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Transparent Stakeholder Engagement in Practice: Lessons Learned from Applying Comprehensive Environmental Assessment to Research Planning for Nanomaterials

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ABSTRACT

As efforts to develop new applications of engineered nanoscale materials (ENMs) continue to grow, so too has interest in the environmental, health, and safety (EHS) implications of these materials. However, thorough evaluation and interpretation of such implications could require substantial resources (e.g., estimated as >$120 million per year in federal funding 2013–2017). A structured, strategic approach for transparently planning research would support improved linkages between ENM research and risk assessments, and thereby enhance the utility of financial and other resources for EHS studies of ENMs. For this reason, we applied Comprehensive Environmental Assessment (CEA) as an approach to provide transparent input into research planning for 2 types of ENMs: nanoscale titanium dioxide and nanoscale silver. For each of these CEA applications, we employed a collective judgment method known as Nominal Group Technique (NGT) in 2 workshops sponsored by the US Environmental Protection Agency (USEPA). The objective of this paper is to present the outcomes of these CEA applications in the context of how our methodology can inform future efforts to identify collective goals in science (e.g., research priorities) through structured decision support approaches. Outcomes include clear lists of research priorities for each ENM developed through transparently engaging stakeholders having diverse technical and sector perspectives. In addition, we identified several procedural aspects that could be refined, including emphasizing breakout group interactions, identifying broad information priorities before more detailed research questions, and using rating rather than ranking prioritization methods. Beyond the research directions identified for specific ENMs, lessons learned about engaging stakeholders in research planning are expected to inform future research planning efforts for ENMs and other emerging materials across the scientific community. *Integr Environ Assess Manag* 2014;9999:XX–XX. © 2014 SETAC

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INTRODUCTION

A rise in research and development of nanoscale materials is driving an increasing amount of environmental, health, and safety (EHS) research on these materials (Roco 2005; Maynard et al. 2011). Indeed, the value of products incorporating engineered nanomaterