be a priority area for funding (Priority not ranked).

3.7. Priority 7: Using Mechanism of Action (MOA) Information to Drive Toxicity Testing

3.7.1. Breakout Group Members

Gary Ginsberg, Srikanth Nadadur, Geoffrey Sunahara, Jeffery Steevens, and John Veranth

3.7.2. Short Description

For a well-defined nano-Ti[O₂] material, what are the adverse biological effects across multiple species, how does it produce these effects (MOA), what is the dose response for the adverse effects and upstream effects, and how does this relate to dose response for conventional materials? What is the interpretation of this information for risk assessment at environmentally relevant concentrations?

3.7.3. Why this Research/Information is Needed and of High Importance

This information needs to be used to develop a toxicity testing paradigm tailored to detect the types of effects produced by nano-TiO₂ materials.

- Identify key dose metrics for dose-response evaluation using MOA.
- Identify key response metrics for upstream indicators (i.e., reactive oxygen species [ROS], cell signaling).
- Use metrics to understand if conventional and nano-TiO₂ will have same MOA.
- Predict if interactions will occur (e.g., light, metals, other chemicals).
- Provide biological basis for [structure-activity relationship] (SAR) approaches.

3.7.4. Extended Description

Mechanism of Action. How does nano-TiO₂ produce changes at the molecular, cellular, organism (e.g., skin, lungs, internal organs) and whole-animal level? This may include generation of ROS, photoactivation, binding to receptors, cell signaling, and gene expression. MOA can be used to identify key dosimetrics for dose-response evaluation (surface area, particle size, surface charge, etc.).

- Dosimetric – what is really doing the damage and how is it measured?
- Response-metric – identify the most sensitive upstream indicator effects that can be plugged into dose-response endpoints.

Use MOA information to understand whether conventional and nano-TiO₂ have the same MOA and whether the major distinction is simply in terms of potency.

Interactions. Use MOA information to understand how nano-TiO₂ can interact with light energy and other toxicants (particularly metals) to produce novel effects. MOA is our bridge to developing SAR-type approaches for nanomaterials.

Dose-Response. How do the biological effects and MOA change when going from high dose to environmentally relevant doses? The dose-response relationship in sensitive species and age groups is needed for developing estimates of potency used in risk assessment. This dose-response and mechanistic information needs to be informed by an up-front literature review and evaluation that identifies whether risk assessment is possible with the current information and what key data need to exist to facilitate risk assessment.

Testing Strategy. Standard toxicity testing may not capture the effects produced by nano-TiO₂ materials. MOA needs to inform toxicity testing (e.g., incorporate photoactivation into testing protocols) to ensure that nano-Ti[O₂] effects are captured.

3.7.5. Other Related Priority Areas

This priority is related to many other priority areas (Figure 3-2). It will be necessary to start with physical and chemical characterization (Priority 4). Next, it is necessary to look at

manufacturing processes and products (i.e., what is it?) and relevant form and environmental matrix (Priorities 2 and 6) to compile databases (Priority 10). Then, aim to determine kinetics and realistic dose (Priority 9), particularly to sensitive populations (Priority 5), that will cause effects (Priority 1) using specific endpoints (Priority 8). In order to do these things, the MOA must be known (Priority 7). This research also depends on the development of nomenclature (Priority 11) and prototype/reference materials (Priority 12).

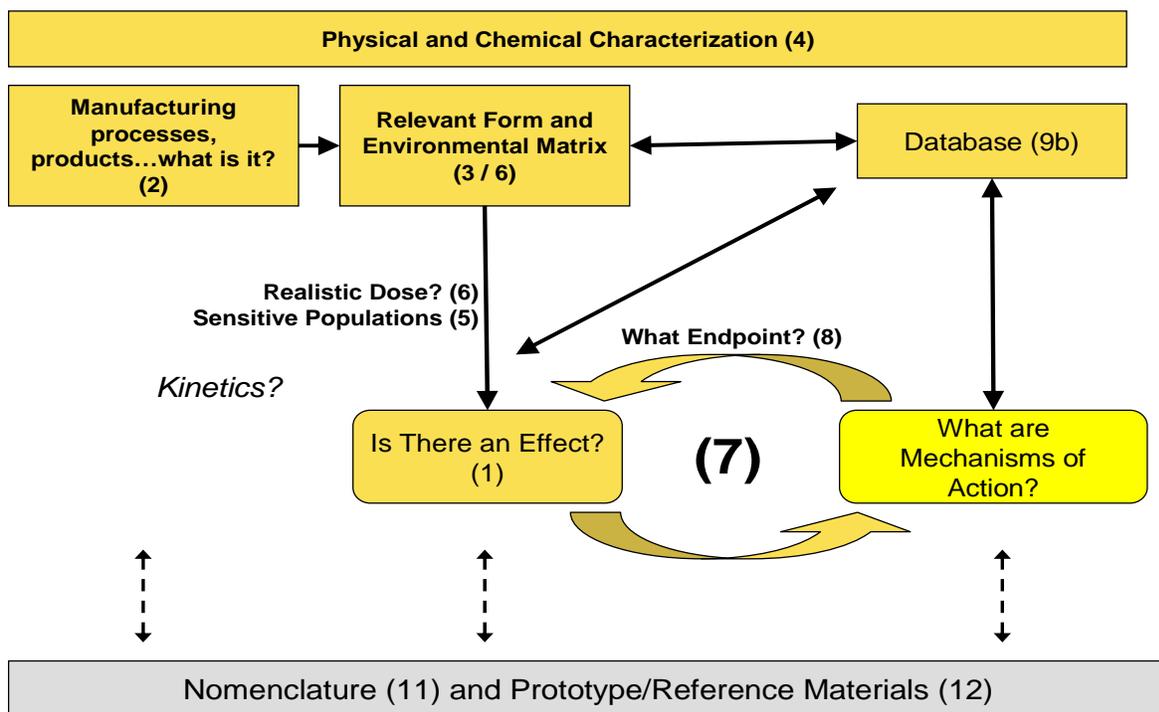


Figure 3-2. Priority Areas Related to Priority 7

3.8. Priority 8: Long-Term Effects

3.8.1. Breakout Group Members

Eula Bingham, Paul Howard, Rebecca Klaper, Margaret MacDonell, Nancy Monteiro-Riviere, Paul Mushak, and Nigel Walker

3.8.2. Short Description

- What are the long-term human effects following exposure to nanomaterials?
 - Are in vitro (e.g., high throughput screening assays) appropriate for prioritizing specific nano-TiO₂ for further long-term evaluation?
 - Assessment of kinetics of TiO₂ in mammalian systems (in vivo).
 - Long-term exposure outcomes
 - human (epidemiology) and animal models (subchronic to chronic).
 - oral
 - inhalation
 - dermal
- What are the long-term ecological effects following exposure to nanomaterials?
 - Long-term assays (organism to ecosystem measures).
 - Organism/population (key organisms in aquatic, terrestrial, and air).
 - Number that survive, kinetics, reproductive problems, other endpoints (e.g., tumors, biomarkers of effect).
 - Community and ecosystem impacts (functional community, total population).
 - Microbial functional community
 - Nutrient cycling changes

3.8.3. Why this Research/Information is Needed and of High Importance

Risk is a combination of exposure and hazard. The work in this area will assess the hazard and dose response for effects of concern. Both short-term and long-term data are required for proper assessment of potential risks. If there is no adverse effect, there is no risk. The outcomes of short-term studies do not necessarily predict long-term effects.

3.8.4. Extended Description

This topic area is determining the long-term effects of nano-TiO₂ on ecosystems and humans, allowing the determination of risk (hazard × exposure). The descriptions, herein, apply to nano-TiO₂ and to other nanomaterials, in general; however, the elements described were developed in view of the specific case of nano-TiO₂.

In this risk-assessment document there are limited data on acute effects of TiO₂; however, there is a significant lack of data on long-term effects that would drive the risk assessment models.

To determine long-term human effects for nanomaterial exposure the following is needed:

- Evaluate the appropriateness of in vitro (e.g., high throughput screening assays) for prioritizing specific nano-TiO₂ for further long-term evaluation.
- Assess kinetics of TiO₂ in mammalian systems.
- Generate and collect research data on long-term exposures.

For the near-term research agenda, this means models of chronic animal exposure. For the longer-term research agenda, this means data on human epidemiology. One practical solution is to use assessment of the ecological data to prioritize the materials that will be used to test in humans (as with PCB's, aquatic bioaccumulation identified the priorities for which PCBs to test).

3.8.5. Other Related Priority Areas

How can EPA partner with other agencies and industry to better achieve the goals of the CEA (the priority questions from this workshop)? Although these are all related priorities, [they] should not all be responsibility of EPA (considering resources, funding, and expertise)? Should there be collaborations with other agencies, industry, and academia (Priority not ranked)?

Related priority areas include:

- Routes of exposure and most sensitive populations (Priority 5).
- Adequacy of protocol (Priority 1).
- Characterization methods; if you don't know what you are testing, you don't know how it relates to the nanomaterial in environment (Priority 3).
- Manufacturing, use and release (Priority 2).
- Coating and modifications, physical chemical properties, and how effect biopersistence and bioaccumulation (Priority 4).
- Spatial, release, sources of exposure (Priority 6).
- Mechanism of action and dose response (Priority 7).

Also related are the following:

- Priority 9 – Is the available ecotoxicity evidence adequate to support ecological risk assessment for nano-TiO₂? If not, what is needed? What are the sensitive ecological endpoints? How do abiotic factors in the environment, such as UV, pH, oxygen level, and other chemicals, affect nano-TiO₂ and its ecological effects?

- Priority 10 – Should EPA set up comprehensive, user friendly databases with all information (such as metrics, toxicity data (current database), characterization, fate, etc.) to support comprehensive environmental assessments? What has the EPA learned about the quality of the TiO₂ data in the open literature as applied to nano-TiO₂ and other particles?
- Priority 11 – What needs to be standardized as terminology/nomenclature/ properties for current and future use? Should the EPA promote a surface chemistry nomenclature system for use in particle life cycle analyses? What is nano-TiO₂? Is the definition of less than 100 nm adequate? Or, should a dimension be derived based on the toxicological properties?
- Priority 13 – What parameters should be used to characterize worker (or consumer or general human) exposure in a way that is compatible with hazard information. (Exposure matches hazard.) What concentrations, routes, frequencies, and durations characterize worker exposures to nano-TiO₂ across the life cycle and within certain stages (e.g., manufacturing)?
- Priorities 12 and 15 – What are the important metrics and standards that we need to use to characterize nano-TiO₂? What is the role of standard reference materials for integrating the results of different investigators regarding particle characterization and particle toxicology? What is needed? Can we develop a decision-tree framework and best practices to facilitate environmental assessment of individual nanomaterials? Would a toxicity – application – exposure – life-cycle assessment – order in a decision tree be workable for conducting a CEA for nano-TiO₂? How do we integrate analytical methods used to characterize risk (mass flow, life cycle) to evaluate and compare environmental trade-offs?

Chapter 4. Observations and Next Steps

The ranking results and breakout group reports presented in this document represent only a portion of the data provided by the participants in this process. In particular, the specific issues identified by the individual participants could be examined more extensively to see if some gems were overlooked or lost in the consolidation and voting process. One unstated hope underlying the development of the case studies and the review and workshop associated with the case studies was that bringing a diverse array of technical and stakeholder perspectives to bear on the questions raised by the selected nanomaterial applications might yield insights that would be useful in averting unintended consequences of this emerging technology. Closer examination of specific issues and comments submitted by the participants and other reviewers may still uncover such insights. Also, more detailed analyses of the ranking data in Appendices K and L remain to be done.

Various aspects of the workshop could have been done differently and probably improved. Given that the ranking results of the two NGT groups were similar, it now seems clear that conducting the workshop with a smaller number of participants would have likely achieved similar outcomes, particularly for the most highly ranked issues. Apart from the reduced expense of having a smaller number of participants, the process of consolidating the two groups' issues in a plenary session could have been avoided and more time freed up for the breakout groups. Many participants completed workshop evaluations forms and referred to the breakout group discussions as one of the best features of the meeting. By allowing more time for the breakout groups, we might have enabled them to develop their thoughts in greater detail or perhaps we could have posed additional questions and tasks for them to address. Also, more time might have allowed for a more formal consensus process among the breakout group members in preparing their reports and presentations.

Some seemingly minor procedural matters may have had some influence on the process and results. For example, for the round-robin sessions, the NWRI NGT workshops (<http://www.nwri-usa.org/>) required participants to come to a lectern and present their views to the group, whereas in the EPA workshop the facilitators allowed participants to remain seated while speaking to the group. Although equivalent time limits on individual statements were imposed in both situations, remaining seated probably saved an appreciable amount of time overall. However, the informality of remaining seated may have contributed to a more casual attitude on the part of some participants and what appeared to be, from this author's non-scientific observation, a corresponding lack of incisiveness in their statements.

Of course, other differences between the NWRI and EPA workshops could have also influenced how the participants approached the round-robin session. It could be that the NWRI participants were more familiar with the NGT process because of their repeated participation in such

meetings. The NWRI workshops are more narrowly focused on water-related issues and intentionally involve experts in that field, so there is a more limited pool of candidates and hence greater likelihood of repeated participation. Prior experience with the process could lead to more effective presentations. In contrast, a greater proportion of participants in the EPA workshop may not have realized the importance of making a cogent argument for their viewpoint, despite (or because of?) the fairly terse instruction in the pre-workshop handout (Appendix I) to be prepared to offer a “statement or description of the research/information need and an explanation of why it is a high priority in relation to a comprehensive environmental assessment of nanoscale titanium dioxide (nano-TiO₂).”

Another observation on the EPA workshop outcomes is that they tended to reflect a high degree of consolidation across several individual issues. As listed in Section 2.4, most of the priority areas subsumed at least 5 questions, and a couple of areas covered 7 questions. This tendency toward convergence may have reflected a propensity for “lumping” as opposed to “splitting” for a majority of the participants, but a more likely explanation is that consolidation was a prominent feature of the workshop and was explicitly encouraged. The problem with too much consolidation is that, at an extreme, one ends up with the highest priority question being “What are the risks of nanomaterials?” – which of course simply begs the question and provides no insight into which specific research areas warrant the most attention. For a group made up predominantly of researchers who may tend to think in terms of specific scientific projects, a push to consolidate related ideas together into a more broadly stated topic area may be appropriate. But for a group that is more heterogeneous in composition, especially one that includes a number of persons already inclined (or instructed) to think about the “big picture,” less encouragement to consolidate multiple issues might be appropriate.

Among the next steps to be taken to follow up the 2009 EPA workshop are plans to hold another workshop using a case study focusing on nanoscale silver in spray disinfectants. At this time, we presume we will use an NGT process again, although modifications of the process, reflecting observations made above, are likely. The objective in developing a series of nanomaterial case studies and holding workshops to identify and prioritize research needs is not simply to see how different nanomaterials compare to each other. Rather, the ultimate goal is to develop a broad, long-range strategy for determining where research should be directed to best support efforts to conduct comprehensive environmental assessments of nanomaterials. This new research strategy will likely evolve as different case studies are considered and as new information on existing case studies becomes available. Thus, it will not be a static document, but one that reflects an evolving understanding of nanomaterials and their (broadly defined) environmental implications. We believe that however it evolves, it will benefit from a process that takes advantage of formally tapping the collective judgments of diverse groups of technical experts and stakeholders.

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

APPENDIX A. Nano-TiO₂ Case Studies Document

Nanomaterial Case Studies: Nanoscale Titanium Dioxide in Water Treatment and in Topical Sunscreen [External Review Draft], U.S. Environmental Protection Agency, National Center for Environmental Assessment, Research Triangle Park, NC, Report No. EPA/600/R-09/057, July 2009, is a 222-page document (U.S. EPA, 2009, [225004](#)) that can be accessed at:

<http://cfpub.epa.gov/ncea/cfm/recorddisplay.cfm?deid=210206>

APPENDIX B. List of Questions from the Nano-TiO₂ Case Studies Report

Chapter 1 of Nano-TiO₂ Case Studies Report: Introduction

Questions about Characterizing Nanoscale Titanium Dioxide

- 1-1.** To evaluate nano-TiO₂ (in these or other applications) or to compare products containing nano-TiO₂, is further standardization or refinement of terminology needed? If so, is such an effort underway and/or what terminology is most important to standardize?
- 1-2.** Have the properties of nano-TiO₂ in different applications been adequately characterized? If not, is the general problem that methods do not exist or that existing methods have not been widely applied? If new methods are needed, what properties should they measure?
- 1-3.** Which coatings, dopings, carriers, dispersants, and emulsion types are most prevalent in different applications of nano-TiO₂?
- 1-4.** What are the potential implications (e.g., in terms of physical and chemical properties) of differences in the composition and mineralogy of different forms of nano-TiO₂ (e.g., rutile and anatase)?
- 1-5.** How do coatings applied for different purposes (e.g., to disperse particles or to decrease photocatalysis) interact or affect other properties of nano-TiO₂?
- 1-6.** What factors determine whether and to what extent aggregation or agglomeration of nano-TiO₂ occurs?
- 1-7.** Are data available that indicate the level of agglomeration/aggregation/dispersion of nano-TiO₂ in specific products? If so, what do the data show?
- 1-8.** Is there a difference between the opacity of nano-TiO₂ aggregates and conventional TiO₂ particles of nominally similar size (e.g., because of light passing through pores in aggregates)? If so, what are the implications of such a difference?
- 1-9.** Regarding the properties of aggregates and agglomerates and proper characterization of particle size, what insight is available from study of other nanoparticles?
- 1-10.** What existing or emerging analytical techniques might be relevant or useful for material characterization? For example, could field flow fractionation (FFF) be used for characterization of particle size and elemental composition?
- 1-11.** Do surface area measurements in air (e.g., BET analysis) correlate to surface area in an aqueous environment? If so, what is the extent of their accuracy and precision?

Chapter 2 of Nano-TiO₂ Case Studies Report: Life Cycle Stages

Questions about Feedstocks

- 2.1-1.** Are certain feedstocks more relevant to producing nano-TiO₂ specifically for water treatment or sunscreen applications?

2.1-2. What contaminants, nanoscale and larger, might be released, and in what quantities, in relation to the procurement and processing of feedstocks for nano-TiO₂?

Questions about Manufacturing

2.2-1. How do various manufacturing processes for nano-TiO₂ affect their physicochemical properties?

2.2-2. How are manufacturing processes likely to evolve with increasing demand for nano-TiO₂?

2.2-3. Are certain manufacturing processes used specifically for nano-TiO₂ as a water treatment agent or as topical sunscreen?

2.2-4. What waste products or other by-products, both nanoscale and larger, might be released, and in what quantities, for nano-TiO₂ manufacturing processes?

2.2-5. Where is nano-TiO₂ manufactured? What is the potential for general population exposure to nano-TiO₂ in these areas?

Questions about Distribution and Storage

2.3-1. How is nano-TiO₂ shipped (i.e., what are the relative frequencies for shipments in bulk, paper bags, or drums, or by truck or rail)? How far is it shipped? In what quantities?

2.3-2. Are data available or can they be collected or estimated for accident rates and routine product releases associated with various modes of shipping and storage? To what degree could best practices reduce such occurrences?

2.3-3. How is nano-TiO₂ stored (e.g., in warehouses, sunscreen manufacturing plants, and water treatment facilities)?

2.3-4. Does the use of “ventilated paper bags” increase the possibility of accidental spillage during shipment and storage? Are any guidelines available on whether protective packaging (e.g., additional polyethylene lining) is warranted?

2.3-5. Could vermin breach storage containers and contribute to environmental releases or become part of an environmental exposure pathway?

2.3-6. Would prolonged storage in adverse or less than ideal climates (e.g., cold or humid environments) alter nano-TiO₂ characteristics and behavior?

2.3-7. How much nano-TiO₂ could be released under various routine and accidental scenarios of distribution and storage?

Questions about Use

2.4-1. To what extent is nano-TiO₂ used or could be used for either drinking water or waste water treatment? Are data available (e.g., volume of water currently treated in the United States for arsenic, amount of TiO₂ needed to treat a given volume of water) that would permit an estimate of potential use?

2.4-2. Which water treatment processes use or would use nano-TiO₂ and in what quantities? Would the type of process depend on the size of a treatment facility or the size of the population served, or both?

2.4-3. What percentage of the nano-TiO₂ would settle out in floc or become part of the filter matrix? What percentage would be released into finished water? Are measurement or monitoring methods adequate to detect such particles?

- 2.4-4.** Water distribution systems often have substantial biofilm or corrosion development, despite the implementation of control practices. Would the presence of nano-TiO₂ influence the bacterial biofilm community or the occurrence of corrosion?
- 2.4-5.** What is the total quantity of nano-TiO₂ used in topical sunscreen products in the United States and worldwide?
- 2.4-6.** What is the maximum quantity and frequency of personal sunscreen use in relation to season, geographic location, demographics, and other variables?
- 2.4-7.** How much nano-TiO₂ enters the environment under different scenarios and conditions of sunscreen use (e.g., ambient air and water temperature, swimming, bathing)? Under what conditions would nano-TiO₂ be released from the sunscreen matrix?

Questions about Disposal

- 2.5-1.** How much residual nano-TiO₂ is present in packaging of the primary material or derived products? How is such packaging disposed of?
- 2.5-2.** If nano-TiO₂ were to become much more widely used and produced at a much higher volume, would packaging and shipping methods of nano-TiO₂ change? If so, how would such change affect the potential release and exposure during transport, storage, and disposal?
- 2.5-3.** In water treatment, how are filter materials and associated waste/waste water containing nano-TiO₂ disposed of or recycled?
- 2.5-4.** How are large quantities of sunscreen (e.g., sub-par batches rejected during manufacturing) handled?
- 2.5-5.** How much nano-TiO₂ is present in sunscreen containers that are discarded? Are there any circumstances where such discarded product could enter a microenvironment at significant levels?

Chapter 3 of Nano-TiO₂ Case Studies Report: Fate and Transport

- 3-1.** What are the relative contributions of different stages of the life cycles of water treatment and sunscreen products to environmental levels of nano-TiO₂ and associated contaminants in air, water, and soil?
- 3-2.** How do specific physicochemical properties, including particle surface treatments and aggregation/agglomeration, affect the fate and transport of nano-TiO₂ in various environmental media?
- 3-3.** Are available fate and transport models applicable to nano-TiO₂? If not, can they be adapted, or are new models required?
- 3-4.** Is information on environmental fate and transport of other substances available that might provide insights applicable to nano-TiO₂?
- 3-5.** If nano-TiO₂ production were to increase greatly, the packing and transport methods are likely to be changed as well. How would this affect the fate and transport of nano-TiO₂?
- 3-6.** How might nano-TiO₂ affect the fate and transport of metals and other potentially toxic substances in water or other environmental media?

- 3-7. What is the bioavailability of nano-TiO₂ in land-applied sludge to both terrestrial and aquatic organisms? Is bioavailability likely to change when nano-TiO₂ is incorporated into sludge and is allowed to “age” (in- situ weathering)?
- 3-8. What effect, if any, do coatings, dopings, carriers, dispersants, and emulsion types have on biopersistence and bioaccumulation?
- 3-9. Can the photocatalytic properties of nano-TiO₂ cause other unintended substances to form, for example, degradation products, in various environmental media?
- 3-10. Will nano-TiO₂ affect the efficacy of other major elements of water treatment processes (e.g., chemical disinfection, the coagulant concentration necessary for effective organics removal)?
- 3-11. What influence could other drinking water contaminants, including arsenic, have on the chemical properties or behavior of nano-TiO₂?
- 3-12. Irradiated photocatalytic nano-TiO₂ is potentially biocidal and antimicrobial. What is the potential for interactions of nano-TiO₂ with microbes needed in water treatment systems?
- 3-13. What are the key environmental factors (e.g., pH, natural organic matter type and concentration, temperature) that facilitate or hinder nano-TiO₂ stability in the aqueous environment? Would humic acids or other common constituents or contaminants in water undergoing treatment affect the fate, including agglomeration/aggregation properties, of TiO₂?
- 3-14. What is the impact to nutrient and metals cycling and microbial diversity when sludge with nano-TiO₂ is applied to soils?
- 3-15. How do sunscreen ingredients affect nano-TiO₂ fate and transport?
- 3-16. Can agglomeration/disagglomeration in the environment be predicted on the basis of physical properties of the particle, for example, size, shape, or coating?
- 3-17. What is the likelihood that nano-TiO₂ in biosolids will become part of the food web and ground water contamination?
- 3-18. What is the potential for plant uptake of nano-TiO₂ from contaminated soil and irrigation water?

Chapter 4 of Nano-TiO₂ Case Studies Report: Exposure-Dose Characterization

- 4-1. Which sources, pathways, and routes pose the greatest exposure potential to nano-TiO₂ for biota? ...for humans?
- 4-2. What is the potential for biota and human (both occupational and general population) exposure to secondary contaminants (e.g., waste or transformation products) associated with the entire life cycle of water treatment or sunscreen applications of nano-TiO₂?
- 4-3. Do particular species of biota and populations of humans have greater exposure potential (e.g., high-end exposures due to unusual conditions or atypical consumption)? In particular, do children get a higher exposure and/or dose?
- 4-4. What is the total population that could be exposed to nano-TiO₂ via drinking water? ...via topical sunscreens?
- 4-5. Approximately how many workers are involved in nano-TiO₂ production, distribution, and use?

- 4-6.** What concentrations, routes, frequencies, and durations characterize worker exposures to nano-TiO₂ across the life cycle and within certain stages (e.g., manufacturing)?
- 4-7.** What management practices exist to control occupational exposures to nano-TiO₂?
- 4-8.** What personal protective equipment do workers use at the various life cycle stages of nano-TiO₂ applications? How effective is such equipment in controlling exposures by all routes?
- 4-9.** Are occupational monitoring methods available or in place for all relevant stages of the life cycle for nano-TiO₂ applications?
- 4-10.** Are available methods adequate to characterize nano-TiO₂ exposure via air, water, and food? What properties of nano-TiO₂ should be included in such exposure characterizations?
- 4-11.** Given the potential for greater uptake of certain substances in the presence of nano-TiO₂, should monitoring and exposure studies include a suite of substances that might interact with nano-TiO₂?
- 4-12.** What happens when nano-TiO₂ is trapped in the stratum corneum and the dead skin flakes off? Is there a potential for dead-skin nano-TiO₂ to settle around households, or be inhaled? How much might accumulate after a day (or a few days) in the sun (and numerous reapplications)?
- 4-13.** Since nano-TiO₂ may increase the uptake of other pollutants, such as arsenic, would nano-TiO₂ be a greater concern for exposure and ecological effects in areas with high concentrations of certain pollutants than in other areas? If so, how do we predict or identify such “hot spots”?
- 4-14.** Which, if any, exposure models have been evaluated for applicability to nano-TiO₂?
- 4-15.** Which physiologically-based pharmacokinetic models are optimal for understanding absorption, distribution, and elimination of nano-TiO₂ in humans?
- 4-16.** Are exposure-dose models available (and adequate) to quantitatively extrapolate the exposure used in animal toxicology studies (by inhalation, instillation, oral, dermal, and in vitro) to the human exposure that would result in an equivalent dose to the target of interest?
- 4-17.** What is the potential for nano-TiO₂ to transfer to or accumulate in the food web and cause adverse effects on ecological receptors?
- 4-18.** Nano-TiO₂ has been shown to attach to the surfaces of algae and fish as well as bioaccumulate in fish. Does nano-TiO₂ biomagnify?

Chapter 5 of Nano-TiO₂ Case Studies Report: Characterization of Effects

Questions about Ecological Effects

- 5.2-1.** Are current EPA standard testing protocols adequate to determine nano-TiO₂ ecotoxicity? If not, what modifications or special considerations, if any, should be made in current ecological tests? For example, what are the differences in characterization of testing material (as raw material, in media, and in organisms), dispersion methods, and realistic exposure routes between testing conventional materials and nanomaterials?
- 5.2-2.** What are the ecological effects of waste and other by-products of nano-TiO₂ manufacturing?
- 5.2-3.** Could ecological effects of pure nano-TiO₂ be predictive of effects from products containing nano-TiO₂ (e.g., containing stabilizers or surfactants)?

- 5.2-4.** How can contributions of various nano-TiO₂ physicochemical properties to nano-TiO₂ ecological effects be identified or compared? For example, could a retrospective analysis of many studies and computer modeling identify patterns that would not be evident in individual studies? Is a structure activity relationship (SAR) approach applicable for predicting nano-TiO₂ ecological effects?
- 5.2-5.** What might be the primary mechanism(s) of action of toxic effects in different species?
- 5.2-6.** Are the mechanisms of cellular responses different at low and high concentrations of nano-TiO₂?
- 5.2-7.** How do abiotic factors in the environment, such as UV, pH, oxygen level, and other chemicals, affect nano-TiO₂ and its ecological effects?
- 5.2-8.** How do in vivo biochemical processes alter nano-TiO₂ physicochemical characteristics and toxicity?
- 5.2-9.** What are the ecological effects of long-term exposure to nano-TiO₂?
- 5.2-10.** What are the indirect ecological effects (e.g., on soil or water chemistry) of nano-TiO₂?
- 5.2-11.** Nano-TiO₂ has anti-bacterial and anti-fungal properties. What are the effects of both photocatalytic and photostable nano-TiO₂ on the biodiversity of microorganisms?
- 5.2-12.** In addition to arsenic and cadmium, do other compounds show different uptake in the presence of nano-TiO₂? Are the toxicities of arsenic, cadmium, or other chemicals affected by nano-TiO₂? Conversely, do other compounds affect the uptake and toxicity of nano-TiO₂?
- 5.2-13.** Is the available ecotoxicity evidence adequate to support ecological risk assessment for nano-TiO₂? If not, what is needed?

Questions about Health Effects

- 5.3-1.** Are the current EPA harmonized health test guidelines for assessing toxicity adequate to determine the health effects/toxicity of nano-TiO₂?
- 5.3-2.** Is the current information on nano-TiO₂ skin penetration sufficient for risk assessment?
- 5.3-3.** Would nano-TiO₂ penetrate into living cells in flexed, “soaked,” or damaged skin (such as sunburned, scratched, eczematous skin)?
- 5.3-4.** How important is testing nano-TiO₂ skin penetration on different races and at different ages?
- 5.3-5.** Do certain formulations of nano-TiO₂ sunscreens generate hydroxyl radicals when applied to skin?
- 5.3-6.** Given that nano-TiO₂ is a good antimicrobial agent, how does it affect skin flora? Does application of sunscreen promote the colonization of skin by potentially harmful bacteria (e.g., staph)?
- 5.3-7.** To what extent do photocatalytic properties of nano-TiO₂ contribute to dermal effects?
- 5.3-8.** What kind of studies would provide the most suitable data to understand dose-response of nano-TiO₂ occupational exposure and health effects in humans?
- 5.3-9.** What is the potential for reproductive and developmental effects of nano-TiO₂?

5.3-10. Is ingested nano-TiO₂ carcinogenic?

5.3-11. Is inhaled nano-TiO₂ carcinogenic at exposure levels below those that induce particle overload?

APPENDIX C. List of Reviewers

C.1.1. External Reviewers (of November 2007 draft of Case Study 1: Water Treatment)

Pratim Biswas, Washington University
Bernard Goldstein, University of Pittsburgh
Judith A. Graham, Private Consultant
Fred Klaessig, Degussa (now Evonik)
Rebecca Klaper, University of Wisconsin
Terry Medley, DuPont (with David Warheit, Gary Whiting, Scott Frerichs, and Brian Coleman)
Gunter Oberdorster, University of Rochester
John A. Small, National Institute of Standards and Technology (with Richard Holbrook)
Jeffrey Steevens, U.S. Army Corps of Engineers
Mark Wiesner, Duke University (with Christine Robichaud)
Srikanth Nadadur, National Institute of Environmental Health Sciences

C.1.2. Interagency Reviewers

Sarah Gerould, U.S Geological Survey
Jo Ellen Hinck, U.S. Geological Survey
Carlos Peña, Federal Department of Agriculture
Loretta Schuman, Occupational Safety and Health Administration

C.1.3. EPA Workgroup Members

J. Michael Davis (**Chair**), ORD, NCEA, Research Triangle Park
Jacqueline McQueen (**Co-Chair**), ORD, OSP, Washington DC
Christian Andersen, ORD, NHEERL, Corvallis
Rochelle Araujo, ORD, NERL, Research Triangle Park
Fred Arnold, OPPTS, OPPT, Washington DC
Ayaad Assaad, OPPTS, OPP, Washington DC
Norman Birchfield, ORD, OSA, Washington DC
Deborah Burgin, OSWER, OSRTI, Washington DC
Jim Caldwell, OAR, OTAQ, Washington DC
David Cleverly, ORD, NCEA, Washington DC
Michele Conlon, ORD, NERL, Research Triangle Park
Mary Ann Curran, ORD, NHEERL, Cincinnati
Walter Cybulski, ORD, OSP, Washington DC
Jane Denne, ORD, NERL, Las Vegas
Steve Diamond, ORD, NHEERL, Duluth
Jaimee Dong, OAR, OTAQ, Washington DC
Kevin Dreher, ORD, NHEERL, Research Triangle Park
Jeremiah Duncan, ORD, NCER, Washington DC
Brian Englert, OW, OST, Washington DC
Patricia Erickson, ORD, NHEERL, Cincinnati
Cathy Fehrenbacher, OPPTS, OPPT, Washington DC
Gina Ferreira, Region 2, New York City
Kathryn Gallagher, ORD, OSA, Washington DC
Michael Gill, Region 9, San Francisco
Michael Gonzalez, ORD, NRMRL, Cincinnati
Maureen Gwinn, ORD, NCEA, Washington DC
Kathy Hart, OPPTS, OPPT, Washington DC
Tala Henry, OPPTS, OPPT, Washington DC

Ross Highsmith, ORD, NERL, Research Triangle Park
Lee Hofmann, OSWER, ORCR, Washington DC
Marion Hoyer, OAR, OTAQ, Ann Arbor
Joe Jarvis, ORD, ORMA, Washington DC
Bernine Khan, ORD, NRMRL, Research Triangle Park
David Lai, OPPTS, OPPT, Washington DC
Wen-Hsiung Lee, OPPTS, OPPT, Washington DC
Laurence Libelo, OPPTS, OPPT, Washington DC
Diana Locke, OPPTS, OPPT, Washington DC
Gregory Miller, OPEI, NCEE, Washington DC
David Meyer, ORD, NRMRL, Cincinnati
J. Vincent Nabholz, OPPTS, OPPT, Washington DC
Nhan Nguyen, OPPTS, OPPT, Washington DC
Carlos Nunez, ORD, NRMRL, Research Triangle Park
David Olszyk, ORD, NHEERL, Corvallis
Martha Otto, OSWER, OSRTI, Washington DC
Scott Prothero, OPPTS, OPPT, Washington DC
Kim Rogers, ORD, NERL, Las Vegas
Zubair Saleem, OSWER, ORCR, Washington DC
Nora Savage, ORD, NCER, Washington DC
Phil Sayre, OPPTS, OPPT, Washington DC
Rita Schoeny, OW, OST, Washington DC
Walter Schoepf, Region 2, New York City
Najm Shamim, OPPTS, OPP, Washington DC
Deborah Smegal, OA, OCHPEE, Washington DC
Jose Solar, OAR, OTAQ, Washington DC
Neil Stiber, ORD, OSA, Washington DC
Timothy Taylor, OSWER, ORCR, Washington DC
Susan Thornehoe, ORD, NRMRL, Research Triangle Park
Dennis Utterback, ORD, OSP, Washington DC
Amy Wang, ORD, NCEA, Research Triangle Park
Eric Weber, ORD, NERL, Athens
Randy Wentsel, ORD, IO, Washington DC
Doug Wolf, ORD, NHEERL, Research Triangle Park

Organization Abbreviations:

IO	Immediate Office
NCEA	National Center for Environmental Assessment
NCER	National Center for Environmental Research
NERL	National Exposure Research Laboratory
NHEERL	National Health and Ecological Effects Laboratory
NRMRL	National Risk Management Research Laboratory
OA	Office of the Administrator
OAR	Office of Air and Radiation
OCHPEE	Office of Children's Health Protection and Environmental Economics
OPEI	Office of Policy, Economics, and Innovation
OPP	Office of Pesticide Programs
OPPT	Office of Pollution Prevention and Toxics
OPPTS	Office of Prevention, Pesticides, and Toxic Substances
ORCR	Office of Resource Conservation and Recovery
ORD	Office of Research and Development
ORMA	Office of Resource Management and Administration
OSA	Office of Science Advisor
OSP	Office of Science Policy
OSRTI	Office of Superfund Remediation and Technology Innovation
OST	Office of Science and Technology
OSWER	Office of Solid Waste and Emergency Response
OTAQ	Office of Transportation and Air Quality
OW	Office of Water

APPENDIX D. Web Site Forms and Information

D.1. Web Site Text for Initial Inquiry

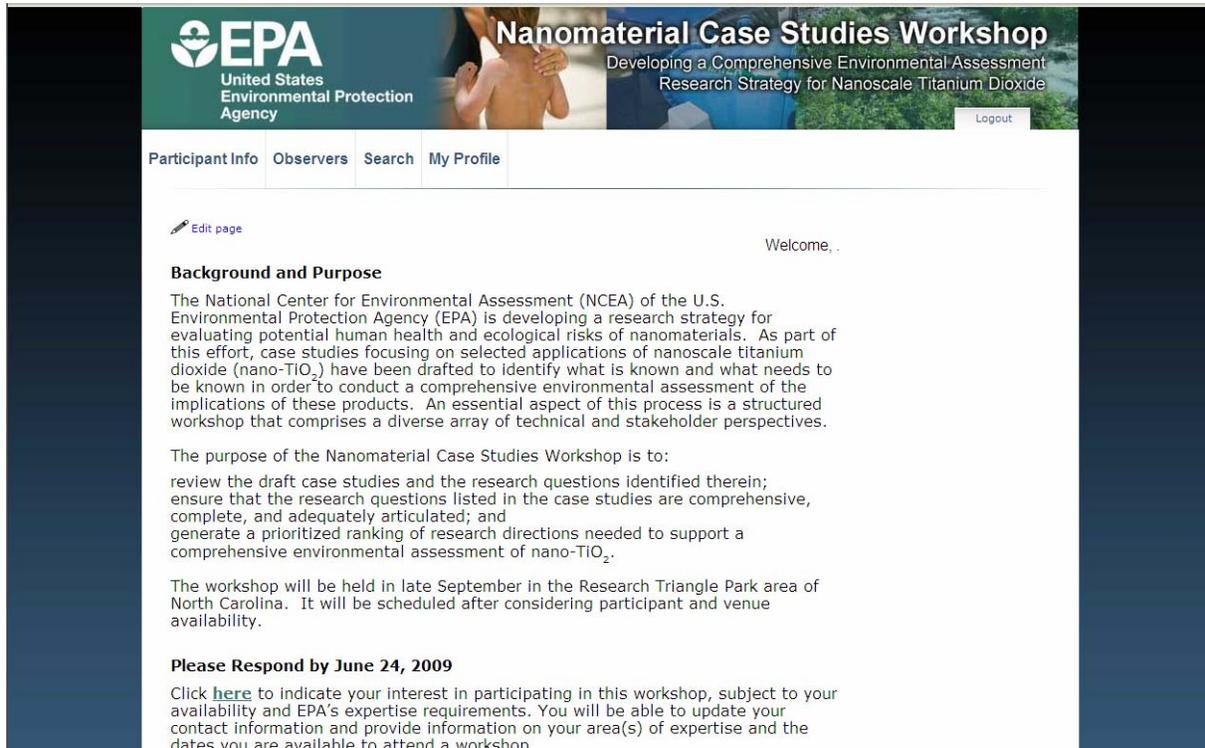


Figure D-1. Background information about the Nanomaterial Case Studies Workshop

D.2. Demographic Information Requested via Web form

Sector

Please indicate the sector(s) you represent. Select all that apply.

- Academia
- Industry
- Other
- Government
- NGO

Based on the sector(s) you selected above, please indicate the applicable descriptor(s) below:

- **Academia:** please specify department(s).
- **Government:** select... Federal, State and Local, or Other (please describe).
- **Industry:** select...Manufacturer, User, Trade Association, or Other (please describe).
- **NGO:** select...Consumer, Labor, Environment / Public Health, or Other (please describe).
- **Other:** select...Consultant, Journalist, Research Institution, or Miscellaneous (please describe).

Area of Expertise

Please indicate your primary area(s) of expertise. Select all that apply. Note: Your area of expertise does not have to be specific to nanoscale titanium dioxide.

Manufacturing

Production
Shipping
Other (Please describe)

Water Treatment

Potable Water
Wastewater
Other (Please describe)

Fate & Transport

Water
Air
Soil
Other (Please describe)

Exposure-Dose

Ecological
General Population
Occupational
Dosimetry/PBPK
Other (Please describe)

Ecology

Aquatic Effects
Terrestrial Effects
Other (Please describe)

Health Route

Inhalation
Oral
Dermal
Other (Please describe)

Health Endpoint

Neurotoxicology
Immunotoxicology
Reproductive/Developmental
Cancer/Genetox
Other (Please describe)

Health Method

Animal Toxicology
Epidemiology
Human Clinical
Other (Please describe.)

Evaluation

Human Health Risk Assessment
Ecological Risk Assessment
Integrated Risk Assessment
Life cycle Analysis
Industrial
Ecology
Other (Please describe)

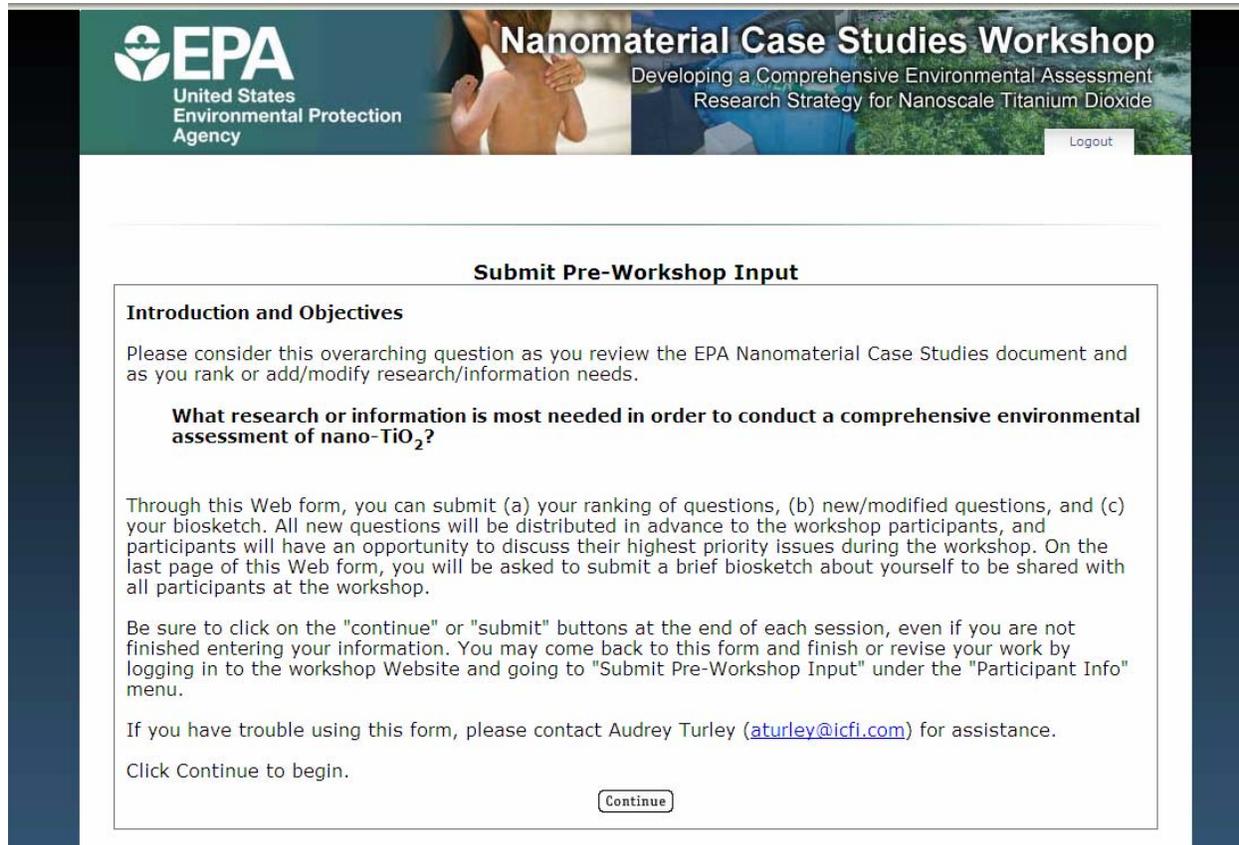
Risk Management

Environmental Health & Safety
Public Health
Natural Resources
Green Chemistry

Other Area of Expertise

Analytical Methods
Materials Science
Miscellaneous (Please describe)

D.3. Instructions for Pre-Workshop Activities



The screenshot shows the EPA logo on the left and the workshop title 'Nanomaterial Case Studies Workshop' in the center. Below the title is the subtitle 'Developing a Comprehensive Environmental Assessment Research Strategy for Nanoscale Titanium Dioxide'. A 'Logout' button is visible on the right. The main content area is titled 'Submit Pre-Workshop Input' and contains the following text:

Introduction and Objectives

Please consider this overarching question as you review the EPA Nanomaterial Case Studies document and as you rank or add/modify research/information needs.

What research or information is most needed in order to conduct a comprehensive environmental assessment of nano-TiO₂?

Through this Web form, you can submit (a) your ranking of questions, (b) new/modified questions, and (c) your biosketch. All new questions will be distributed in advance to the workshop participants, and participants will have an opportunity to discuss their highest priority issues during the workshop. On the last page of this Web form, you will be asked to submit a brief biosketch about yourself to be shared with all participants at the workshop.

Be sure to click on the "continue" or "submit" buttons at the end of each session, even if you are not finished entering your information. You may come back to this form and finish or revise your work by logging in to the workshop Website and going to "Submit Pre-Workshop Input" under the "Participant Info" menu.

If you have trouble using this form, please contact Audrey Turley (aturley@icfi.com) for assistance.

Click Continue to begin.

Figure D-2. Web Site Text for Pre-Workshop Activities

Ranking the Questions

Instructions: We are seeking from you the following rankings of the questions presented in the nano-TiO₂ case studies report:

1. Ranked list of the top 10 needs: Identify and rank the top 10 priorities by assigning a score of 10 to the question you believe is most important of all identified, a score of 9 to the question you think is the second most important, a score of 8 for the third most important, and so on.
2. Top 25 needs: Your top 10 priorities will automatically be included in this group. Select an additional 15 questions you believe are among your 25 most important. In the Web form, select "High (not ranked)" for these 15 questions.
3. The 10 lowest or "zero" priority needs: Identify up to 10 questions that you believe are not important or the lowest priority of all of the questions. In the Web form, mark these questions as "Low."

These rankings will be assembled as a starting point for our discussion at the workshop.

On the next page of this Web form, you will have the opportunity to submit any new questions not already contained in the case studies report.

Note: We recommend using the separate list of questions excerpted from the document to make notes about your rankings before entering them into the Web form.

Adding New and Modified Questions

Instructions: If there are high priority question(s) that are not already presented in the case studies report, you can submit them on this form. You can also submit revisions of existing questions.

You will need to type (or copy and paste) any new questions in the spaces provided. You should identify the case studies chapter to which each question belongs:

Chapter 1: Introduction

Chapter 2: Life Cycle Stages

Chapter 3: Fate and Transport

Chapter 4: Exposure-Dose Characterization

Chapter 5: Characterization of Effects

“Multiple”: Cross-cutting issues

If you are modifying an existing question, please indicate the number of the original question and enter the revised wording. Please limit modifications to questions that are among your top 25. You should rank the original question if it is among your top 10.

The Web form can accommodate submittal of up to 10 questions, each with a maximum of 250 characters. If you have more than 10 new research questions, please email your entire list to Audrey Turley (aturley@icfi.com).

APPENDIX E. Biosketches of Workshop Participants

Dr. David Andrews is a Senior Scientist at the Environmental Working Group. He is utilizing his background in chemistry and nanomaterials to investigate environmental and human health issues. Dr. Andrews' recent work has focused on the U.S. reliance on voluntary programs to collect health and safety information on chemicals, nanomaterials in consumer products, and reviewing ingredients in cosmetic products. Dr. Andrews holds a B.A. in chemistry from Wesleyan University and a Ph.D. in chemistry from Northwestern University. He has authored over 10 peer-reviewed publications and currently has 1 patent pending.

Jeff Baker is a Regional Manager at TSI, Incorporated, and has over 15 years of experience in water and air quality. TSI serves a global market by investigating, identifying, and solving measurement problems. As an industry leader in the design and production of precision measurement instruments, TSI partners with research institutions and customers around the world to set the standard for measurements relating to aerosol science, air flow, indoor air quality, fluid dynamics, and biohazard detection. Mr. Baker has published several papers in various journals and has worked closely with the development of environmental monitoring systems for nanomaterials.

Dr. Brenda E. Barry is Senior Director for the Long-Range Research Initiative at the American Chemistry Council, a program that supports scientific research to advance our understanding of the effects of chemicals on human health and the environment. Dr. Barry's areas of expertise include toxicology, nanotechnology, health effects of indoor and outdoor environmental agents, biosafety, and occupational health and safety. As a senior environmental consultant, Dr. Barry's recent work focused on strategic business planning activities regarding nanotechnology and the related human health, environmental, and regulatory concerns. Previously, she was senior project manager for numerous investigations on indoor and outdoor environmental quality issues and occupational health concerns. She is the author of two chapters in the recent book, *Nanotechnology: Health and Environmental Risks*. Dr. Barry received her doctorate in pathology from Duke University and completed her post-doctoral studies at the Harvard School of Public Health. She received her B.S. in zoology and M.S. in biophysics from the University of Rhode Island. Dr. Barry is a member of the Society of Toxicology, ASTM International Committee E56 on Nanotechnology, International Society of Exposure Science, and the American Biological Safety Association where she is certified as a Registered Biosafety Professional.

Dr. Catherine Barton has been an Environmental Engineer with DuPont since 1987. Dr. Barton has been a registered Professional Engineer in the State of Delaware since 1989. Her experience at DuPont includes environmental field work (groundwater monitoring well installation and sampling, air and soil sampling), wastewater treatability testing and system design, regulatory advocacy, air dispersion modeling, air quality issues and risk, and exposure assessment. Her risk and exposure assessment expertise extends from site specific manufacturing operations to chemical-specific global assessments. She has taken a life cycle approach to assessing exposure and risk in multiple assessments, including the assessment used in the DuPont Light Stabilizer Framework Example in the Nano Risk Framework. She is interested in establishing best practices to establish exposure information and hazard information that is compatible and therefore usable in assessing potential risk. She graduated from Virginia Tech with a B.S. in Civil Engineering and a Masters in Environmental Engineering. Her Ph.D. is from the University of Delaware, also in Environmental Engineering.

Dr. Eula Bingham (IOM) is Professor of Environmental Health at the University of Cincinnati College of Medicine. Her interests include regulatory toxicology, environmental carcinogenesis, occupational health, and risk assessment. She was U.S. Assistant Secretary of Labor for the Occupational Safety and Health Administration (OSHA) from 1977–1981. Throughout her career, Dr. Bingham has served on numerous national and international advisory groups, including advisory committees of the Food and Drug Administration, Department of Labor, National Institute for Occupational Safety and Health, National Institutes of Health, Natural Resources Defense Council, and the International Agency for Research on Cancer. The committees addressed issues concerning research needs in health risk assessment and the potential health effects of environmental

exposure to chemicals. Dr. Bingham has a Ph.D. from the University of Cincinnati in zoology (physiology and ecology). She is a member of the NAS Institute of Medicine who has served on numerous committees of the National Academies.

Dr. Pratim Biswas is the Stifel and Quinette Jens Professor at Washington DC University in St. Louis, and the Chair of the newly created Department of Energy, Environmental, and Chemical Engineering (www.eec.wustl.edu). His expertise is in aerosol science and technology, nanoparticle technology, particle control and environmentally benign energy production. He was Professor and Director of the Environmental Engineering and Science Division at the University of Cincinnati before he moved to Washington DC University in 2000. He has advised and graduated 35 doctoral students, and published more than 200 refereed journal papers with them. 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. He was elected as a Fellow of the Academy of Science, St. Louis in 2003. He recently finished his term as President of the American Association for Aerosol Research, and serves on several National and International Committees. He served on the Review Committee of the National Academy of Science that reviewed the Nanotechnology Environmental, Health, and Safety Document. Dr. Pratim Biswas received his B.Tech. degree from the Indian Institute of Technology, Bombay in Mechanical Engineering in 1980; his M.S. degree from the University of California, Los Angeles in 1981 and his doctoral degree from the California Institute of Technology in 1985.

Dr. Jean-Claude J. Bonzongo is an Associate Professor in the Department of Environmental Engineering Sciences at the University of Florida, Gainesville, Florida. His current research focuses on aquatic biogeochemistry, remediation of metal-contaminated environments, and mercury in terrestrial and aquatic systems. Dr. Bonzongo is also interested in environmental fate and implications of manufactured nanomaterials as well as sustainable design of nanomaterials. Dr. Bonzongo received his Ph.D. in Environmental Chemistry and Microbiology from the University of Rennes I in France.

Steven Brown is a Certified Industrial Hygienist employed by Intel Corporation and has over 27 years of experience in the field of Industrial Hygiene, including work in heavy manufacturing industries, aerospace, and semiconductor fabrication. He is responsible for the development and implementation of health, safety, and environmental guidelines on the use of nanomaterials within Intel's global semiconductor manufacturing facilities. Mr. Brown is the Convener of the International Standards Organization (ISO) Technical Committee #229 Work Group #3 on Nanotechnology. Work Group #3's mandate is to develop ISO Standards on the safe and environmentally benign use of nanomaterials. The ISO TC229 WG#3 is currently developing over 9 different ISO standards on the safe use of nanomaterials. He is involved in several industry consortiums focused on promoting the sound use of nanomaterials such as the International Council on Nanotechnology (ICON) and the completed Nanotechnology Occupational Safety Health consortium. Mr. Brown has a Masters of Science Degree in Industrial Hygiene and a Bachelors of Science Degree in Biology/Chemistry.

Mark Bunger is a Research Director at Lux Research, with 18 years of business strategy experience as a management consultant and technology analyst. In this time, he has advised more than 40 Fortune 500 corporations, led hundreds of engagements, and authored over 60 reports and other publications. Mr. Bunger joined Lux Research in 2005, and launched and leads Lux Research's Bioscience Intelligence Service. Mr. Bunger and his work have figured in leading media outlets in the United States and Europe, including CNN, PBS, CNBC, NPR, The Wall Street Journal, the Financial Times, Genetic Engineering and Biotechnology News, American Chemical Society Nano Letters, and other technical, regional, and trade publications and channels. Mr. Bunger's business education was in International Marketing at Mälardalen Polytechnic in Sweden, and Market Research at the University of Texas at Austin. His ongoing technical education includes extension courses and lab work in neurology and bioengineering at University of California (Berkeley) and San Francisco (UCSF), where he currently works in the Desai lab.

Carolyn Nunley Cairns is an Environmental Health Scientist and Product Safety Specialist in the Technical Department's Product Safety and Health Department at Consumers Union, an

independent, non-profit organization that publishes Consumer Reports magazine. She leads the Product Safety program, which includes research and testing to evaluate safety concerns associated with products containing nano-engineered substances. As an international expert in human health risk assessment, she has held positions government agencies, private industry, and non-profit organizations. She holds undergraduate degrees in Chemistry and Government, and a Masters in Public Health from Yale School of Medicine.

Dr. Richard A. Canady is an expert in regulatory risk assessment and nanotechnology regulatory policy having led multidisciplinary teams of policy and technical experts in the resolution of a wide range of cutting edge health risk management issues over a 20 year career that includes genomics, nanotechnology, biotechnology, obesity, contaminants in foods and medical products (including mercury, dioxins, perchlorate, and acrylamide), and medical product development. His experience includes government regulatory policy for health risk assessment from the executive level, integrating across product review centers for the FDA Office of the Commissioner and across Federal Agencies for the Executive Office of the President. His experience includes substantial international work, leading policy, and technical analysis teams within the Organization for Economic Cooperation and Development, the World Health Organization, and the Food and Agriculture Organization as well as in direct bilateral interactions with major U.S. trading partners on chemical risk management issues facing FDA. He received a Ph.D. in neurophysiology, physiology, and behavior from Rockefeller University and a B.S. in psychology and biology from the University of Michigan. Dr. Canady is a Diplomat of the American Board of Toxicology (DABT).

Janet Carter is a Senior Health Scientist in the Directorate of Standards and Guidance with the Occupational Safety and Health Administration (OSHA). In addition, she worked for 15 years at Procter & Gamble, Inc. as a Respiratory Toxicologist and Study Director researching the mechanisms of particle-induced pulmonary inflammation/tumorigenesis and nanoparticle toxicity. She has (co)authored over 35 publications and technical reports with more than 40 presentations and invited-talks at national and international conferences. In addition, she has participated on numerous review panels for nanomaterials with the National Academies Institute of Medicine, EPA, NIOSH, and USDA. She is an active member of the Society of Toxicology (SOT), former Vice-Chair of the International Life Science Institute/Health and Environmental Science Institutes (ILSI/HESI) Nanomaterials Safety Committee, and a member of the organizing committee for the SOT Nanotoxicology Specialty Section. Ms. Carter received a B.S. in Zoology from Miami University, M.S. in Molecular and Cell Biology from the University of Cincinnati and currently attends Emory University Rollin's School of Public Health in Epidemiology.

Dr. Elizabeth Casman is an Associate Research Professor, in the Department of Engineering & Public Policy at Carnegie Mellon University. Dr. Casman is interested in the challenges of performing risk assessment with incomplete information. She has studied the problem of dealing with mixed levels of uncertainty in integrated assessment models. She has also developed a bounding analysis methodology for attributing risks with multiple causative factors. A major new direction of her research is the risk posed by nanomaterials in the environment. In addition to risk assessment, she has been involved in a number of health-related projects. With regards to bioterrorism responses, her recent research has included the following projects: the potential of urban ecosystems to support rodent-borne plague epidemics, risk communication strategies for rapidly changing and complex bioterrorism scenarios, rapid detection of covert bio-attacks, the impact of human behavior on pandemic influenza epidemics, and the effect of the USAPATRIOT Act and the Bioterrorism Preparedness Act on microbiological research. She is also interested in drinking water and health connections in developing countries, watershed management, and biotechnology policy. She holds a B.S. in Microbiology from Syracuse University, an M.S. in Microbiology from Northern Arizona University, and a Ph.D. Geography & Environmental Engineering from The Johns Hopkins University.

Dr. Sylvia Chan Remillard is an Environmental Scientist with Golder Associates and HydroQual Laboratories in Calgary, Alberta. She was awarded an Alberta Ingenuity Industry Associate working on an Industrial post doctorate, jointly through Golder Associates and HydroQual Laboratories Ltd. She is studying the fate and effects of nanoscale particles on the environment and

developing a risk based framework to evaluate the products of nanotechnology. She obtained her Ph.D. in Food Science and Technology from the University of Alberta. Her Ph.D. examined the ability of dairy derived probiotics and bioactive peptides in altering intestinal microbial ecology in the treatment of gastrointestinal disorders such as inflammatory bowel disease and colon cancer. She was nominated for the Governor General Gold Medal Award for her Ph.D. research. She has received several research grants for her work through the National Research Council in Canada and The Natural Sciences and Engineering Research Council of Canada and the Alberta Ingenuity Fund. She has participated in and presented her current and previous work at numerous international and local conferences including several SETAC conferences and NATO Advanced Research Workshops. Dr. Chan Remillard's interest in nanotechnology lie in studying the fate and effects of nanoscale particle once they have entered into the environment and in developing a suite of nano-compatible testing methods that are suitable for industry for regulatory compliance.

Dr. Shaun Clancy heads the Product Regulatory Service group, a Product Stewardship group, for Evonik Degussa in North America that supports many of the company's businesses. Areas of interest outside of nanotechnology include chemical control laws (TSCA, CEPA, FFDCA, FIFRA, PCPA) as well as topics related to hazard communication and transportation. In nanotechnology he is interested in all aspects that pertain to EHS topics with a particular interest in the relationship between material characterization and toxicology. He received his B.S. at the University at Buffalo - SUNY and completed his doctoral studies at Northwestern.

Dr. Raymond David is the Manager of Toxicology for Industrial Chemicals in BASF Corporation. He received his Ph.D. in Pharmacology from the University of Louisville, after which he was a Postdoctoral Fellow at the Chemical Institute of Toxicology in Research Triangle Park. Dr. David worked for 8 years at Microbiological Associates in Bethesda, Maryland where he managed the Inhalation and Mammalian Toxicology Departments. He also spent 14 years at Eastman Kodak in Rochester New York as Senior Toxicologist before joining BASF in 2006. Dr. David has experience conducting inhalation, pulmonary, reproductive, and systemic toxicity studies. He was responsible for EH&S issues for nanotechnology at Eastman Kodak Company, and is currently responsible for nanotechnology issues in BASF Corporation.

Dr. Joan E. Denton is Director of the Office of Environmental Health Hazard Assessment (OEHHA), a department within the California Environmental Protection Agency. She is responsible for scientific risk assessments for use in regulation of chemicals in the environment and implementing the California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65). Dr. Denton also provides overall scientific guidance and consultation to the Secretary of the California Environmental Protection Agency. Dr. Denton earned a B.S. from the University of San Francisco, a M.S. from the University of Nevada, Las Vegas, and a Ph.D. in biology from the University of California, Santa Barbara. In 2005, she was on a Blue Ribbon Panel created in California to advise policymakers on increasing the capacity of nanotechnology in the state. OEHHA staff have expertise in particle toxicology which has resulted in the identification of diesel exhaust as a toxic air contaminant and state particulate matter standards. OEHHA has also prepared assessments on metals (including arsenic) in water. Finally, OEHHA is currently funding a research project within the University of California San Francisco which will suggest a framework for conducting risk assessments on nanomaterials.

Dr. Gary Ginsberg is a Toxicologist at the Connecticut Department of Public Health within the Division of Environmental and Occupational Health Assessment. He has responsibility for human health risk assessments conducted in the state. Dr. Ginsberg serves as adjunct faculty at the Yale School of Medicine and is an Assistant Clinical Professor at the University of Connecticut School of Medicine. He has served on several National Academy of Science Panels (Biomonitoring and U.S. EPA risk methods) and has been invited to testify at Congressional hearings on toxics issues on a number of occasions. He received a Ph.D. in toxicology from the University of Connecticut (Storrs) and was a post-doctoral fellow in carcinogenesis/mutagenesis at the Coriell Institute for Medical Research. Dr. Ginsberg's toxicology experience has involved a variety of settings: basic research, teaching, working within the pesticide and consulting industries, and now working in public health. He has published in the areas of toxicology, carcinogenesis, physiologically-based pharmacokinetic modeling, inter-individual variability and children's risk assessment. Dr. Ginsberg

is also co-author of a book on toxics for the lay public, “What’s Toxic, What’s Not” Berkley Books, December 2006.

Dr. Pertti (Bert) Hakkinen joined the Division of Specialized Information Services, National Library of Medicine, National Institutes of Health in June 2008 as Senior Toxicologist in the Office of the Director, and serves as NLM’s Toxicology and Environmental Health Science Advisor. As a member of the SIS staff, Dr. Hakkinen provides leadership on the development of new resources in toxicology and enhancements to existing NLM resources in this field. He also represents NLM on various committees, and provides leadership for NLM’s participation in national and international efforts in toxicology-related information. During his career Dr. Hakkinen has held numerous leadership positions in the field of toxicology and risk assessment. Dr Hakkinen served on the staff of the European Commission (EC) at the EC’s Institute for Health and Consumer Protection, Joint Research Centre, in Ispra, Italy from 2003–2006. He has also held positions with Toxicology Excellence for Risk Assessment (TERA) and Gradient Corporation in the United States, and at the Procter and Gamble Company in the United States and Japan. He continues to serve as the Vice-chair of the Scientific Advisory Panel for the Mickey Leland National Urban Air Toxics Research Center. Dr. Hakkinen earned a B.A. in Biochemistry and Molecular Biology from the University of California, Santa Barbara, and received his Ph.D. in Comparative Pharmacology and Toxicology from the University of California, San Francisco. Dr. Hakkinen is a member of the Society of Toxicology (SOT) and a charter member of the Society for Risk Analysis (SRA) and the International Society of Exposure Science (ISES). He was a co-editor and co-author of the latest edition of the Encyclopedia of Toxicology, and of the new edition of the Information Resources in Toxicology book. Dr. Hakkinen has authored and co-authored numerous other publications, including on consumer product-related exposures and risks. He was a work group leader of a 2008 NATO workshop on nanomaterials.

Jaydee Hanson is Policy Director at the International Center for Technology Assessment. He works on issues related to medical, cosmetic, food, and sunscreen uses of nanotechnology and the convergence of nanotechnology with other technologies, especially nano-vectors for gene transfer. He and his colleague, George Kimbrell, coordinated the development of “Principles for the Oversight of Nanotechnologies and Nanomaterials” with more than 80 groups on six continents. Mr. Hanson is the US Co-chair for the Nanotechnology Taskforce of the Transatlantic Consumers Dialogue and coordinates an annual meeting of U.S. non-governmental groups working on nanotechnology policy. He has degrees from the University of the Pacific and the University of Hawaii. He has additional course work in bioethics and environmental ethics. He was an environmental policy fellow at the East-West Center and is currently a fellow at the Institute on Biotechnology and the Human Future.

Dr. Patricia Holden is a Professor of Environmental Microbiology at the Bren School of Environmental Science & Management at the University of California, Santa Barbara. Dr. Holden’s research surrounds bacteria in the context of environmental water quality, and in the contexts of fate and transport of pollutants. Dr. Holden’s research also involves investigation of microbial ecology of the vadose zone and sediment environments as context to better understanding the responses of indigenous microorganisms to environmental perturbation including pollution. Dr. Holden’s education is in Civil & Environmental Engineering (B.S., M.S., M.E.) and in Soil Microbiology (Ph.D., U.C. Berkeley).

Dr. Paul Howard is the Director of the Office of Scientific Coordination at the U.S. Food and Drug Administration’s National Center for Toxicological Research (NCTR) (Director, 2009; Deputy Director 2007–2009) which is responsible for coordinating/administering an interagency agreement between the National Toxicology Program/NIEHS and NCTR/FDA to conduct toxicological studies of compounds of regulatory interest to the FDA and NIEHS. In addition, Dr. Howard is the FDA Liaison to the National Toxicology Program, is the Acting Director of the NCTR Nanotechnology Core Facility, and Director of the National Toxicology Program Center for Phototoxicology (at NCTR). Dr. Howard’s research interests include: the biodistribution and toxicity of nanoscale materials; the phototoxicity and photocarcinogenicity of chemicals; the toxicity, phototoxicity and photodecomposition of tattoo and permanent ink constituents; the toxicity and biodistribution and toxicity of nanoscale materials. Dr. Howard received a Ph.D. in Biochemistry from the University of

Arkansas for Medical Sciences in 1981. After post-doctoral training in Chemical Carcinogenesis (NCTR, 1981–1983), he joined the faculty at the Case Western Reserve University (CWRU) School of Medicine (Assistant Professor, 1983–1989; Associate Professor, 1989–1993. Dr. Howard joined the staff at NCTR in 1993 as a Staff Scientist in the Division of Biochemical Toxicology.

Sheila Kaplan is a longtime environmental, science and political journalist who works in print and broadcast media. She is the recipient of numerous national journalism honors, among them: the John S. Knight Professional Fellowship for Journalists at Stanford University; the Investigative Reporters and Editors prize for distinguished investigative reporting, the Lowell Mellett prize for media criticism, and several Emmy nominations. Ms. Kaplan lives in the San Francisco Bay Area and is currently writing a book on the science and policy issues related to neurotoxicants. The book is for a general audience and will be published by Basic Books in 2010. She is a fellow at the Nation Institute, affiliated with The Nation magazine in NYC. Last year, Ms. Kaplan was a lecturer in political reporting at the University of California, Berkeley, Graduate School of Journalism. She has worked as a producer for ABC News, MSNBC on the Internet, and the PBS series Frontline. She has also been a senior writer for U.S. News & World Report, Legal Times and the Hartford Courant. She is a former investigative editor for Mother Jones magazine. Her freelance work has appeared in numerous newspapers and magazines, among them, The Washington DC Post, Discover and The New Republic.

Dr. Fred Klaessig is currently with Pennsylvania Bio Nano Systems, a small firm focusing on reference materials used in investigating chromatographic effects at the nanoscale. In recent years, he was first the Technical Director for Aerosil & Silanes and later the Business Director for the Aerosil Business Line, which are currently part of the Inorganic Materials Business Unit of Evonik Degussa GmbH. His assignments ranged from commercial overview (Product Management, Production, Sales) to technical responsibilities involving customer support, new product introduction, liaison with the R&D Department in Germany and regulatory matters. AEROSIL® is a trade name for fumed silica, which has been manufactured for 60 years and which is often cited as an example of a nanoparticle. Fumed silica, fumed titania and other fumed metal oxides are utilized in many fields for reinforcement, rheology control, abrasion and UV absorption. In recent years, the great interest in nanotechnology has raised safety and registration concerns about materials of this class. These issues, both everyday technology and EHS, led to his involvement in ASTM (E56), ISO (TC229) and industry organizations addressing these broader topics. Dr. Klaessig received a B.Sc. in Chemistry from the University of California, Berkeley and a Ph.D. in Physical Chemistry from Rensselaer Polytechnic Institute. His earlier industrial experiences were with Bio Rad Laboratories as a Quality Control Chemist and various R&D management positions at Betz Laboratories, now a division of GE Water Services, where his responsibilities involved scale, corrosion and microbiological control in many chemical industrial processes.

Dr. Rebecca Klaper is a tenure-track Associate Scientist at the Great Lakes WATER Institute, University of Wisconsin-Milwaukee. She uses a combination of genomics and proteomics with traditional toxicological measurements to determine the impact of human alterations of the environment on ecologically relevant species. One of the major areas of her current research involves examining the impact of emerging contaminants, specifically nanomaterials and pharmaceuticals, on environmental and human health. The Klaper laboratory has published several peer-reviewed articles on the impacts of nanomaterials of differing chemical properties on the survival, behavior, and physiology of aquatic species and the potential for uptake of nanomaterials by these species. She has served as an invited expert on several technical panels to evaluate government documents surrounding the issue of nanomaterial risk assessment and the current state of the science. These include: Technical reviewer for U.S. EPA Office of Research and Development Research Plan for Nanotoxicology (2008); Nanotechnology Policy Framework Committee for the State of California (2008); Invited scientific expert/speaker for the International Organization for Economic and Cooperative Development (OECD) (2005); Nanotechnology Technical Committee, Society of Environmental Toxicology and Chemistry (2007–Present); Technical Expert reviewer of EPA Potential Environmental Impacts of Nanomaterials White Paper (2007).

Dr. Todd Kuiken is a research associate with the Foresight and Governance Project and the Project on Emerging Nanotechnologies at the Woodrow Wilson International Center for Scholars;

focusing on the environmental health and safety and public policy aspects of nanotechnology. Todd holds a Ph.D. in environmental science and chemistry from Tennessee Tech University where his research focused on the air/surface exchange of mercury associated with forest ecosystems. As part of his dissertation he synthesized these results with other studies associated with mercury cycling, public health threats, and policy alternatives to bring attention to the threats and need for an improved public policy dealing with mercury pollution. After completing his B.S. in Environmental Management and Technology at Rochester Institute of Technology he worked directly with renowned scientists on the biogeochemical cycling of mercury at the Department of Energy's Oak Ridge National Laboratory. He earned an M.A. in Environmental and Resource Policy from The George Washington DC University concentrating on the scientific, economic and community development aspects of environmental issues. While there he worked at various environmental non-profits including the National Wildlife Federation. He worked within the Clean the Rain campaign that dealt with the environmental and public health threats associated with mercury pollution.

Dr. John P. LaFemina is the Vice-President and Director of Operations for Toxicology Northwest, part of the Battelle Health and Life Sciences Global Business. Dr. LaFemina joined Battelle from the Pacific Northwest National Laboratory, where he spent 15 years in a variety of research and executive management positions, including Director of Quality, and leading the Environmental Management Market Sector. Prior to coming to the Laboratory, Dr. LaFemina was a Captain in the United States Army, teaching chemistry and physics at the United States Military Academy and serving as the Deputy Director of the Science Research Laboratory and the Thomas H. Johnson Photonics Research Center at West Point. Dr. LaFemina earned his Ph.D. in Chemistry at The Pennsylvania State University under the direction of Professor John P. Lowe in 1985. He has written or contributed to than 50 scientific papers and made over 100 presentations on a variety of scientific and technological topics ranging from the photophysics of polymers to the atomic and electronic structure of semiconductor and mineral surfaces and interfaces. He was the Series Editor of "The Chemistry and Physics of Surfaces and Interfaces" published by CRC Press and is a member of the American Chemical Society.

Thomas Lee is a business reporter at the Minneapolis Star Tribune where he covers emerging and growth companies with a special focus on medical technology and biotechnology. He is also a freelance writer for China Daily USA and has previously written for the St. Louis Post-Dispatch, Seattle Times, the Oregonian, and Newsday. Mr. Lee was recently awarded a Knight Kavli Science Journalism Fellowship at the Massachusetts Institute of Technology. He was one of 15 journalists across the country who participated in a three day workshop on nanotechnology. Mr. Lee is primarily interested in the commercialization of nanotechnology and what opportunities/pitfalls this emerging field poses for companies.

Dr. Shannon Lloyd is the Sustainability Discipline Director at Concurrent Technologies Corporation (CTC). She provides technical leadership in developing and applying analytical tools to assess the economic and environmental implications of policy, process, and technology alternatives. She has conducted environmental life cycle assessments of products in the automotive, chemical, nanotechnology, agribusiness, and building construction industries. Dr. Lloyd recently completed a study for the Army Environmental Policy Institute (AEPI) that provided recommendations for evaluating and managing the potential lifecycle risks of nanomaterials within the U.S. Army. She received a PhD in Engineering and Public Policy and an M.S. in Civil and Environmental Engineering from Carnegie Mellon University and a B.S. in General Engineering from the University of Illinois at Urbana-Champaign.

Dr. Christopher Long is a Principal Scientist in Environmental Health & Air Quality with Gradient, a Massachusetts-based environmental consulting company. His central interests are indoor and outdoor air quality and health risk assessment, and he has particular expertise in exposure assessment, air pollution epidemiology and toxicology, air sampling and measurement, and airborne particulate matter (PM). He has investigated exposures and health risks associated with a number of airborne PM types, such as ambient PM, diesel exhaust particulates, carbon black, asbestos, and engineered nanoparticles, as well as a variety of gaseous criteria and hazardous air pollutants. Dr. Long's practice area includes evaluating product safety, with specific interests in airborne exposures and engineered nanoparticles. He is co-director of Gradient's Nanotechnology Risk practice and is a

technical editor of Gradient's nanotechnology newsletter "EH&S Nano News." Dr. Long has a Sc.D. in Environmental Health from the Harvard School of Public Health and a M.S. in Environmental Engineering from MIT, and he has prepared a number of peer-reviewed articles in the general areas of indoor and outdoor air pollution and exposure assessment.

Dr. Margaret MacDonell is in the Environmental Science Division of Argonne National Laboratory, where she conducts environmental health risk analyses to support risk management and communication/educational outreach for federal programs. Projects involve evaluating technologies and assessing exposures and potential health effects, including fate and susceptibility context, while integrating toxicity information that extends from acute and short-term to chronic. Activities have included developing practical approaches for assessing cumulative risk across combined hazards and exposures. She is also an adjunct professor at Northwestern University (risk assessment and environmental impact analysis), member of the National Council on Radiation Protection and Measurements Scientific Committee on Environmental Radiation and Radioactive Waste Issues, and fellow of the Society for Risk Analysis. Dr. MacDonell received her B.S. in Biology from the University of Notre Dame, M.S. in Civil/Environmental Health Engineering from Notre Dame, and Ph.D. in Civil/Environmental Health Engineering from Northwestern University.

Dr. Fred J. Miller is currently an independent consultant in dosimetry and inhalation toxicology. His primary research interests include pulmonary toxicology, dosimetry of gases and particles, extrapolation modeling, and risk assessment. From 1991–2005, Dr. Miller was employed in various capacities at the Chemical Industry Institute of Toxicology, serving most recently as Vice President for Research. During his career as a U.S. Public Health Service Officer assigned to the U.S. EPA, Dr. Miller served in various leadership positions and was noted for bringing together interdisciplinary teams of scientists to solve important public health problems. In 1989, Dr. Miller joined the faculty of Duke University Medical Center, continuing his long-standing interest in extrapolation modeling. He is internationally recognized for his research on the dosimetry of reactive gases and has authored or co-authored more than 160 publications. Dr. Miller received a number of Scientific and Technical Achievement awards from EPA and also the PHS' Outstanding Service Medal. In 2005, he was awarded the Career Achievement Award by the Inhalation Specialty Section of the Society of Toxicology (SOT) in recognition for his contributions to the field of inhalation toxicology. He has served on EPA's Clean Air Science Advisory Committee and on numerous other peer review panels.

Dr. Nancy A. Monteiro-Riviere is a Professor of Investigative Dermatology and Toxicology at the Center for Chemical Toxicology Research and Pharmacokinetics, North Carolina State University (NCSU) and in the Joint Department of Biomedical Engineering at UNC-Chapel Hill/NCSU, as well as a Research Adjunct Professor of Dermatology, School of Medicine at UNC Chapel Hill. She received her M.S. and Ph.D. in Anatomy and Cell Biology from Purdue University and a postdoctoral fellowship in toxicology at CIIT in Research Triangle Park, NC. She was past-President of both the Dermal Toxicology and In Vitro Toxicology Specialty Sections of the National Society of Toxicology. Dr. Monteiro-Riviere is a Fellow in The Academy of Toxicological Sciences, and in the American College of Toxicology. She serves as Associate Editor for Wiley Interdisciplinary Reviews in Nanomedicine and Nanobiotechnology and serves on six toxicology editorial boards. She also serves on several national panels, including many in nanotoxicology, such as the National Research Council of the National Academies Review of the Federal Strategy to Address Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials. She has published over 200 manuscripts in the field of skin toxicology and is Editor of the book "Nanotoxicology: Characterization and Dosing and Health Effects." Currently, her research interest is on the mechanisms of nanoparticle cellular uptake in cells and their subsequent translocation through the body.

Dr. Paul Mushak is a toxicologist and human health risk assessor, working as a partner in PB Associates, a consulting practice in Durham, N.C. He is also a visiting professor, Albert Einstein College of Medicine, Bronx, N.Y. Earlier, he was a faculty member in various capacities from 1971 to 1993 at the University of North Carolina - Chapel Hill School of Medicine, Pathology Department. He works in the area of contaminant/toxic metals, metalloids, and organometals. His doctoral (University of Florida, Gainesville) and postdoctoral (Yale University Department of

Molecular Biophysics and Biochemistry) training were in the areas of metal chemistry, biochemistry, enzymology, and toxicology. He has more than 40 years of widely published research and advisory expertise in the areas of exposures and their determinants, analytical pediatric toxicology, toxicokinetics, modeling and health risk assessments. He has served on numerous peer/advisory committees of Federal and international agencies and those of the NAS/NRC, chairing several U.S. Environmental Protection Agency review panels for reports to Congress. He has been qualified as a testifying expert in the above areas by a number of U.S. Federal and state courts and has testified before Congress on lead and child health.

Dr. Srikanth Nadadur is Program Director at National Institute of Environmental Health Sciences, NIH, overseeing extramural research efforts on environmental cardiovascular and pulmonary health and health implications of Nanotechnology. Dr. Nadadur received his M.S. and Ph.D. in molecular physiology from Sri Venkateswara University, India and had postdoctoral training in molecular biology, cancer chemotherapeutics, and chemical carcinogenesis at Roswell Park Cancer Institute, Buffalo, NY. Prior to joining NIEHS, Dr. Nadadur worked as Principal Investigator at ORD, US EPA, where his research efforts were focused on molecular toxicology and cardiopulmonary health effects of criteria air pollutants. Dr. Nadadur also serves as member of NIH Nano Taskforce and the organizing committee of National Nanotechnology Initiative Program Managers Workshop.

Dr. Michele Ostraat, Senior Director for RTI International's Center for Aerosol Technology, has expertise in aerosol technology, nanoparticle applications, submicron particle processing, micro- and nanofiber filtration, portable nanoparticle detection, nanoparticle occupational safety and health, and inhalation toxicology. She has experience in integrating emerging market needs with technology capability to define organizational strategies, prioritizing programs for market development, and commercialization. Before joining RTI, Dr. Ostraat worked at DuPont with primary responsibilities in aerosol synthesis and characterization of sub-micron and nanoparticles for electronic and materials applications and was Program Manager for the Nanoparticle Occupational Safety and Health Consortium with focus on 1) developing methods to generate well-characterized aerosols of solid nanoparticles and measuring aerosol behavior as a function of time; 2) developing air sampling methodologies and instrumentation; and 3) measuring barrier efficiency of filter media to specific engineered aerosol nanoparticles. Prior to joining DuPont, Dr. Ostraat was a Member of Technical Staff at Bell Labs and Agere Systems where she examined the synthesis of rare-earth doped aerosol nanoparticles and investigated the behavior of chalcogenide phase change materials. She earned her Ph.D. and M.S. degrees in Chemical Engineering from the California Institute of Technology. She holds a B.S. Chemistry degree from Trinity University.

Dr. Anil Patri leads a multi-disciplinary research team in his role as the Deputy Director of the Nanotechnology Characterization Laboratory (NCL) at the National Cancer Institute at Frederick. His research is focused on translation of nanotech-derived drugs, diagnostics and imaging agents to clinic. He interfaces with many sponsors from federal agencies, academia and small business on projects related to nanotechnology. He serves as NCL's liaison with NIST and FDA and facilitates characterization and standards development activities at ASTM and ISO. He directs a chemistry lab at NCL and collaborates with many ATP labs and intramural NCI investigators on nanomaterial evaluation. Prior to joining NCL, Dr. Patri served as a research faculty at the Center for Biologic Nanotechnology, University of Michigan Medical School, and developed multifunctional nanomaterial for targeting, imaging, and drug delivery application for cancer. He received his Ph.D. in Chemistry from the University of South Florida. He worked for a pharmaceutical company and as a lecturer before pursuing a career in research.

Maria Victoria Peeler is the senior policy specialist responsible for the development and implementation of the emerging contaminants policy at the Washington DC State Department of Ecology (Ecology). Ecology has delegated authority from U.S. EPA for most environmental regulations, including RCRA and CWA. Ecology has authority under independent state law to restrict the use, management, and disposal of several PBTs, including mercury, lead and PBDE. Emerging contaminants included in the policy development are pharmaceuticals, biotech and nanotech. She has worked in the environmental field for over 25 years in areas such as state-owned land management, utilities and transportation oversight, emergency management, CERCLA and state

remediation agreements, as well as in-water construction projects, and NEPA/SEPA EIS. Maria Victoria has undergraduate degrees in biology and chemistry; master's degrees in technical writing, and environmental engineering (emphasis on engineering management); and is currently attending the University of Washington DC school of engineering, CEE, researching potential bioassays and chemical analysis that could be used to properly "designate" engineered nanoparticles that become waste.

Dr. Richard C. Pleus, Intertox managing director and toxicologist, has over 25 years experience assessing the risk to humans exposed to chemical and biological agents via food, consumer products, therapeutic agents, and the environment. Dr. Pleus' current focus is on developing environmental health and safety (EHS) standards for nanomaterials and assisting in the evaluation of EHS risks from exposure to engineered nanoparticles. He is a U.S. delegate on the International Organization for Standardization (ISO) Technical Committee (TC) 229, Nanotechnologies. While serving on TC 229, Dr. Pleus is leading the U.S. Technical Advisory Group (TAG) Working Group 3 to develop a comprehensive list of physical and chemical characterization parameters of engineered nano-objects for toxicologic assessment. Intertox is also assisting on a number of product-related nanotechnology issues with companies around the world. Dr. Pleus is a co-founder of the Nanotechnology Health and Safety Forum. Dr. Pleus has been asked to serve on the review panel for NIOSH intramural proposals for the NIOSH Nanotechnology Research Center. Dr. Pleus' credentials include a B.S. in Physiology, with honors, from Michigan State University, an M.S. and a Ph.D. in Environmental Toxicology from the University of Minnesota, and postdoctoral research in neuropharmacology at the University of Nebraska Medical Center.

Dr. John Small is the Division Chief of the Surface and Microanalysis Science Division at the National Institute for Standards and Technology (NIST). Dr. Small received his B.S. degree in Chemistry from The College of William and Mary in Virginia in 1971 and his Ph. D. in Chemistry from the University of Maryland in 1976 and has worked at NIST, formerly the National Bureau of Standards (NBS) since that time. During his 32-year career with NBS/NIST, his research has been in the general area of accuracy in quantitative analysis of materials focusing on the high spatial resolution quantitative chemical analysis of individual particles using x-ray microanalytical techniques. Over the years, his research activities have included the development of a method for the quantitative analysis of particles, and the establishment of an accuracy base for the measurement of environmental asbestos including the production of the first NBS asbestos SRM. Dr. Small served as the Group leader for the Microscopy Research Group before becoming Division Chief. He is currently a member of the NIST Nano-Safety committee and he has represented NIST on the Federal governments interagency Working Group on Nanotechnology Environmental and Health Implications (NEHI). under the U.S. Nanoscale Science, Engineering, and Technology Subcommittee.

Dr. Jeffery A. Steevens is a Research Biologist and Team Leader of the Environmental Risk Assessment Team at the US Army Engineer Research and Development Center in Vicksburg, MS. He obtained his bachelors degree in biochemistry from the University of Missouri in 1994 and his doctorate degree in pharmacology and toxicology from the University of Mississippi in 1999. His research activities include risk assessment and management of contaminated sediments, bioavailability, and biological effects of military-relevant materials (e.g., explosives, nanomaterials, metals). One of his current responsibilities is leading a multi-disciplinary ERDC research cluster focusing on the fate, transport, and ecotoxicology of military relevant nanomaterials. In addition to his research on nanomaterials, he is also a technical advisor to the World Bank on international projects, EPA Superfund Program, and provides expertise on many contaminated sediments projects. Dr. Steevens has actively published the results of his work and has over 35 peer-reviewed journal publications and 20 book chapters. He is an active member of the Society of Environmental Toxicology and Chemistry, American Chemical Society, and Society of Toxicology. Dr. Steevens is a Technical Advisor for nanomaterials work group for the Materials of Evolving Regulatory Interest Team (MERIT), Office of Secretary of Defense.

Dr. Geoffrey I. Sunahara is a Senior Research Scientist and the Group Leader of Applied Ecotoxicology at the Biotechnology Research Institute (National Research Council-Canada) in Montreal, Canada. He has more than 20 years of professional experience in biochemical toxicology

and environmental risk assessment, having gained this expertise in Canada, the United States and in Europe. He has more than 200 research publications, proceedings, and presentations. Current research interests include the ecotoxicological characterization of emerging environmental contaminants such as nano-biomaterials, as well as recalcitrant soil contaminants such as the energetic substances (TNT, RDX, and HMX) and their metabolites, using bacteria, plants and invertebrate toxicity tests, and cultured cell approaches (mutagenicity and cell proliferation). Dr. Sunahara has served on several editorial boards, and was the Lead Editor of two ecotoxicology books. He has participated on expert advisory committees for Environment Canada, U.S. Strategic Environmental Research and Development Program (SERDP), and U.S. EPA research projects. Dr. Sunahara received his Ph.D. in Pharmacology and Toxicology (University of British Columbia, Canada). He was a Fogarty International Post-doctoral fellow at the NIEHS (North Carolina). He was a co-recipient of the TTCP Frances Beaupré Award for Environmental Awareness (2005). Dr. Sunahara holds academic positions at McGill University and Concordia University.

Dr. Treye Thomas is a toxicologist and leader of the Chemical Hazards Program team in the U.S. Consumer Product Safety Commission's (CPSC) Office of Hazard Identification and Reduction. His duties include establishing priorities and projects to identify and mitigate potential health risks to consumers resulting from chemical exposures during product use. Dr. Thomas has conducted comprehensive exposure assessment studies of chemicals in consumer products and quantified the potential health risks to consumers exposed to these chemicals. Specific activities have included conducting exposure and/or health hazard assessments of flame retardant (FR) chemicals, combustion by-products, indoor air pollutants, and compounds used to pressure-treat wood. Dr. Thomas is the leader of the CPSC nanotechnology team, and is responsible for developing agency activities for nanotechnology. Dr. Thomas has served as a CPSC representative on a number of nanotechnology committees including the ILSI/HESI Nanomaterial Environmental, Health, and Safety Subcommittee, the Federal NSET and NEHI sub-committees, and the International Council on Nanotechnology (ICON). Dr. Thomas received a Bachelors degree in Chemistry from the University of California, Riverside, an MS in Environmental Health Sciences from UCLA, and a PhD in Environmental Sciences at the University of Texas, Health Science Center, Houston. He completed a post-doctoral fellowship in Industrial Toxicology at the Warner-Lambert Corporation (now Pfizer Pharmaceutical).

Dr. John Veranth's research over the past 15 years has evolved from particle formation in combustion systems to the toxicology of particles, with an emphasis on the lung. His background is in mechanical and chemical engineering, but his current position is Research Associate Professor in the Department of Pharmacology and Toxicology at the University of Utah. His laboratory group focuses on lung, colon, and vascular cell culture models, but he has conducted animal inhalation exposure studies in collaboration with Dr. Kent Pinkerton at U.C. Davis, and was a Visiting Scientist with Dr. Gunter Oberdorster at University of Rochester. Prior to becoming an academic researcher Dr. Veranth worked in the energy production, metallurgical, and hazardous waste industries for 25 years. Many of his projects involved air pollution controls. His regulatory experience includes nine years on the Utah Air Quality Board as the representative of organized environmental groups. Education: BS Mechanical Engineering, Massachusetts Institute of Technology, 1971, MS ME with bioengineering emphasis, MIT, 1974, PhD Chemical Engineering, University of Utah, 1997.

Dr. Donald J. Versteeg is an environmental toxicologist and risk assessor with The Procter & Gamble Company with 25 years of experience. He received his Ph.D. from Michigan State University in 1985 and joined P&G as a researcher in the Environmental Science Department. Don is currently a Principal Research Scientist in Central Products Safety where he leads an environmental risk assessment team working to improve environmental risk assessment approaches. Don's research has been diverse including the use of ecotoxicogenomics to understand mode of action in fish to the generation of quantitative structure activity relationships to reduce animal usage in toxicology. Don has over 40 publications in refereed journals on the fate, effects, and environmental risk assessment of pharmaceuticals, personal care products, and emerging contaminants. Dr. Versteeg is a member of the Society of Environmental Toxicology and Chemistry (SETAC) and serves as an Editor of Aquatic Toxicology for the journal Environmental Toxicology & Chemistry.

Dr. Nigel Walker is Deputy Program Director for Science for the National Toxicology Program (NTP) at the National Institute of Environmental Health Sciences (NIEHS), one of National Institutes of Health (NIH). 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. He is currently the lead scientist for the NTP Nanotechnology Safety Initiative that is evaluating the safety of engineered nanoscale materials. He has over 15 years experience in environmental toxicology, quantitative dose response modeling, and risk analysis, with particular emphasis on persistent organic pollutants, has over 80 publications in this area, and has given numerous invited presentations at national and international workshops and symposia. Dr Walker is on several editorial boards (Environmental Health Perspectives and Toxicology and Applied Pharmacology), is a founding member of the Society of Toxicology Nanotoxicology Specialty Section, an adjunct associate professor in the Curriculum in Toxicology at the University of North Carolina at Chapel Hill, and past-President of the North Carolina Society of Toxicology.

Dr. William J. Warren-Hicks is CEO of EcoStat, Inc, a small women-owned company located in Mebane, North Carolina. He holds a Ph.D. from Duke University in environmental statistics. He has a total of 29 years of experience providing consulting expertise in the areas of risk analysis, environmental data analysis, uncertainty analysis, Bayesian inference and decision, probabilistic risk methods, survey design, time-series modeling, messy data analysis, hypothesis testing, multivariate analyses, and model validation studies. He has over 120 peer-reviewed publications, 2 books, and 8 book chapters in the areas of environmental risk assessment, statistics, probabilistic modeling, and decision sciences. In a consulting capacity, he has managed over 200 projects for clients in all major Environmental Protection Agency (EPA) programs. He teaches courses at Duke University and Elon University to both undergraduate and graduate students.

Dr. Paul Westerhoff is the Interim Head of the School of Sustainable Engineering and The Built Environment, and member of the Civil, Environmental and Sustainable Engineering faculty, at Arizona State University. He obtained a Ph.D. from the University of Colorado at Boulder, a MS from University of Massachusetts and BS from Lehigh University. Westerhoff joined ASU in August 1995. Westerhoff has a strong publication and research record, has garnered wide recognition for his work related to treatment and occurrence of emerging contaminants in water, and has been active in multidisciplinary research. He has lead research funded by AWWARF, USEPA, NSF, DOD and local organizations investigating the fate of nanomaterials in water, use of nanomaterial-based technologies for water and reuse treatment, reactions and fate of oxo-anions (bromate, nitrate, arsenate) during water treatment, reactivity of natural organic matter, formation of disinfection by-products, removal of taste and odor micropollutants. He has over 88 peer reviewed journal article publications and has been involved in over 200 conference presentations. He serves on numerous voluntary committees for these organizations. He currently is a member of the AWWARF Expert Panel on EDC/PPCPs, the WaterReuse Foundation Research Advisory Board, and the Water Research Foundation/AWWARF Public Council.

Dr. Mark R. Wiesner serves as Director of the Center for the Environmental Implications of Nanotechnology (CEINT) headquartered at Duke, where he holds the James L. Meriam Chair in Civil and Environmental Engineering with appointments in the Pratt School of Engineering and the Nicholas School of Environment. Dr. Wiesner's research has focused on the applications of emerging nanomaterials to membrane science and water treatment and an examination of the fate, transport, and impacts of nanomaterials in the environment. He co-edited/authored the book "Environmental Nanotechnologies" and serves as Associate Editor of the journal Nanotoxicology. Before joining the Duke University faculty in 2006, Professor Wiesner was a member of the Rice University faculty for 18 years where he held appointments in the Departments of Civil and Environmental Engineering and Chemical Engineering and served as Associate Dean of Engineering, and Director of the Environmental and Energy Systems Institute. Prior to working in academia, Dr. Wiesner was a Research Engineer with the French company the Lyonnaise des Eaux, in Le Pecq, France, and a Principal Engineer with the Environmental Engineering Consulting firm of Malcolm Pirnie, Inc., White Plains, NY. Wiesner received the 1995 Rudolf Hering medal from the American Society of Civil Engineers and the 2004 Frontiers in Research Award from the Association

of Environmental Engineering and Science Professors. In 2004 Dr. Wiesner was also named a “de Fermat Laureate” and was awarded an International Chair of Excellence at the Chemical Engineering Lab of the French Polytechnic Institute and National Institute for Applied Sciences in Toulouse, France. Professor Wiesner is a Fellow of the American Society of Civil Engineers and serves on the Board of the Association of Environmental Engineering and Science Professors.

APPENDIX F. List of Workshop Observers

J. Michael Davis	EPA ORD, NCEA
Jane Denne	EPA ORD, NERL
Steve Diamond	EPA ORD, NHEERL
Trish Erickson	EPA ORD, NRMRL
Maureen Gwinn	EPA ORD, NCEA
Dorothy Miller	AAAS Fellow with EPA ORD
Peter Preuss	EPA ORD, NCEA
Gary Saylor	BOSC / University of Tennessee – Knoxville
Jo Anne Shatkin	CLF Ventures
John Vandenberg	EPA ORD, NCEA
Debra Walsh	EPA ORD, NCEA
Amy Wang	ORISE Post Doctoral Fellow with EPA ORD, NCEA
Doug Wolf	EPA ORD, NHEERL

Abbreviations:

AAAS	American Association for the Advancement of Science
BOSC	Board of Scientific Counselors
EPA	U.S. Environmental Protection Agency
NCEA	National Center for Environmental Assessment
NERL	National Exposure Research Laboratory
NHEERL	National Health and Environmental Effects Research Laboratory
NRMRL	National Risk Management Research Laboratory
ORD	Office of Research and Development
ORISE	Oak Ridge Institute for Science and Education

Meeting Support Contractor (ICF International) Staff

Peter Bonner, Lead Facilitator
Whitney Kihlstrom, Note-taker
Amalia Marenberg, Note-taker
Kimberly Osborn, Work Assignment Manager
Ethan Sanders, Co-facilitator
Audrey Turley, Meeting Coordinator

APPENDIX G. List of New and Modified Questions

G.1. New Questions Submitted by Workshop Participants

G.1.1. Multiple Chapters: Cross-Cutting Issues (New Questions)

- Mult-A.** Are TiO₂ particles transferred through the placental barrier or through milk?
- Mult-B.** Do adequate methods exist to characterize nano-TiO₂ in relevant environmental matrices such as soil, sediment, or biofilms?
- Mult-C.** How do surface coatings affect environmental fate, environmental chemistry, particle chemistry, and toxicity? Do WWTP processed affect surface coatings? What natural particle coatings are added in the environment (e.g., humic & fulvic acids) and how do these natural coating influence environmental fate, chemistry, and toxicity?
- Mult-D.** How do TiO₂ properties change from the manufacturing stage, upon its incorporation into products, during its use, during storage, upon release to the environment, and upon environmental aging?
- Mult-E.** How do variations in water chemistry (pH, ionic strength, divalent cation concentration, etc.) influence the chemistry and toxicity of nano-TiO₂?
- Mult-F.** How effective are existing management practices to control occupational exposure to nano-TiO₂?
- Mult-G.** Is there enough information to quantify the spatial distribution of nano-TiO₂ over time?
- Mult-H.** Is there enough information to quantify the temporal trends in environmental concentrations of nano-TiO₂?
- Mult-I.** Just to re-emphasize the importance of chemical and physical characterization at a number of stages in addressing possible toxicity of nanomaterials.
- Mult-J.** Should the EPA promote a surface chemistry nomenclature system for use in particle life cycle analyses?
- Mult-K.** Should the life cycle analysis be product-specific, meaning manufacturing process specific, and then combined as a second step for an overall analysis?
- Mult-L.** Should there be a database of reliable information regarding NPs created and made available (the equivalent of the Wikipedia or Google search)?
- Mult-M.** Should TiO₂ particles with coatings and strongly chemisorbed species be evaluated separately for the purposes of environmental transport, ecotoxicity, and toxicity?
- Mult-N.** There should to be a question dealing with metrology and whether or not the instrumentation is available and what needs to be developed in order to do long term field monitoring of nanoparticles.

Mult-O. To what degree is sequestration of TiO₂ to specific compartments expected to affect fate and exposures to receptors (human or ecological)?

Mult-P. What abatement/management practices are recommended to control emissions from manufacturing operations that make or use nanomaterials?

Mult-Q. What are each scientific field's roadblocks that currently limit scientific reliability/reproducibility and the public's confidence in the resulting risk assessments? What are the cross-disciplinary impediments?

Mult-R. What is the potential for TiO₂ particles to accumulate in internal organs and the brain? What developmental effects occur in offspring after exposure during pregnancy?

Mult-S. What makes one type of nanoparticle more active or toxic than another?

Mult-T. What set of widely shared reference samples of nano- and conventional TiO₂ would be most useful for integrating the results of different investigators regarding particle characterization and particle toxicology?

Mult-U. While comprehensive studies are underway, and issues being debated (such as in this workshop), should a group of experienced individuals (such as in this workshop) try to propose "guidelines" for safe use?

G.1.2. Chapter 1: Introduction (New Questions)

1-A. By region and environmental segment (soil, water, etc.), what is known about the background concentration of nano-TiO₂ due to natural or nonanthropogenic processes?

1-B. Do the surface coatings wash off or become diluted when nano-TiO₂ is formulated into products?

1-C. Do we have comprehensive physicochemical characterization data (non-proprietary) on nano-TiO₂ used in sunscreen or water treatment products?

1-D. How can naturally occurring versus engineered NanoTiO₂ be differentiated across the environment (i.e., in air, water, soil, plants, animals)? How can nano-TiO₂ from sunscreens be differentiated from nano-TiO₂ from waste water processes?

1-E. How reliable are the methods to detect various forms of TiO₂ in complex matrices such as wastewater? Will there be validated methods?

1-F. Is comprehensive environmental assessment (CEA) the most appropriate framework from which to approach the development of a research strategy for assessing nanomaterial risks?

1-G. Is it possible to predict the reactive oxygen species (ROS)-generating potential of nano-TiO₂ in the lungs from measurements taken on airborne nano-TiO₂?

1-H. Morphology is a key determinant of biological interaction of other nanomaterials. Have adequate toxicological studies on the effect of morphology been conducted for TiO₂ nanoparticles?

1-I. Should a recommended list of instruments and techniques to characterize nano-TiO₂ be compiled?

1-J. What are the important metrics that we need to use to characterize nano-TiO₂?

1-K. What is nano-TiO₂? Is the definition of less than 100 nm adequate? Or, should a dimension be derived based on the toxicological properties?

1-L. What is the potential for methods to biomonitor TiO₂ in humans?

1-M. What precise definition distinguishes nano-TiO₂ from the smallest particles found in conventional TiO₂ powder mixtures? Is there a continuum between powders deliberately enriched in sub-100 nm primary particles and the tail of the size distribution produced as conventional TiO₂?

G.1.3. Chapter 2: Life Cycle Stages (New Questions)

2-A. Does nano TiO₂ settle out in water? (Important for exposure considerations.)

2-B. Highlight high potential areas for use of nano-TiO₂. What forms will it be potentially used?

2-C. How can nano TiO₂ be removed from water?

2-D. How might the product be misused (intentionally or unintentionally)? How would this change the use-phase exposure?

2-E. Is nano-TiO₂ even used in any commercial scale drinking water treatment? Is any drinking water utility using it in their routine treatment process? [If no, come up with better applications to evaluate]

2-F. Is the carbon footprint of supplying and producing nano-TiO₂ greater than for conventional TiO₂?

2-G. Large containers of TiO₂ used in sunscreens in storage facilities may change over time and could precipitate out. What is the long-term effect? Does size change? Degradation of TiO₂ could occur and it would no longer be the same product that it was. What is the recommendation for how long TiO₂ will remain stable? Changes in temperature can affect aggregation.

2-H. Radioactive materials are present in ilmenite and natural rutile. Should there be a concern?

2-I. Should we examine data from existing manufacturing facilities for TiO₂? Have there been any issues or problems? How does this correlate to nano-TiO₂, if at all? Are there lessons to be learned?

2-J. How much ilmenite is released in the air /environment during the surface mining process? Has this been measured? Would it have inhalation concerns?

2-K. What are the effects of different storage conditions and periods on TiO₂ properties related to it as a potential hazard?

2-L. What exposure pathways could potentially be affected if release of these waste products occurred?

2-M. What is the proper method of disposal for the by-products generated from the making of TiO₂?

2-N. What materials does nano-TiO₂ replace in sunscreens and waste water treatment? Is there a net positive environmental impact to replacing these materials?

2-O. What size and how much TiO_2 can get through the filtration methods? Amounts that get through could be harmful. However, there is no discussion or cited reports on the long term repetitive oral dosing or oral toxicity studies. How can we decide if TiO_2 will be a concern?

G.1.4. Chapter 3: Fate and Transport (New Questions)

3-A. Are there any data available on the physical and chemical behavior of nano- TiO_2 in air or water in relationship to its surface chemistry?

3-B. Are there any generalized principles for study of fate and transport of Nanoparticles in the environment? What are the important parameters that govern fate and transport of Nanoparticles?

3-C. Are there any methods available to measure nano TiO_2 particles in diverse matrices?

3-D. By region, what is the background concentration of nanomaterials in wastewater due to nonanthropogenic processes?

3-E. Can existing information, perhaps data, regarding uptake and transformation of engineered nanoparticles as medium characteristics change, such as sediments from estuarine to marine environments?

3-F. Has Ti been analyzed in finished/potable water, and if so how much and can it be attributable to TiO_2 ?

3-G. How do natural waters of different solution chemistries affect the physicochemical characteristics of nano- TiO_2 and its effects on aquatic biota?

3-H. How do TiO_2 and other nanomaterials differ from larger scale particles or aggregates of nanoparticles or other particles in their fate and transport in the environment and how might that affect our ability to use predictive modeling?

3-I. How does nano- TiO_2 interact with chlorine in disinfected water supplies? Will it create higher levels of disinfection byproducts or novel byproducts?

3-J. Is the use of classic 48-hr, 96-hr, etc. microbiotests adequate for nano- TiO_2 toxicity studies? Would the bio-effects be different if exposure times were used?

3-K. Plants and seeds can bioaccumulate TiO_2 and other heavy metals. How does this affect the edible vegetation? If only less than 1% of the US agricultural land uses treated sewage sludge, should we be concerned? This is extremely small.

3-L. What are stabilities of coatings? What is weathered TiO_2 ?

3-M. What are the long-term (centuries to geological timescale) sinks for nano- TiO_2 ?

3-N. What happens to nano-Ti when it is incinerated? Does it agglomerate or does the particles' size go down?

3-O. What is the available evidence regarding the likelihood that various TiO_2 coatings will be degraded under different environmental conditions, and are there coatings that are more resistant to environmental degradation?

- 3-P.** What is the current background level of nano-TiO₂ in various ecosystems? Recent field flow fractionation (FFF) studies have indicated significant amounts of metal-containing nanoparticles that appear to be widespread, and may be of natural origin.
- 3-Q.** What knowledge do we have of the potential surface modifications of nano-TiO₂ in air, water, or biological fluids?

G.1.5. Chapter 4: Exposure-Dose Characterization (New Questions)

- 4-A.** Are available measurement methods able to adequately discriminate nano-TiO₂ from conventional TiO₂ or other nanoparticles? What suite of methods is currently optimal for identifying nano-TiO₂?
- 4-B.** Benthopelagic species could potentially be exposed to the settling of TiO₂ aggregates; however, aggregates are probably larger than some of these species. Therefore, is it a concern?
- 4-C.** Does nano-TiO₂ bioaccumulate in humans?
- 4-D.** How do TiO₂ and other nanoparticles differ from what we already know about other compounds including macroparticles with respect to exposure-dose and how might that affect predictive modeling?
- 4-E.** How does the presence of nano-TiO₂ cause unique reactions to occur or produce products or destroy necessary organisms that have negative environmental implications?
- 4-F.** How much (metric tons) nano-TiO₂ is used in sunscreens, cosmetics and other products that are contained in products that may be disposed down the drain? If any of the pigment and other TiO₂ sources contain a fraction which is nano, this mass should be added into the volume. Further, the volume should be split out into different surface coatings, dopings, and size fractions.
- 4-G.** What is the concentration of TiO₂ in public swimming pools? Eye is a small surface area to be affected.
- 4-H.** Fish can take up TiO₂ from waste water runoffs and ingest TiO₂ along with the prey that has been exposed to TiO₂. Major Gap is people then eat the fish which could have bioaccumulated the TiO₂. What are the health effects in humans after ingestion with TiO₂ contaminated fish? Remember the mercury situation in large fish.
- 4-I.** If nano-TiO₂ is part of the packaging, will it leach into the product?
- 4-J.** Is nano-TiO₂ used in any products or packaging for products intended for very young children?
- 4-K.** Is the skin on the forearms (which is used for dermal studies) identical to skin on the face and lips (where most of the applications of TiO₂ sunscreen is applied). (If so, it would appear that little TiO₂ penetrates the skin surface.)
- 4-L.** Nano-TiO₂ on the organism's surface might cause toxicity even if TiO₂ does not enter cells? Release of other pollutants? Must enter cells or cause damage to cells to exert toxicity, e.g., cross cell membranes.
- 4-M.** Powders and particles have been produced for many decades in the Industrialized world. Is there any epidemiological data from manufacturing sites of particles? Any adverse health data?

- 4-N.** The release of TiO₂ from treated products may depend on product use and misuse. How will product use/misuse impact release of TiO₂ and subsequent exposure to humans and the environment?
- 4-O.** What are the relevant exposure metrics for TiO₂, and what is their relative importance in terms of toxicologic relevance?
- 4-P.** What could be considered as relevant range of nano-TiO₂ concentrations in aquatic systems with regard to dose-exposure studies using model aquatic organisms?
- 4-Q.** What is nano-TiO₂ removal in wastewater treatment? Does wastewater treatment affect aggregate size? This should be understood for each of the different surface coatings, dopings, and size fractions. Note: there is one published removal study. Additional studies looking at other treatment processes are needed.
- 4-R.** What is the effect after repetitive or multiple dosing of TiO₂ over time? Could penetrate deeper into the skin and be available for systemic absorption.
- 4-S.** What is the potential for inhalation and ingestion exposures to nano-TiO₂ from sunscreen? What are the dominant sizes of TiO₂ aggregates/agglomerates during spraying, and what is the potential for inhalation exposure to nano-TiO₂ during spraying? What is the potential for hand-to-mouth intake of nano-TiO₂ from sunscreen usage?
- 4-T.** What is the ultimate sink for nano-TiO₂ in the environment? What are surface water, sediment, and soil nano-TiO₂ concentrations? This should be understood for each of the different surface coatings, dopings, and size fractions. Are there background concentrations? If so, natural nano-TiO₂ should be fully characterized.

G.1.6. Chapter 5: Characterization of Effects (New Questions)

- 5-A.** Are the biological responses that have been observed for elevated nano-TiO₂ exposures different from those elicited for exposures to other small particles? If so, how?
- 5-B.** Are there existing, simple, inexpensive state, Canadian, European Union or other standard testing protocols that could do preliminary testing of chronic/sublethal effects with simple end points, such as weight?
- 5-C.** How do TiO₂ and other nanomaterials differ from larger scale particles, aggregates of nanomaterials or other particle types, or solutions of pollutants in their effects on species (human and ecological) and how does that affect pharmacokinetics and effects of exposure?
- 5-D.** How relevant are intratracheal installations to humans? Rats are obligatory nose breathers, not humans. Forcing large amounts of TiO₂ is not a normal scenario.
- 5-E.** If tested on mouse skin, would nano-TiO₂ be an initiator, promoter, complete carcinogen, or none of the above?
- 5-F.** Is nano-TiO₂ toxicity and reactive oxygen species (ROS) generation on the skin enhanced by exposure to sunlight?
- 5-G.** Is there any evidence for nano-TiO₂ and conventional TiO₂ inducing distinctly different pathways of cell signaling or gene transcription? Do nano and conventional TiO₂ have different toxicological mechanisms of action or do the two materials simply have a surface-area or surface-coating dependent difference in potency?

- 5-H.** Mostly everything including water can cause conjunctivitis of the eye. Very small surface area. Is this a concern? Eye protection can be worn during manufacturing etc.
- 5-I.** No long term repetitive oral toxicity studies or sensitization studies have been conducted with different concentrations of TiO₂, sizes or surface coatings in skin.
- 5-J.** What are the effects of long-term or repeated use of sunscreen containing nano-TiO₂?
- 5-K.** What are the fundamental biological responses of nano-TiO₂ interaction(s) at cellular level (as dictated by its physical and chemical characteristics)?
- 5-L.** What are the known effects due to exposures to nano TiO₂?
- 5-M.** What is the interaction between nano-TiO₂ and the various branches of the immune system? Is there a threshold for nano-TiO₂ perturbation of the immune system?
- 5-N.** What is the potential for TiO₂ particles to accumulate in internal organs and the brain? What developmental effects occur in offspring after exposure during pregnancy?
- 5-O.** What is the relationship between nano-TiO₂ particle size and transport into the central nervous system?
- 5-P.** What is the relevance of short-term pulmonary effects observed in animals at high airborne concentration levels to human exposures at lower environmental concentration levels? What is the real-world relevance of toxicity studies that rely on sonication, ultrafiltration, and other techniques for dispersing TiO₂?
- 5-Q.** What properties are most closely tied to the observed biological responses in TiO₂ toxicity studies, and can we develop predictive models of TiO₂ toxicity based on properties data?
- 5-R.** What quantities/concentrations of TiO₂ nanoparticles are unsafe? Is there an LD10, LD50, etc for TiO₂ nanoparticles?
- 5-S.** Which organisms are most likely to be exposed to each of the sources of nano-TiO₂? Which organisms are likely to take up particles via endocytosis? Which organisms are likely to be most susceptible to free radical effects?

G.2. Revised Questions Submitted by Participants

G.2.1. Chapter 1: Introduction (Revised Questions)

- 1-2. Suggest that the focus be on reasonably foreseeable applications, not “different applications.”
- 1-3. Suggest that this be modified to include “and other ingredients.”
- 1-4. (Added text in CAPS.) What are the potential implications (e.g., in terms of physical and chemical properties AND RELATED FATE, EXPOSURE, and TOXICITY) of differences in the composition and mineralogy of different forms of nano-TiO₂ (e.g., rutile and anatase), PARTICULARLY FOR CURRENTLY COMMERCIALIZED FORMULATIONS?
- 1-5. What are the “accepted standard” ways of testing materials today?

- 1-6. What existing or emerging analytical techniques might be relevant or useful for emissions characterization at any stage of the life cycle? For example, could field flow fractionation (FFF) be used for characterization of particle size and elemental composition?

G.2.2. Chapter 2: Life Cycle Stages (Revised Questions)

- 2.3-3-2.3-6. (These questions could be combined and summarized with 4-8 as follows.) What factors are critical to ensure that nanomaterials are contained and remain stable?
- 2.4-5. Suggest that this be modified from “topical sunscreen products” to “topical sunscreen products and other topical personal care products.”
- 2-5-4. How are large quantities of waste (e.g., out of spec nanomaterials, sub-par batches of sunscreen) handled?

G.2.3. Chapter 3: Fate and Transport (Revised Questions)

- 3-3. Are available fate and transport models applicable to nanomaterials? If not, can they be adapted, or are new models required?
- 3-4. Is information on environmental fate and transport of other substances available that might provide insights applicable to nanomaterials?
- 3-7. (Added text in CAPS.) What is the bioavailability of nano-TiO₂ in land-applied sludge to PLANTS AND terrestrial and aquatic organisms? Is UPTAKE FROM CONTAMINATED SOIL AND WATER POSSIBLE AND IS bioavailability likely to change when nano-TiO₂ is incorporated into sludge and is allowed to “age” (in situ weathering) (NOTE: this change is intended to combine this question with 3-17 and 18 which is very similar)
- 3-8. What is their persistence with TiO₂ when sunscreen is used?
- 3-12. (Added text in CAPS.) Irradiated photocatalytic nano-TiO₂ is potentially biocidal and antimicrobial. What is the potential for interactions of nano-TiO₂ with microbes needed in water treatment systems AND ENVIRONMENTAL MEDIA EXPOSED TO WATER AND SLUDGE FROM SUCH SYSTEMS? (intended to combine this question with question 3-9)

G.2.4. Chapter 4: Exposure-Dose Characterization (Revised Questions)

- 4-1. (Add to existing question) At what concentrations?
- 4-6. What parameters should be used to characterize worker (or consumer or general human) exposure in a way that is compatible with hazard information?
- 4-7. What management practices are recommended to control occupational exposures to nanomaterials?
- 4-8. (Consider changing this question to the following.) What protective equipment are effective in containing nanomaterials and what are the factors most important for ensuring that nano-TiO₂ is not released and does not expose workers?
- 4-12. Suggest that this be modified from the focus on inhalation to include potential oral and dermal exposures.

4-15. Which physiologically-based pharmacokinetic models are optimal for understanding absorption, distribution, and elimination of nanomaterials in humans?

G.2.5. Chapter 5: Characterization of Effects (Revised Questions)

5.2-1. (Combine with 5.3-1; added text in CAPS.) Are current EPA test protocols adequate to assess human and ecological toxicity of nano-TiO₂, PARTICULARLY FOR COMMERCIALIZED FORMULATIONS?

5.2-7. How do abiotic factors in the environment, such as UV, pH, oxygen level, and other chemicals, affect nanomaterials and their ecological effects?

5.3-3. This could be worded in a clearer, more comprehensive way to include potential skin hydrated conditions that can occur under occluded skin conditions, e.g., from wearing of diapers, feminine hygiene pads, and band aids. (Also need to consider how hydration occurring in patch tests could impact penetration, and how such data should be considered in exposure and risk assessments.)

5.3-4. Suggest that this question be broadened (or an additional question created) to include: 1) different disease states and 2) conditions that seek to represent reasonably foreseeable consumer product usage and occupational exposure scenarios.

5.3-8. What kind of studies would provide the most suitable data to understand dose-response of occupational exposure to nanomaterials and health effects in humans?

5.3-9. (Added text in CAPS.) What is the potential for NEUROLOGICAL, reproductive and developmental effects...?

5.3-10. (Combine with 5.3-11.) Is nano TiO₂ carcinogenic? If so, by which routes of exposure?

APPENDIX H. Pre-Workshop Ranking Results

The following steps describe the procedure used to calculate the pre-workshop rankings based on the rankings received from the participants.

- Added three placeholder questions so there are a total of 100 questions (to simplify presentation of analysis and results).
- For the ranked questions (top 10 for most participants, although a few submitted only 9), converted the score of 10 to 100, score of 9 to 99, score of 8 to 98, etc.
- For the unranked high questions, assigned a random value between 76 and 90. This was done to facilitate calculation of means and standard deviations for the vote tallies for each question. The range of random numbers varied depending on how many ranked questions the participant submitted.
- For the unranked low questions, assigned a random value between 1 and 10. Again, this range of random numbers may be smaller or larger than 10, depending on how many low questions the participant submitted. This range always began at 1.
- For the ones that were not ranked or selected as high or low (left blank in the Web ranking form), assigned a random value between 11 and 75. The placeholder questions were included in this group. This range of random numbers varied from participant to participant based on how many ranked, low, and high questions were submitted by that participant.
- Calculated total points, mean score, and standard deviation for each question.
- Ran a Monte Carlo simulation 100 times, storing the total points, mean score, and standard deviation for each run. Only the randomly assigned numbers changed from run to run—the ranked questions always kept the same order and points from 100 down to 92 or 91, depending on how many the participant ranked.
- Averaged the results of all Monte Carlo simulations to get the final results shown in the tables that follow.

Ranking Results (1 - 10)

*Shown in ranked order beginning with question awarded most total points (Question 4-10).

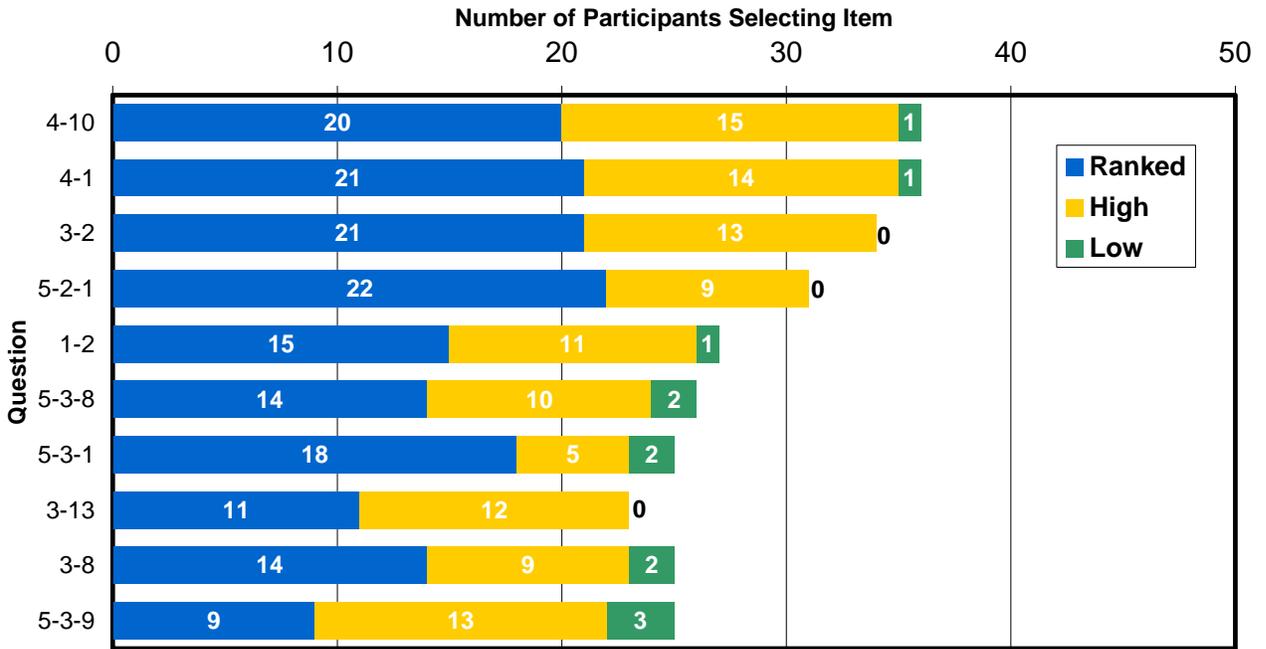


Figure H-1. Ranking Results 1-10.

Ranking Results (11 - 40)

*Shown in ranked order beginning with question ranked 11th (Question 2-4-7).

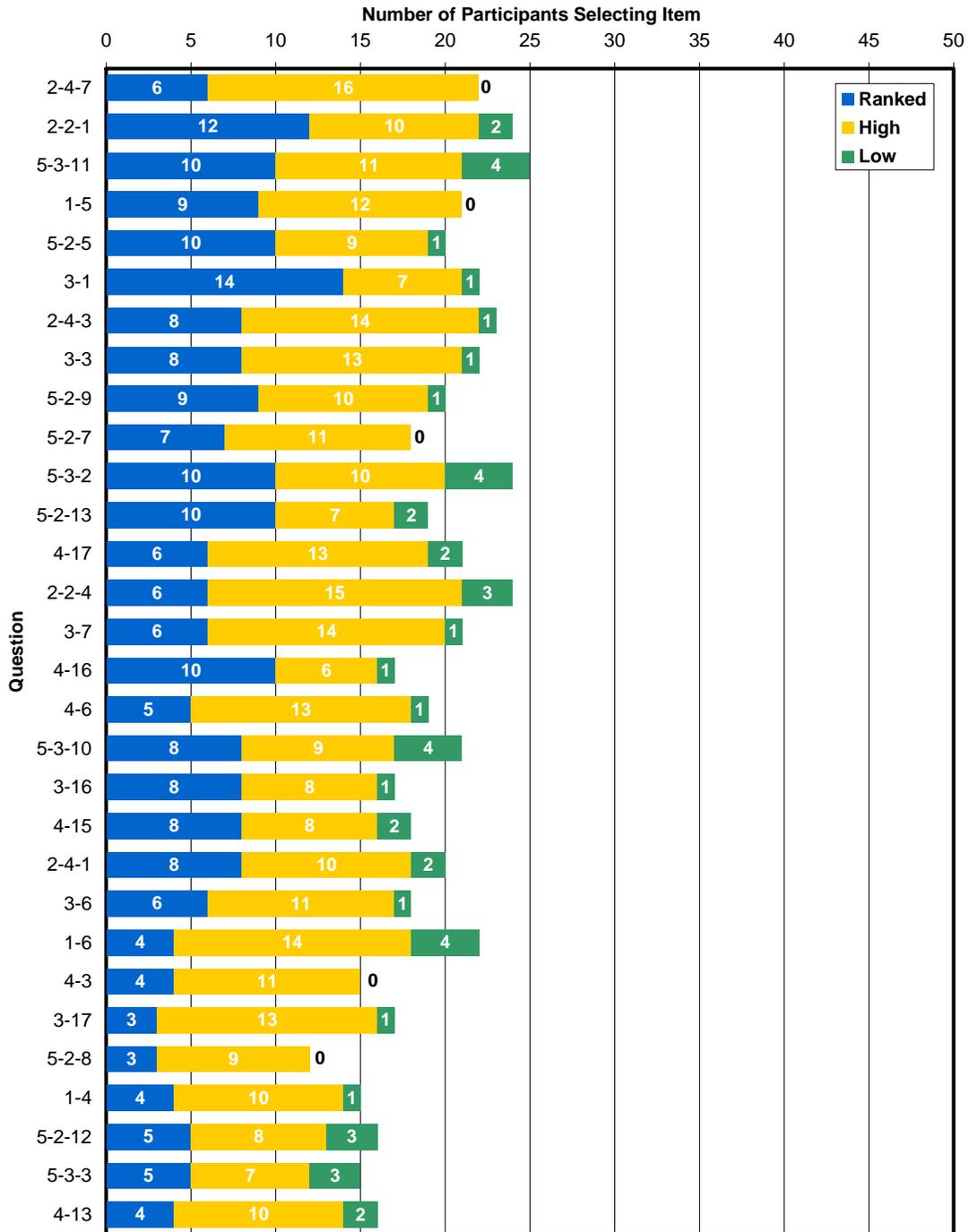


Figure H-2. Ranking Results 11-40.

Ranking Results (41 - 70)

*Shown in ranked order beginning with question ranked 41st (Question 4-9).

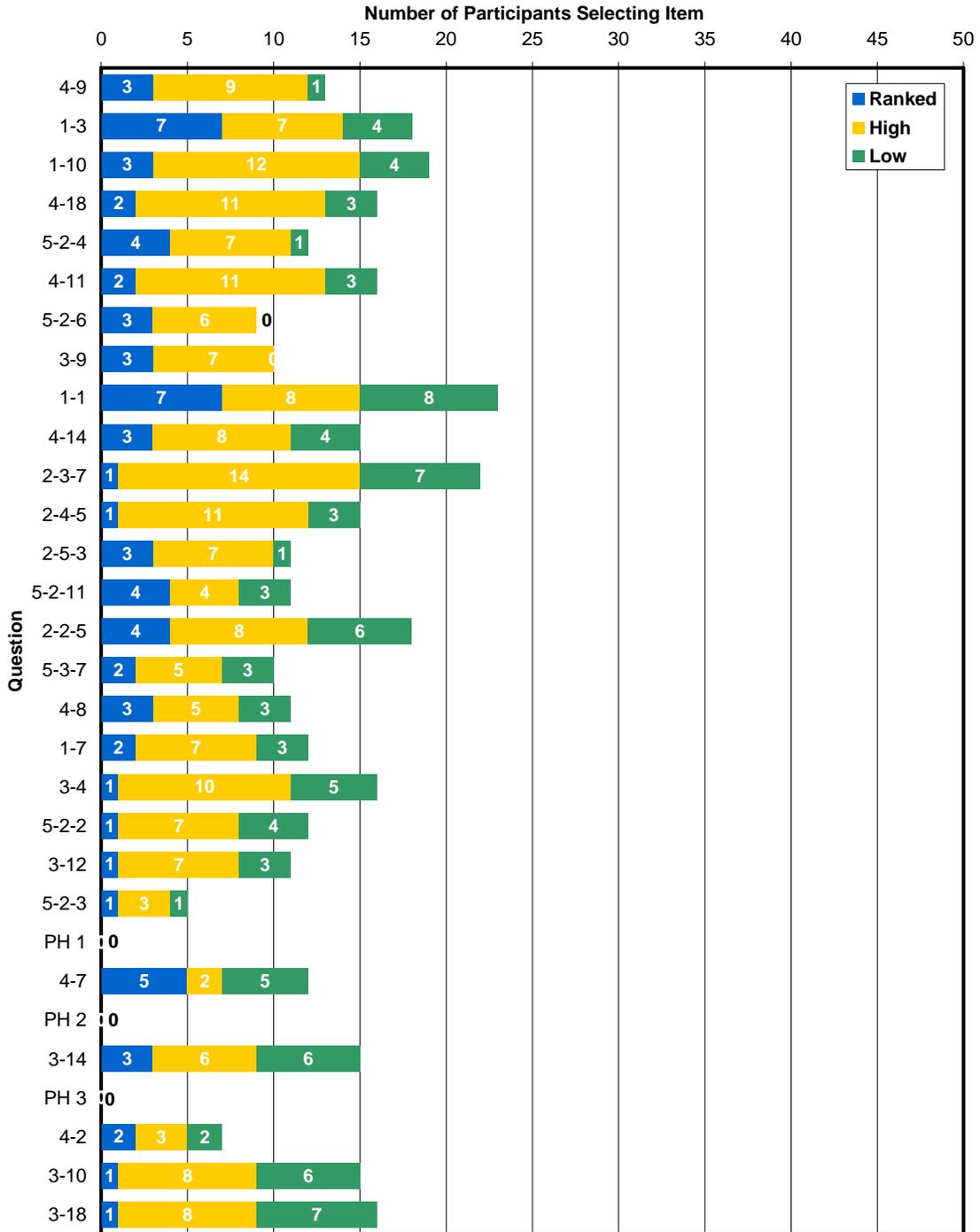


Figure H-3. Ranking Results 41-70.

Ranking Results (71 - 100)

*Shown in ranked order beginning with question ranked 71st (Question 5-2-10).

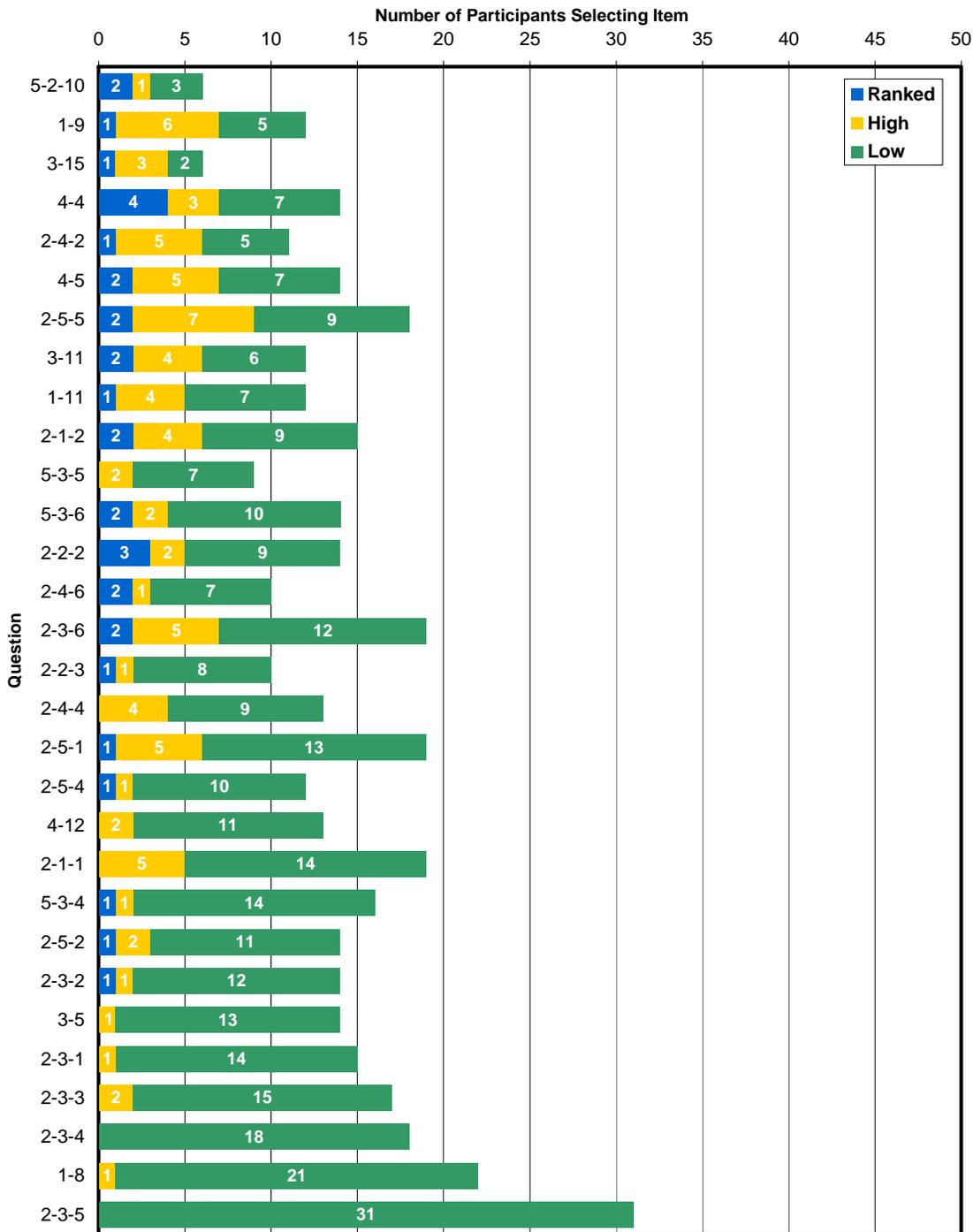


Figure H-4. Ranking Results 71-0.

Table H-1. Pre-Workshop questions in ranked order, beginning with the question awarded the most points

Rank	Question		Total Points	Mean	Std. Dev.	Number of Participants Who...			
						Ranked in Top 10	Selected as High	Selected as Low	Did Not Select
1	4-10	Are available methods adequate to characterize nano-TiO ₂ exposure via air, water, and food? What properties of nano-TiO ₂ should be included in such exposure characterizations?	3,754	76.6	25.0	20	15	1	13
2	4-1	Which sources, pathways, and routes pose the greatest exposure potential to nano-TiO ₂ for biota? ...for humans?	3,750	76.5	26.3	21	14	1	13
3	3-2	How do specific physicochemical properties, including particle surface treatments and aggregation/agglomeration, affect the fate and transport of nano-TiO ₂ in various environmental media?	3,734	76.2	26.1	21	13	0	15
4	5-2-1	Are current EPA standard testing protocols adequate to determine nano-TiO ₂ ecotoxicity? If not, what modifications or special considerations, if any, should be made in current ecological tests? For example, what are the differences in characterization of testing material (as raw material, in media, and in organisms), dispersion methods, and realistic exposure routes between testing conventional materials and nanomaterials?	3,633	74.1	27.6	22	9	0	18
5	1-2	Have the properties of nano-TiO ₂ in different applications been adequately characterized? If not, is the general problem that methods do not exist or that existing methods have not been widely applied? If new methods are needed, what properties should they measure?	3,302	67.4	28.0	15	11	1	22
6	5-3-8	What kind of studies would provide the most suitable data to understand dose-response of nano-TiO ₂ occupational exposure and health effects in humans?	3,249	66.3	29.3	14	10	2	23

Rank	Question		Total Points	Mean	Std. Dev.	Number of Participants Who...			
						Ranked in Top 10	Selected as High	Selected as Low	Did Not Select
7	5-3-1	Are the current EPA harmonized health test guidelines for assessing toxicity adequate to determine the health effects/toxicity of nano-TiO ₂ ?	3,221	65.7	30.6	18	5	2	24
8	3-13	What are the key environmental factors (e.g., pH, natural organic matter type and concentration, temperature) that facilitate or hinder nano-TiO ₂ stability in the aqueous environment? Would humic acids or other common constituents or contaminants in water undergoing treatment affect the fate, including agglomeration/aggregation properties, of TiO ₂ ?	3,135	64.0	28.0	11	12	0	26
9	3-8	What effect, if any, do coatings, dopings, carriers, dispersants, and emulsion types have on biopersistence and bioaccumulation?	3,134	64.0	30.0	14	9	2	24
10	5-3-9	What is the potential for reproductive and developmental effects of nano-TiO ₂ ?	3,098	63.2	28.2	9	13	3	24
11	2-4-7	How much nano-TiO ₂ enters the environment under different scenarios and conditions of sunscreen use (e.g., ambient air and water temperature, swimming, bathing)? Under what conditions would nano-TiO ₂ be released from the sunscreen matrix?	3,053	62.3	27.2	6	16	0	27
12	2-2-1	How do various manufacturing processes for nano-TiO ₂ affect their physicochemical properties?	3,043	62.1	29.9	12	10	2	25
13	5-3-11	Is inhaled nano-TiO ₂ carcinogenic at exposure levels below those that induce particle overload?	3,037	62.0	29.9	10	11	4	24
14	1-5	How do coatings applied for different purposes (e.g., to disperse particles or to decrease photocatalysis) interact or affect other properties of nano-TiO ₂ ?	3,033	61.9	27.7	9	12	0	28
15	5-2-5	What might be the primary mechanism(s) of action of toxic effects in different species?	3,013	61.5	28.6	10	9	1	29

Rank	Question		Total Points	Mean	Std. Dev.	Number of Participants Who...			
						Ranked in Top 10	Selected as High	Selected as Low	Did Not Select
16	3-1	What are the relative contributions of different stages of the life cycles of water treatment and sunscreen products to environmental levels of nano-TiO ₂ and associated contaminants in air, water, and soil?	3,011	61.5	30.1	14	7	1	27
17	2-4-3	What percentage of the nano-TiO ₂ would settle out in floc or become part of the filter matrix? What percentage would be released into finished water? Are measurement or monitoring methods adequate to detect such particles?	2,995	61.1	28.8	8	14	1	26
18	3-3	Are available fate and transport models applicable to nano-TiO ₂ ? If not, can they be adapted, or are new models required?	2,983	60.9	27.9	8	13	1	27
19	5-2-9	What are the ecological effects of long-term exposure to nano-TiO ₂ ?	2,981	60.8	27.6	9	10	1	29
20	5-2-7	How do abiotic factors in the environment, such as UV, pH, oxygen level, and other chemicals, affect nano-TiO ₂ and its ecological effects?	2,959	60.4	26.8	7	11	0	31
21	5-3-2	Is the current information on nano-TiO ₂ skin penetration sufficient for risk assessment?	2,929	59.8	30.5	10	10	4	25
22	5-2-13	Is the available ecotoxicity evidence adequate to support ecological risk assessment for nano-TiO ₂ ? If not, what is needed?	2,922	59.6	28.4	10	7	2	30
23	4-17	What is the potential for nano-TiO ₂ to transfer to or accumulate in the food web and cause adverse effects on ecological receptors?	2,911	59.4	27.7	6	13	2	28
24	2-2-4	What waste products or other by-products, both nanoscale and larger, might be released, and in what quantities, for nano-TiO ₂ manufacturing processes?	2,910	59.4	29.2	6	15	3	25
25	3-7	What is the bioavailability of nano-TiO ₂ in land-applied sludge to both terrestrial and aquatic organisms? Is bioavailability likely to change when nano-TiO ₂ is incorporated into sludge and is allowed to "age" (in-situ weathering)?	2,893	59.0	28.1	6	14	1	28

Rank	Question		Total Points	Mean	Std. Dev.	Number of Participants Who...			
						Ranked in Top 10	Selected as High	Selected as Low	Did Not Select
26	4-16	Are exposure-dose models available (and adequate) to quantitatively extrapolate the exposure used in animal toxicology studies (by inhalation, instillation, oral, dermal, and in vitro) to the human exposure that would result in an equivalent dose to the target of interest?	2,881	58.8	28.1	10	6	1	32
27	4-6	What concentrations, routes, frequencies, and durations characterize worker exposures to nano-TiO ₂ across the life cycle and within certain stages (e.g., manufacturing)?	2,848	58.1	27.0	5	13	1	30
28	5-3-10	Is ingested nano-TiO ₂ carcinogenic?	2,841	58.0	29.1	8	9	4	28
29	3-16	Can agglomeration/ disagglomeration in the environment be predicted on the basis of physical properties of the particle, for example, size, shape, or coating?	2,814	57.4	27.4	8	8	1	32
30	4-15	Which physiologically-based pharmacokinetic models are optimal for understanding absorption, distribution, and elimination of nano-TiO ₂ in humans?	2,812	57.4	27.9	8	8	2	31
31	2-4-1	To what extent is nano-TiO ₂ used or could be used for either drinking water or waste water treatment? Are data available (e.g., volume of water currently treated in the United States for arsenic, amount of TiO ₂ needed to treat a given volume of water) that would permit an estimate of potential use?	2,804	57.2	29.2	8	10	2	29
32	3-6	How might nano-TiO ₂ affect the fate and transport of metals and other potentially toxic substances in water or other environmental media?	2,755	56.2	28.1	6	11	1	31
33	1-6	What factors determine whether and to what extent aggregation or agglomeration of nano-TiO ₂ occurs?	2,730	55.7	29.1	4	14	4	27
34	4-3	Do particular species of biota and populations of humans have greater exposure potential (e.g., high-end exposures due to unusual conditions or atypical consumption)? In particular, do children get a higher exposure and/or dose?	2,725	55.6	26.2	4	11	0	34

Rank	Question		Total Points	Mean	Std. Dev.	Number of Participants Who...			
						Ranked in Top 10	Selected as High	Selected as Low	Did Not Select
35	3-17	What is the likelihood that nano-TiO ₂ in biosolids will become part of the food web and ground water contamination?	2,714	55.4	26.8	3	13	1	32
36	5-2-8	How do in vivo biochemical processes alter nano-TiO ₂ physicochemical characteristics and toxicity?	2,663	54.3	24.9	3	9	0	37
37	1-4	What are the potential implications (e.g., in terms of physical and chemical properties) of differences in the composition and mineralogy of different forms of nano-TiO ₂ (e.g., rutile and anatase)?	2,659	54.3	27.2	4	10	1	34
38	5-2-12	In addition to arsenic and cadmium, do other compounds show different uptake in the presence of nano-TiO ₂ ? Are the toxicities of arsenic, cadmium, or other chemicals affected by nano-TiO ₂ ? Conversely, do other compounds affect the uptake and toxicity of nano-TiO ₂ ?	2,654	54.2	27.2	5	8	3	33
39	5-3-3	Would nano-TiO ₂ penetrate into living cells in flexed, "soaked," or damaged skin (such as sunburned, scratched, eczematous skin)?	2,620	53.5	27.5	5	7	3	34
40	4-13	Since nano-TiO ₂ may increase the uptake of other pollutants, such as arsenic, would nano-TiO ₂ be a greater concern for exposure and ecological effects in areas with high concentrations of certain pollutants than in other areas? If so, how do we predict or identify such "hot spots?"	2,613	53.3	27.1	4	10	2	33
41	4-9	Are occupational monitoring methods available or in place for all relevant stages of the life cycle for nano-TiO ₂ applications?	2,604	53.1	25.1	3	9	1	36
42	1-3	Which coatings, dopings, carriers, dispersants, and emulsion types are most prevalent in different applications of nano-TiO ₂ ?	2,599	53.0	30.0	7	7	4	31
43	1-10	What existing or emerging analytical techniques might be relevant or useful for material characterization? For example, could field flow fractionation (FFF) be used for characterization of particle size and elemental composition?	2,597	53.0	28.4	3	12	4	30

Rank	Question		Total Points	Mean	Std. Dev.	Number of Participants Who...			
						Ranked in Top 10	Selected as High	Selected as Low	Did Not Select
44	4-18	Nano-TiO ₂ has been shown to attach to the surfaces of algae and fish as well as bioaccumulate in fish. Does nano-TiO ₂ biomagnify?	2,591	52.9	26.4	2	11	3	33
45	5-2-4	How can contributions of various nano-TiO ₂ physicochemical properties to nano-TiO ₂ ecological effects be identified or compared? For example, could a retrospective analysis of many studies and computer modeling identify patterns that would not be evident in individual studies? Is a structure activity relationship (SAR) approach applicable for predicting nano-TiO ₂ ecological effects?	2,585	52.8	25.9	4	7	1	37
46	4-11	Given the potential for greater uptake of certain substances in the presence of nano-TiO ₂ , should monitoring and exposure studies include a suite of substances that might interact with nano-TiO ₂ ?	2,568	52.4	27.4	2	11	3	33
47	5-2-6	Are the mechanisms of cellular responses different at low and high concentrations of nano-TiO ₂ ?	2,566	52.4	24.0	3	6	0	40
48	3-9	Can the photocatalytic properties of nano-TiO ₂ cause other unintended substances to form, for example, degradation products, in various environmental media?	2,507	51.2	25.5	3	7	0	39
49	1-1	To evaluate nano-TiO ₂ (in these or other applications) or to compare products containing nano-TiO ₂ , is further standardization or refinement of terminology needed? If so, is such an effort underway and/or what terminology is most important to standardize?	2,494	50.9	32.2	7	8	8	26
50	4-14	Which, if any, exposure models have been evaluated for applicability to nano-TiO ₂ ?	2,449	50.0	27.0	3	8	4	34
51	2-3-7	How much nano-TiO ₂ could be released under various routine and accidental scenarios of distribution and storage?	2,442	49.8	29.8	1	14	7	27
52	2-4-5	What is the total quantity of nano-TiO ₂ used in topical sunscreen products in the United States and worldwide?	2,439	49.8	27.8	1	11	3	34

Rank	Question		Total Points	Mean	Std. Dev.	Number of Participants Who...			
						Ranked in Top 10	Selected as High	Selected as Low	Did Not Select
53	2-5-3	In water treatment, how are filter materials and associated waste/waste water containing nano-TiO ₂ disposed of or recycled?	2,418	49.3	26.5	3	7	1	38
54	5-2-11	Nano-TiO ₂ has anti-bacterial and anti-fungal properties. What are the effects of both photocatalytic and photostable nano-TiO ₂ on the biodiversity of microorganisms?	2,413	49.2	25.6	4	4	3	38
55	2-2-5	Where is nano-TiO ₂ manufactured? What is the potential for general population exposure to nano-TiO ₂ in these areas?	2,401	49.0	29.4	4	8	6	31
56	5-3-7	To what extent do photocatalytic properties of nano-TiO ₂ contribute to dermal effects?	2,393	48.8	24.7	2	5	3	39
57	4-8	What personal protective equipment do workers use at the various life cycle stages of nano-TiO ₂ applications? How effective is such equipment in controlling exposures by all routes?	2,374	48.4	25.8	3	5	3	38
58	1-7	Are data available that indicate the level of agglomeration/aggregation/dispersion of nano-TiO ₂ in specific products? If so, what do the data show?	2,356	48.1	26.5	2	7	3	37
59	3-4	Is information on environmental fate and transport of other substances available that might provide insights applicable to nano-TiO ₂ ?	2,343	47.8	27.8	1	10	5	33
60	5-2-2	What are the ecological effects of waste and other by-products of nano-TiO ₂ manufacturing?	2,322	47.4	25.4	1	7	4	37
61	3-12	Irradiated photocatalytic nano-TiO ₂ is potentially biocidal and antimicrobial. What is the potential for interactions of nano-TiO ₂ with microbes needed in water treatment systems?	2,311	47.2	25.5	1	7	3	38
62	5-2-3	Could ecological effects of pure nano-TiO ₂ be predictive of effects from products containing nano-TiO ₂ (e.g., containing stabilizers or surfactants)?	2,289	46.7	22.4	1	3	1	44
63	PH 1	Placeholder Question #1	2,280	46.5	19.0	—	—	—	—

Rank	Question		Total Points	Mean	Std. Dev.	Number of Participants Who...			
						Ranked in Top 10	Selected as High	Selected as Low	Did Not Select
64	4-7	What management practices exist to control occupational exposures to nano-TiO ₂ ?	2,258	46.1	27.4	5	2	5	37
65	PH 2	Placeholder Question #2	2,254	46.0	19.2	—	—	—	—
66	3-14	What is the impact to nutrient and metals cycling and microbial diversity when sludge with nano-TiO ₂ is applied to soils?	2,248	45.9	28.1	3	6	6	34
67	PH 3	Placeholder Question #3	2,242	45.8	19.0	—	—	—	—
68	4-2	What is the potential for biota and human (both occupational and general population) exposure to secondary contaminants (e.g., waste or transformation products) associated with the entire life cycle of water treatment or sunscreen applications of nano-TiO ₂ ?	2,232	45.6	24.3	2	3	2	42
69	3-10	Will nano-TiO ₂ affect the efficacy of other major elements of water treatment processes (e.g., chemical disinfection, the coagulant concentration necessary for effective organics removal)?	2,224	45.4	27.3	1	8	6	34
70	3-18	What is the potential for plant uptake of nano-TiO ₂ from contaminated soil and irrigation water?	2,210	45.1	27.9	1	8	7	33
71	5-2-10	What are the indirect ecological effects (e.g., on soil or water chemistry) of nano-TiO ₂ ?	2,201	44.9	22.8	2	1	3	43
72	1-9	Regarding the properties of aggregates and agglomerates and proper characterization of particle size, what insight is available from study of other nanoparticles?	2,187	44.6	26.3	1	6	5	37
73	3-15	How do sunscreen ingredients affect nano-TiO ₂ fate and transport?	2,149	43.9	23.6	1	3	2	43
74	4-4	What is the total population that could be exposed to nano-TiO ₂ via drinking water? ...via topical sunscreens?	2,139	43.7	27.6	4	3	7	35
75	2-4-2	Which water treatment processes use or would use nano-TiO ₂ and in what quantities? Would the type of process depend on the size of a treatment facility or the size of the population served, or both?	2,134	43.6	26.1	1	5	5	38

Rank	Question		Total Points	Mean	Std. Dev.	Number of Participants Who...			
						Ranked in Top 10	Selected as High	Selected as Low	Did Not Select
76	4-5	Approximately how many workers are involved in nano-TiO ₂ production, distribution, and use?	2,123	43.3	27.3	2	5	7	35
77	2-5-5	How much nano-TiO ₂ is present in sunscreen containers that are discarded? Are there any circumstances where such discarded product could enter a microenvironment at significant levels?	2,111	43.1	28.9	2	7	9	31
78	3-11	What influence could other drinking water contaminants, including arsenic, have on the chemical properties or behavior of nano-TiO ₂ ?	2,098	42.8	26.7	2	4	6	37
79	1-11	Do surface area measurements in air (e.g., BET analysis) correlate to surface area in an aqueous environment? If so, what is the extent of their accuracy and precision?	2,030	41.4	26.5	1	4	7	37
80	2-1-2	What contaminants, nanoscale and larger, might be released, and in what quantities, in relation to the procurement and processing of feedstocks for nano-TiO ₂ ?	2,011	41.0	27.7	2	4	9	34
81	5-3-5	Do certain formulations of nano-TiO ₂ sunscreens generate hydroxyl radicals when applied to skin?	2,005	40.9	23.3	0	2	7	40
82	5-3-6	Given that nano-TiO ₂ is a good antimicrobial agent, how does it affect skin flora? Does application of sunscreen promote the colonization of skin by potentially harmful bacteria (e.g., staph)?	2,003	40.9	26.3	2	2	10	35
83	2-2-2	How are manufacturing processes likely to evolve with increasing demand for nano-TiO ₂ ?	2,001	40.8	27.9	3	2	9	35
84	2-4-6	What is the maximum quantity and frequency of personal sunscreen use in relation to season, geographic location, demographics, and other variables?	1,931	39.4	25.6	2	1	7	39
85	2-3-6	Would prolonged storage in adverse or less than ideal climates (e.g., cold or humid environments) alter nano-TiO ₂ characteristics and behavior?	1,909	39.0	29.4	2	5	12	30

Rank	Question		Total Points	Mean	Std. Dev.	Number of Participants Who...			
						Ranked in Top 10	Selected as High	Selected as Low	Did Not Select
86	2-2-3	Are certain manufacturing processes used specifically for nano-TiO ₂ as a water treatment agent or as topical sunscreen?	1,870	38.2	24.4	1	1	8	39
87	2-4-4	Water distribution systems often have substantial biofilm or corrosion development, despite the implementation of control practices. Would the presence of nano-TiO ₂ influence the bacterial biofilm community or the occurrence of corrosion?	1,864	38.0	25.9	0	4	9	36
88	2-5-1	How much residual nano-TiO ₂ is present in packaging of the primary material or derived products? How is such packaging disposed of?	1,833	37.4	28.5	1	5	13	30
89	2-5-4	How are large quantities of sunscreen (e.g., sub-par batches rejected during manufacturing) handled?	1,785	36.4	24.7	1	1	10	37
90	4-12	What happens when nano-TiO ₂ is trapped in the stratum corneum and the dead skin flakes off? Is there a potential for dead-skin nano-TiO ₂ to settle around households, or be inhaled? How much might accumulate after a day (or a few days) in the sun (and numerous reapplications)?	1,783	36.4	24.8	0	2	11	36
91	2-1-1	Are certain feedstocks more relevant to producing nano-TiO ₂ specifically for water treatment or sunscreen applications?	1,768	36.1	27.3	0	5	14	30
92	5-3-4	How important is testing nano-TiO ₂ skin penetration on different races and at different ages?	1,766	36.0	25.9	1	1	14	33
93	2-5-2	If nano-TiO ₂ were to become much more widely used and produced at a much higher volume, would packaging and shipping methods of nano-TiO ₂ change? If so, how would such change affect the potential release and exposure during transport, storage, and disposal?	1,755	35.8	25.7	1	2	11	35

Rank	Question		Total Points	Mean	Std. Dev.	Number of Participants Who...			
						Ranked in Top 10	Selected as High	Selected as Low	Did Not Select
94	2-3-2	Are data available or can they be collected or estimated for accident rates and routine product releases associated with various modes of shipping and storage? To what degree could best practices reduce such occurrences?	1,700	34.7	25.5	1	1	12	35
95	3-5	If nano-TiO ₂ production were to increase greatly, the packing and transport methods are likely to be changed as well. How would this affect the fate and transport of nano-TiO ₂ ?	1,619	33.0	23.9	0	1	13	35
96	2-3-1	How is nano-TiO ₂ shipped (i.e., what are the relative frequencies for shipments in bulk, paper bags, or drums, or by truck or rail)? How far is it shipped? In what quantities?	1,586	32.4	24.5	0	1	14	34
97	2-3-3	How is nano-TiO ₂ stored (e.g., in warehouses, sunscreen manufacturing plants, and water treatment facilities)?	1,576	32.2	25.2	0	2	15	32
98	2-3-4	Does the use of "ventilated paper bags" increase the possibility of accidental spillage during shipment and storage? Are any guidelines available on whether protective packaging (e.g., additional polyethylene lining) is warranted?	1,406	28.7	23.7	0	0	18	31
99	1-8	Is there a difference between the opacity of nano-TiO ₂ aggregates and conventional TiO ₂ particles of nominally similar size (e.g., because of light passing through pores in aggregates)? If so, what are the implications of such a difference?	1,347	27.5	24.9	0	1	21	27
100	2-3-5	Could vermin breach storage containers and contribute to environmental releases or become part of an environmental exposure pathway?	934	19.1	22.0	0	0	31	18

APPENDIX I. Pre-Workshop Handout: Nominal Group Technique Description

Nanomaterial Case Studies Workshop

Developing a Comprehensive Environmental Assessment Research Strategy
for Nanoscale Titanium Dioxide

Nominal Group Technique

Nominal Group Technique (NGT) is a structured process for a set of individuals to identify and rank a number of choices. Typically, several individuals (nominally a group) are convened and each person is afforded an equal opportunity to offer his or her view(s) about which choices are highest priority. When a large number of choices are under consideration, they may be grouped or consolidated into a more manageable number. A multi-voting process is then used to rank the choices.

In the U.S. EPA Nanomaterial Case Studies Workshop, the participants will be divided into two NGT groups of approximately 25 persons each. Each participant will be asked to state their top priority question (i.e., research or information need) within a 3-minute period (strictly enforced). This brief oral presentation (without visual aids) should include a statement or description of the research/information need and an explanation of why it is a high priority in relation to a comprehensive environmental assessment of nanoscale titanium dioxide (nano-TiO₂). As time permits, additional priorities may also be presented in subsequent rounds. If another participant precedes you and speaks to the issue you intended to present, you may use your time in support of the same issue or you may raise a different issue that you consider to also be a high priority.

Each research/information need will be noted on a large sheet of paper and displayed for the NGT group. A facilitator will work with the group to determine which questions can be consolidated into major research areas, thereby reducing the total number of questions to around 20-30. The consolidation process will be followed by multi-voting, which allows participants to assign weighted votes to the research areas they deem most important (for supporting a comprehensive environmental assessment of nano-TiO₂). The pre-workshop ranking process used multi-voting for the top 10 questions, and essentially the same process will be used during the workshop.

After the two NGT groups have ranked their top 10 priorities, the participants will come together in plenary to compare similarities and differences in their respective rankings. The combined lists of priorities will undergo multi-voting by the entire group of participants to select a final top 10 set of priority research areas. The participants will then be divided into 10 breakout groups, with each group assigned one of the top 10 priorities. The breakout groups will discuss their assigned areas and prepare short written summaries in a format to be provided.

Finally, the participants will reconvene in plenary and each of the 10 summaries will be presented. A primary objective of this final session will be to identify linkages among the 10 research areas.

APPENDIX J. Workshop Agenda



Nanomaterial Case Studies Workshop

Developing a Comprehensive Environmental Assessment Research Strategy
for Nanoscale Titanium Dioxide

September 29 and 30, 2009

Doubletree Guest Suites - Raleigh/Durham
2515 Meridian Parkway, Durham, NC

Final Agenda

Day 1 – Tuesday, September 29, 2009

7:00 – 8:00 AM	Registration / Check In <ul style="list-style-type: none">▪ Please sign in and receive your meeting materials.	Lobby in front of North Carolina Room
8:00 – 9:00 AM	Introduction <ul style="list-style-type: none">▪ Welcome▪ Purpose of workshop▪ Review agenda▪ Brief participant introductions	North Carolina Room <i>John J. Vandenberg & J. Michael Davis, U.S. EPA, National Center for Environmental Assessment</i> <i>Peter Bonner, ICF International</i>
9:00 – 10:00 AM	Presentation of Pre-Workshop Ranking Results <ul style="list-style-type: none">▪ Explain pre-workshop ranking of questions▪ Present pre-workshop rankings▪ Q&A by participants	North Carolina Room <i>Peter Bonner & Audrey Turley, ICF International</i>
10:00 – 10:15 AM	Explanation of the Nominal Group Technique (NGT)	North Carolina Room <i>Peter Bonner, ICF International</i>
10:15 – 10:45 AM	Break	
10:45 – 5:00 PM	NGT Groups Meet <ul style="list-style-type: none">▪ Individual input from each participant▪ Consolidate and prioritize questions▪ Groups break for a 1-hour lunch between 11:30 and 1:00 PM▪ ½-hour break in the afternoon at discretion of facilitators	Group A: North Carolina Room Group B: Durham Room Lunch buffet available in hotel restaurant Piney Point Grill & Seafood Bar (\$11.50/person, including drink)
5:00 – 5:30 PM	Closing for Day 1 & Preview of Day 2	North Carolina Room
5:30 PM	End of Day 1	

Day 2 – Wednesday, September 30, 2009

7:00 AM – 8:00 AM	Check In <ul style="list-style-type: none">▪ Please sign in.	Lobby in front of North Carolina Room
8:00 AM – 9:00 AM	Presentation of NGT Results <ul style="list-style-type: none">▪ Review, discuss, and reconcile two NGT groups' results	North Carolina Room
9:00 – 9:30 AM	Multi-voting Process	North Carolina Room
9:30 – 10:00 AM	Break	
10:00 – 10:30 AM	Discussion of Results of Multi-voting Process <ul style="list-style-type: none">▪ Assign top 10 results to 10 breakout groups	North Carolina Room
10:30 – 11:00 AM	Organization of Breakout Groups and Explanation of Charge	North Carolina Room
11:00 AM – 2:45 PM	Breakout Groups Meet <ul style="list-style-type: none">▪ Groups break for a 1-hour lunch sometime between 11:30 AM and 1:00 PM; buffet available in hotel restaurant Piney Point Grill & Seafood Bar (\$11.50/person, including drink)	Groups 1, 2, & 3: North Carolina Groups 4 & 5: Durham Room A Groups 6 & 7: Durham Room B Group 8: Raleigh Room 1 Group 9: Raleigh Room 2 Group 10: Library
2:45 – 3:00 PM	Break	
3:00 – 4:45 PM	Presentation of Breakout Group Results <ul style="list-style-type: none">▪ Focus on connections among the 10 research areas	North Carolina Room
4:45 – 5:25 PM	Conclusion <ul style="list-style-type: none">▪ Workshop participants offer final 10 words of advice to EPA	North Carolina Room
5:25 – 5:30 PM	Closing Remarks	<i>J. Michael Davis, U.S. EPA National Center for Environmental Assessment</i>
5:30 PM	Workshop Adjourns	

APPENDIX K. Results from Day 1 Nominal Group Technique Groups A and B

Table K-1. NGT Group A Results^{1, 2}

Rank	Points	Question(s) – Group A
A.1	182	<p>Are current EPA standard testing protocols adequate to determine nano-TiO₂ ecotoxicity? If not, what modifications or special considerations, if any, should be made in current ecological tests? For example, what are the differences in characterization of testing material (as raw material, in media, and in organisms), dispersion methods, and realistic exposure routes between testing conventional materials and nanomaterials (<u>commercial use</u>)? (5.2-1)</p> <p>Are the current EPA harmonized health test guidelines for assessing toxicity adequate to determine the health effects/toxicity of nano-TiO₂? (5.3-1)</p> <p>What criteria, especially associated with an inert colloid particle, should the EPA use when evaluating harmonized test protocols? (new)</p> <p>What set of widely shared reference samples of nano- and conventional TiO₂ would be most useful for integrating the results of different investigators regarding particle characterization and particle toxicology? (Mult-T)</p>
A.2	136	<p>How do TiO₂ properties change from the manufacturing stage, upon its incorporation into products, during its use, during storage, upon release to the environment, and upon environmental aging (<u>persistent state</u>)? (Mult-D)</p> <p>How do various manufacturing processes for nano-TiO₂ affect their physicochemical properties? (2.2-1)</p> <p>How do specific physicochemical properties, including particle surface treatments and aggregation/agglomeration, affect the fate and transport of nano-TiO₂ in various environmental media? (3-2)</p> <p>Do we have sufficient information to differentiate decision-critical characteristics across the various nanoscale TiO₂ sunscreens or water-formulations? (new)</p>
A.3	134	<p>Are available methods adequate to characterize nano-TiO₂ exposure via air, water, and food? What properties of nano-TiO₂ should be included in such exposure characterizations? (4-10)</p> <p>Do adequate methods exist to characterize nano-TiO₂ in relevant environmental matrices such as soil, sediment, or biofilms <u>and living organisms</u>? (Mult-B)</p>

¹ Strike-outs in the text of the research priorities indicate text the NGT group removed from the original questions; underlined text indicates text the NGT group added to the original questions. The original question number is given in parentheses following each bulleted questions.

² Two individuals assigned points to an item more than once. In these cases, the larger point quantity was counted and the smaller point quantity was ignored.

Rank	Points	Question(s) – Group A
A.4	123	<p>Which sources, pathways, and routes pose the greatest exposure potential to nano-TiO₂ for biota? ...for humans? (4-1)</p> <p>(Add to existing question) At what concentrations?...and for children? (Rev 4-1)</p> <p>Do particular species of biota and populations of humans have greater exposure potential (e.g., high-end exposures due to unusual conditions or atypical consumption)? In particular, do children get a higher exposure and/or dose? (4-3)</p>
A.5	76	<p>Where does nano-TiO₂ accumulate in the environment and in humans? What is the current background level in humans? (new)</p> <p>Does nano-TiO₂ bioaccumulate in humans? (4-C)</p>
A.6	74	<p>Is the available ecotoxicity evidence adequate to support ecological risk assessment for nano-TiO₂? If not, what is needed? (5.2-13)</p> <p>What are the sensitive environmental endpoints? (new)</p> <p>How do abiotic factors in the environment, such as UV, pH, oxygen level, and other chemicals, affect nano-TiO₂ and its ecological effects? (5.2-7)</p>
A.7	67	<p>What are the key environmental factors (e.g., pH, natural organic matter type and concentration, temperature) that facilitate or hinder nano-TiO₂ stability in the aqueous environment? Would humic acids or other common constituents or contaminants in water undergoing treatment affect the fate, including agglomeration/aggregation properties, of TiO₂? (3-13)</p>
A.8	65	<p>What needs to be standardized as terminology/nomenclature/ properties for current and future use? (new)</p> <p>Should the EPA promote a surface chemistry nomenclature system for use in particle life cycle analyses? (Mult-J)</p> <p>What is nano-TiO₂? Is the definition of less than 100 nm adequate? Or, should a dimension be derived based on the toxicological properties? (1-K)</p>
A.9a (tie)	64	<p>Should EPA set up comprehensive, user friendly databases with all information (such as metrics, toxicity data [current database], characterization, fate, etc.) to support comprehensive environmental assessments? (new)</p> <p>What has the EPA learned about the quality of the TiO₂ data in the open literature as applied to nano-TiO₂ and other particles? (new)</p>
A.9b (tie)	64	<p>What might be the primary mechanism(s) of action and <u>dose</u> of toxic effects in different species <u>or in different materials</u>? (5.2-5)</p> <p>Is there any evidence for nano-TiO₂ and conventional TiO₂ inducing distinctly different pathways of cell signaling or gene transcription? Do nano and conventional TiO₂ have different toxicological mechanisms of action or do the two materials simply have a surface-area or surface-coating dependent difference in potency? (5-G)</p>

Rank	Points	Question(s) – Group A
A.11	59	<p>Powders and particles have been produced for many decades in the industrialized world. Is there any epidemiological data from manufacturing sites of particles? Any adverse health data? (4-M)</p> <p>What kind of studies would provide the most suitable data to understand dose-response of occupational exposure to nanomaterials and health effects in humans? (including users – e.g., high end) (Rev 5.3-8)</p>
A.12	51	<p>What effect, if any, do coatings, dopings, carriers, dispersants, and emulsion types have on biopersistence and bioaccumulation? (3-8)</p> <p>Should TiO₂ particles with coatings and strongly chemisorbed species be evaluated separately for the purposes of environmental transport, ecotoxicity, and toxicity? (Mult-M)</p>
A.13	49	What are the ecological effects of long-term exposure to nano-TiO ₂ ? (5.2-9)
A.14	33	Are available fate and transport models applicable to nano-TiO ₂ ? If not, can they be adapted, or are new models required? (3-3)
A.15	25	<p>What are the relative contributions of different stages of the life cycles of water treatment and sunscreen products to environmental levels of nano-TiO₂ and associated contaminants in air, water, and soil? (3-1)</p> <p>What is the maximum quantity and frequency of personal sunscreen use in relation to season, geographic location, demographics, and other variables? (2.4-6)</p> <p>How much (metric tons) nano-TiO₂ is used in sunscreens, cosmetics and other products that are contained in products that may be disposed down the drain? If any of the pigment and other TiO₂ sources contain a fraction which is nano, this mass should be added into the volume. Further, the volume should be split out into different surface coatings, dopings, and size fractions (<u>also consumer exposure</u>). (4-F)</p>
A.16	22	What are each scientific field's roadblocks that currently limit scientific reliability/reproducibility and the public's confidence in the resulting risk assessments? What are the cross-disciplinary impediments (<u>worker bio monitoring</u>)? (Mult-Q)
A.17	18	What is the concentration of each unique TiO ₂ material in WWTP effluent, sediment near WWTPs, and soils amended with sewage sludge? (new)
A.18	15	<p>What are the surface properties, particularly with respect to reactive oxygen species, of various forms of nano-TiO₂ in the deep lung, on the skin, and in drinking water (with respect to chlorine chemistry)? What predictive tests will describe their effects in ways useful for risk assessment? What happens when you burn TiO₂? (new)</p> <p>What properties drive induction of an adverse response at environmentally and human-relevant levels and are there thresholds in context of "background" body burdens - and accounting for PK: distribution in considering whether/what tissue-specific body burden should be used as the dose metric - and how this can inform a population threshold (toward identifying a 'safe' level)? (new)</p>

Rank	Points	Question(s) – Group A
A.19	10	Do adequate methods exist to char Nano-TiO ₂ has anti-bacterial and anti-fungal properties. What are the effects of both photocatalytic and photostable nano-TiO ₂ on the biodiversity of microorganisms? (5.2-11)
A.20	9	What is the potential for reproductive and developmental effects of nano-TiO ₂ ? (5.3-9)
A.21	8	To assure appropriate linking of environmental/exposure and internal dose metrics, what common features should be characterized and standardized for environmental and human-relevant conditions? (new)
A.22	6	Is dermal penetration a prerequisite to health effects, including immunological effects? (new)
A.23	5	What properties are most closely tied to the observed biological responses in TiO ₂ toxicity studies, and can we develop predictive models of TiO ₂ toxicity based on properties data? (5-Q)
A.24	0	Do we need to consider comparative ecotox and human risks across nanomaterials for a specific purpose (e.g., nano-TiO ₂ and nano-ZnO in sunscreens)? (new)

Table K-2. NGT Group B Results¹

Rank	Points	Question(s) – Group B
B.1	155	<p>How do surface coatings <u>and physical and chemical properties</u> affect environmental chemistry, and toxicity? Do WWTP processes affect surface coatings? What natural particle coatings are added in the environment (e.g., humic and fulvic acids) and how do these natural coatings influence environmental fate, chemistry, and toxicity? (Mult. C)</p> <p>How do specific physicochemical properties, including particle surface treatments and aggregation/agglomeration affect the fate and transport of nano-TiO₂ in various environmental media? <u>How can species be described as they move from source to sink?</u> (3-2)</p> <p>What effect, if any, do coatings, dopings, carriers, dispersants, and emulsion types have on biopersistence and bioaccumulation? (3-8)</p> <p>What factors determine whether and to what extent aggregation or agglomeration of Nano-TiO₂ occurs? (1-6)</p>
B.2	123	Are available methods adequate to characterize nano-TiO ₂ exposure via air, water, and food? What properties of nano-TiO ₂ should be included in such exposure characterizations? (4-10)

¹ Strike-outs in the text of the research priorities indicate text the NGT group removed from the original questions; underlined text indicates text the NGT group added to the original questions. The original question number is given in parentheses following each bulleted questions.

Rank	Points	Question(s) – Group B
B.3	111	<p>Are current EPA standard testing protocols adequate to determine nano-TiO₂ ecotoxicity/health effects? If not, what considerations, if any, should be made in current ecological tests? For example, what are the differences in characterization of testing materials (as raw material, in media, and in organisms), dispersion methods, and realistic exposure routes between testing conventional materials and nanomaterials? (5.2-1)</p> <p>Are the current EPA harmonized health test guideline for assessing toxicity adequate to determine the health effects/toxicity of nano-TiO₂? (5.3-1)</p> <p>Are we sure we are assessing TiO₂ (or other nanomaterials) in the experiments we perform (eco/human)? (new)</p>
B.4	110	<p>Which sources, pathways and routes pose the greatest exposure potential to nano-TiO₂ for biota? For humans? (<u>Epi studies – human and environmental</u>) (4-1)</p> <p>What are the relative contributions of different stages of life cycles of water treatment, sunscreen, <u>and other applications</u> and products to environmental levels of nano-TiO₂ and associated contaminants in air, water, and soil? (3-1)</p>
B.5	103	<p>What are the effects of long-term exposures in relevant human and ecological populations for specific nano-mixtures of concern (e.g., neurological, reproductive, integument “skin”)? Need to develop comprehensive health data. (new)</p> <p>How do you prioritize to get specific health effects data on specific TiO₂s of concern, based on levels in the environment or based on short-term effect data? (Think PCBs) (new)</p> <p>What are the chronic, long-term effects of nano-TiO₂ (eco and human effects)? (new)</p>
B.6	101	<p>Just to re-emphasize the importance of chemical and physical characterization at a number of stages in addressing possible toxicity of nanomaterials. (Mult. I)</p> <p>What makes one type of nanoparticle more active or toxic than another? (Mult. S)</p>
B.7	70	<p>What is the global environmental content of nano-TiO₂ now and in the future? (new)</p> <p>Ecologically is TiO₂ a point source or regional exposure problem? If a regional distribution issue, what are concentration gradients in key media? (new)</p> <p>By region and environmental segment (soil, water, etc.), what is known about the background concentration <u>and characteristics</u> of nano-TiO₂ due to natural or non anthropogenic processes? (1A)</p>

Rank	Points	Question(s) – Group B
B.8	67	<p>What parameters should be used to characterize worker (or consumer or general human) exposure in a way that is compatible with hazard information? (<u>Exposure matches hazard</u>) (Rev 4-6)</p> <p>What concentrations, routes, frequencies, and durations characterize worker exposures to nano-TiO₂ across the life cycle and within certain stages (e.g., manufacturing) (4-6)</p>
B.9	60	<p>Is the available <u>biological effects</u> evidence adequate to support ecological risk assessment for nano-TiO₂? If not, what is needed? (5.2-13)</p> <p>What are the fundamental biological responses of nano-TiO₂ interactions at the cellular level (as dictated by its physical and chemical characteristics)? (<u>Dose interactions</u>) (5-K)</p> <p>What might be the primary mechanisms of action of toxic effects in different species? (5.2-5)</p>
B.10	59	<p>How do TiO₂ properties change from the manufacturing stage, upon its incorporation into products, during its use, during storage, upon release to the environment, upon environmental aging, <u>and in different compartments</u>? (Mult D)</p> <p>Have the life cycle <u>flows (intentional and unintentional) and properties of nano-TiO₂ in different applications been adequately characterized? If not, is the general problem that methods do not exist or that existing methods have not been widely applied? If methods are needed, what properties should they measure?</u> (1-2)</p>
B.11a (tie)	55	<p>What are the important metrics <u>and standards</u> that we need to use to characterize nano-TiO₂? (1-J)</p> <p><u>What is the role of standards or reference materials for integrating the results of different investigators regarding particle characterization and particle toxicology? What standards or reference materials are needed?</u> (Mult T, modified)</p>
B.11b (tie)	55	<p>Can we develop a decision-tree framework and best practices to facilitate environmental assessment of individual nanomaterials? (new)</p> <p>Would a toxicity – application – exposure – LCA – order in a decision tree be workable for conducting a CEA for nano-TiO₂? (new)</p> <p>How do we integrate analytical methods used to characterize risk (mass flow, life cycle) to evaluate and compare environmental trade-offs? (new)</p>
B.13	38	<p>What is the difference between nano-TiO₂ and non-nano-TiO₂? (new)</p>
B.14a (tie)	36	<p>Screen nano-mixtures of concern using modern methods in toxicology for determining potential adverse effects (human and eco)? (new)</p> <p>Are there data and methods that allow us to expand nano-scale TiO₂ information into comprehensive chemical computational chemistry, toxicology, neurobiology? If not, what do we need to do to achieve such a goal? (new)</p>

Rank	Points	Question(s) – Group B
B.14b (tie)	36	Are available fate and transport models applicable to nano-TiO ₂ ? If not, can they be adapted, or are new models required?
B.16a (tie)	24	How do abiotic factors in the environment, such as UV, pH, oxygen level, and other chemicals affect nano-TiO ₂ and its ecological/ <u>human</u> effects? (5.2-7) How do different lighting scenarios in different matrices cause coatings, size, and geometry to affect TiO ₂ surface reactions? (new) To what extent do photocatalytic properties of nano-TiO ₂ contribute to dermal effects? (5.3-7)
B.16b (tie)	24	What waste products, <u>feedstocks</u> , or other byproducts, both nanoscale and larger, might be released, and in what quantities, for nano-TiO ₂ manufacturing processes? (<u>Collateral damage</u>) (2.2-4)
B.18	20	Can <u>any</u> the photocatalytic properties of or <u>interactions</u> with nano-TiO ₂ cause other unintended substances to form, for example, degradation products in various environmental media; or <u>to degrade/destroy</u> (e.g., <u>biological activity</u>)? (3-9)
B.19a (tie)	18	Do we have comprehensive physicochemical characterization data (non-proprietary) on nano-TiO ₂ used in sunscreen or water treatment products? (1-C)
B.19b (tie)	18	What is the ultimate sink for nano-TiO ₂ in the environment? What are surface water, sediment, and soil nano-TiO ₂ concentrations? This should be understood for each of the different surface coatings, dopings, and size fractions. Are there background concentrations? If so, natural nano-TiO ₂ should be fully characterized. (4-T)
B.21a (tie)	17	In addition to arsenic and cadmium, do other compounds, <u>such as metal organic frameworks (MOFs)</u> , show different uptake <u>and/or bioaccumulation</u> in the presence of nano-TiO ₂ ? Are the <u>toxicities and/or bioaccumulation</u> of arsenic, cadmium and other chemicals affected by nano-TiO ₂ ? Conversely, do other compounds, <u>such as MOFs</u> , affect the uptake, toxicity, <u>and/or bioaccumulation</u> of nano-TiO ₂ ? (5.2-12)
B.21b (tie)	17	Is the current information on nano-TiO ₂ skin permeation sufficient for risk assessment, <u>in particular, regarding the roles of particle properties and skin condition or factors affecting skin penetration</u> ? (5.3-2)
B.23	14	How can EPA partner with other agencies and industry to better achieve the goals of the CEA? (new)

Rank	Points	Question(s) – Group B
B.24	13	What materials does nano-TiO ₂ replace in sunscreens and waste water treatment? Is there a net positive environmental impact to replacing these materials? (2-N)
B.25	9	At what level of ecological organization are we concerned given TiO ₂ is mildly toxic based on Table 5-3 in the Case Study? (new)
B.26	0	Can we characterize the nano-TiO ₂ effect as it would respond in a mixture? (new)

APPENDIX L. Results from Day 2 Plenary Multi-Voting

Table L-1. Plenary Multi-voting^{1,2}

Research Priority ¹		Consolidated NGT Priorities	Points ²
1	Are current EPA standard testing protocols adequate to determine nano-TiO ₂ ecotoxicity? If not, what modifications or special considerations, if any, should be made in current ecological tests? For example, what are the differences in characterization of testing material (as raw material, in media, and in organisms), dispersion methods, and realistic exposure routes between testing conventional materials and nanomaterials (<u>commercial use</u>)? (5.2-1)		
	Are the current EPA harmonized health test guidelines for assessing toxicity adequate to determine the health effects/toxicity of nano-TiO ₂ ? (5.3-1)	A.1 B.3	337
	What criteria, especially associated with an inert colloid particle, should the EPA use when evaluating harmonized test protocols? (new)		
	What set of widely shared reference samples of nano- and conventional TiO ₂ would be most useful for integrating the results of different investigators regarding particle characterization and particle toxicology? (Mult-T)		

¹ Strike-outs in the text of the research priorities indicate text the NGT group removed from the original questions; underlined text indicates text the NGT group added to the original question. The original question number is given in parentheses following each bulleted question.

² A few individuals assigned points incorrectly. They either assigned points to an item more than once or assigned points to an item that was not eligible, i.e., lower-ranked items that were not on the slate for voting. In cases where items that received more than one set of points, the higher point quantity was counted and the lower point quantity was ignored. Ineligible items assigned points were ignored.

Research Priority ¹	Consolidated NGT Priorities	Points ²
<p>2</p> <p>How do TiO₂ properties change from the manufacturing stage, upon its incorporation into products, during its use, during storage, upon release to the environment, upon environmental aging, <u>and in different compartments</u>? (Mult D)</p> <p>How do various manufacturing processes for nano-TiO₂ affect their physicochemical properties? (2.2-1)</p> <p>How do specific physicochemical properties, including particle surface treatments and aggregation/agglomeration, affect the fate and transport of nano-TiO₂ in various environmental media? (3-2)</p> <p>Do we have sufficient information to differentiate decision-critical characteristics across the various nanoscale TiO₂ sunscreens or water-formulations? (new)</p> <p>Have the life cycle <u>flows (intentional and unintentional)</u> and properties of nano-TiO₂ in different applications been adequately characterized? (1-2)</p>	<p>A.2 B.10</p>	<p>274</p>
<p>3</p> <p>Are available methods adequate to characterize nano-TiO₂ exposure via air, water, and food? What properties of nano-TiO₂ should be included in such exposure characterizations? (4-10)</p> <p>Do adequate methods exist to characterize nano-TiO₂ in relevant environmental matrices such as soil, sediment, or biofilms <u>and living organisms</u>? (Mult-B)</p>	<p>A.3 B.2</p>	<p>260</p>

Research Priority ¹	Consolidated NGT Priorities	Points ²
<p>4</p> <p>How do surface coatings <u>and physical and chemical properties</u> affect environmental chemistry, and toxicity? Do WWTP processes affect surface coatings? What natural particle coatings are added in the environment (e.g., humic and fulvic acids) and how do these natural coatings influence environmental fate, chemistry, and toxicity? (Mult. C)</p> <p>How do specific physicochemical properties, including particle surface treatments and aggregation/agglomeration affect the fate and transport of nano-TiO₂ in various environmental media? <u>How can species be described as they move from source to sink?</u> (3-2)</p> <p>What effect, if any, do coatings, dopings, carriers, dispersants, and emulsion types have on biopersistence and bioaccumulation? (3-8)</p> <p>What factors determine whether and to what extent aggregation or agglomeration of Nano-TiO₂ occurs? (1-6)</p> <p>Just to re-emphasize the importance of chemical and physical characterization at a number of stages in addressing possible toxicity of nanomaterials. (Mult. I)</p> <p>What makes one type of nanoparticle more active or toxic than another? (Mult. S)</p>	<p>B.1 B.6</p>	<p>239</p>
<p>5</p> <p>Which sources, pathways, and routes pose the greatest exposure potential to nano-TiO₂ for biota? ...for humans? (4-1)</p> <p>(Add to existing question) At what concentrations? <u>...and for children?</u> (Rev 4-1)</p> <p>Do particular species of biota and populations of humans have greater exposure potential (e.g., high-end exposures due to unusual conditions or atypical consumption)? In particular, do children get a higher exposure and/or dose? (4-3)</p> <p>What are the relative contributions of different stages of life cycles of water treatment, sunscreen, <u>and other applications</u> and products to environmental levels of nano-TiO₂ and associated contaminants in air, water, and soil? (3-1)</p>	<p>A.4 B.4</p>	<p>237</p>

Research Priority ¹	Consolidated NGT Priorities	Points ²
<p>6</p> <p>What is the global environmental content of nano-TiO₂ now and in the future? (new)</p> <p>Ecologically is TiO₂ a point source or regional exposure problem? If a regional distribution issue, what are concentration gradients in key media? (new)</p> <p>By region and environmental segment (soil, water, etc.), what is known about the background concentration <u>and characteristics</u> of nano-TiO₂ due to natural or non anthropogenic processes? (1A)</p> <p>Where does nano-TiO₂ accumulate in the environment and in humans? What is the current background level in humans? (new)</p> <p>Does nano-TiO₂ bioaccumulate in humans? (4-C)</p>	<p>A.5 B.7</p>	<p>185</p>
<p>7</p> <p>What might be the primary mechanism(s) of action <u>and dose</u> of toxic effects in different species <u>or in different materials</u>? (5.2-5)</p> <p>Is there any evidence for nano-TiO₂ and conventional TiO₂ inducing distinctly different pathways of cell signaling or gene transcription? Do nano and conventional TiO₂ have different toxicological mechanisms of action or do the two materials simply have a surface-area or surface-coating dependent difference in potency? (5-G)</p> <p>Is the available <u>biological effects</u> evidence adequate to support ecological risk assessment for nano-TiO₂? If not, what is needed? (5.2-13)</p> <p>What are the fundamental biological responses of nano-TiO₂ interactions at the cellular level (as dictated by its physical and chemical characteristics)? (<u>Dose interactions</u>) (5-K)</p>	<p>A.9b B.9</p>	<p>155</p>
<p>8</p> <p>What are the effects of long-term exposures in relevant human and ecological populations for specific nano-mixtures of concern (e.g., neurological, reproductive, integument "skin")? Need to develop comprehensive health data. (new)</p> <p>How do you prioritize to get specific health effects data on specific TiO₂s of concern, based on levels in the environment or based on short-term effect data? (Think PCBs) (new)</p> <p>What are the chronic, long-term effects of nano-TiO₂ (eco and human effects)? (new)</p>	<p>A.13 B.5</p>	<p>152</p>

Research Priority ¹		Consolidated NGT Priorities	Points ²
9a (tie)	<p>Is the available ecotoxicity evidence adequate to support ecological risk assessment for nano-TiO₂? If not, what is needed? (5.2-13)</p> <p>What are the sensitive ecological endpoints? (new)</p> <p>How do abiotic factors in the environment, such as UV, pH, oxygen level, and other chemicals, affect nano-TiO₂ and its ecological effects? (5.2-7)</p>	A.6	66
9b (tie)	<p>Should EPA set up comprehensive, user friendly databases with all information (such as metrics, toxicity data [current database], characterization, fate, etc.) to support comprehensive environmental assessments? (new)</p> <p>What has the EPA learned about the quality of the TiO₂ data in the open literature as applied to nano-TiO₂ and other particles? (new)</p>	A.9a	66
11	<p>What needs to be standardized as terminology/nomenclature/properties for current and future use? (new)</p> <p>Should the EPA promote a surface chemistry nomenclature system for use in particle life cycle analyses? (Mult-J)</p> <p>What is nano-TiO₂? Is the definition of less than 100 nm adequate? Or, should a dimension be derived based on the toxicological properties? (1-K)</p>	A.8	64
12	<p>What are the important metrics and standards that we need to use to characterize nano-TiO₂? (1-J)</p> <p><u>What is the role of standard reference materials</u> for integrating the results of different investigators regarding particle characterization and particle toxicology? <u>What is needed?</u> (Mult T, modified)</p>	B.11a	61
13	<p>What parameters should be used to characterize worker (or consumer or general human) exposure in a way that is compatible with hazard information. (<u>Exposure matches hazard</u>) (Rev 4-6)</p> <p>What concentrations, routes, frequencies, and durations characterize worker exposures to nano-TiO₂ across the life cycle and within certain stages (e.g., manufacturing) (4-6)</p>	B.8	59
14	<p>What are the key environmental factors (e.g., pH, natural organic matter type and concentration, temperature) that facilitate or hinder nano-TiO₂ stability in the aqueous environment? Would humid acids or other common constituents or contaminants in water undergoing treatment affect the fate, including agglomeration/aggregation properties, of TiO₂? (3-13)</p>	A.7	43

Research Priority ¹		Consolidated NGT Priorities	Points ²
15	<p>Can we develop a decision-tree framework and best practices to facilitate environmental assessment of individual nanomaterials? (new)</p> <p>Would a toxicity – application – exposure – LCA – order in a decision tree be workable for conducting a CEA for nano-TiO₂? (new)</p> <p>How do we integrate analytical methods used to characterize risk (mass flow, life cycle) to evaluate and compare environmental trade-offs? (new)</p>	B.11b	38
16	<p>Powders and particles have been produced for many decades in the industrialized world. Is there any epidemiological data from manufacturing sites of particles? Any adverse health data? (4-M)</p> <p>What kind of studies would provide the most suitable data to understand dose-response of occupational exposure to nanomaterials and health effects in humans? (Rev 5.3-8)</p>	A.11	33
17	<p>What effect, if any, do coatings, dopings, carriers, dispersants, and emulsion types have on biopersistence and bioaccumulation? (3-8)</p> <p>Should TiO₂ particles with coatings and strongly chemisorbed species be evaluated separately for the purposes of environmental transport, ecotoxicity, and toxicity? (Multi-M)</p>	A.12	29

APPENDIX M. Template and Instructions for Breakout Group Reports – Word Document

Nanomaterial Case Studies Workshop – Report from Breakout Group []

Title of priority area (as assigned):

Breakout group members:

Short description:

[Prepare short paragraph, individual sentences, or bullet statements referring to specific questions subsumed under this priority area.]

Why this research/information is needed and of high importance:

[Explain how it will support comprehensive environmental assessment efforts.]

Extended description (1-3 pages):

[This text should flesh out the topic as fully as possible.

Start with an overview description of the topic area.

Include discussion of the generality/specificity of the topic area, i.e.: Does it pertain to only a specific application of nano-TiO₂? Does it pertain to nano-TiO₂ generally but only to nano-TiO₂? Does it pertain to certain nanomaterials other than nano-TiO₂ or to nanomaterials in general?

Elaborate on each specific question (research / information need) consolidated under this heading, explaining how each relates to or supports the general topic.

State the generality/specificity of each specific question, i.e.: Is it limited to a specific application using nano-TiO₂? Does it pertain to nano-TiO₂ generally but only to nano-TiO₂? Does it pertain to certain nanomaterials other than nano-TiO₂ or to nanomaterials in general?]

Other, related priority areas:

[Refer to any of the other 9 top priority areas and explain how this topic is connected to them (e.g., progress in one area will facilitate another, one is logically necessary before the other can be done, both need to be done simultaneously or in alternating sequence).]

APPENDIX N. Template and Instructions for Breakout Group Reports – PowerPoint Presentation

Breakout Group [] Summary

Title of priority area:

Members:

Description:

[Short description (sentences or bullet statements referring to specific questions subsumed under this Priority area)]

Why this work is needed and is of high importance:

[One to two sentences saying why this work/information is needed and of high importance]

Other, related priority areas:

[Refer to any of the other 9 top priority areas and briefly explain how this topic is connected]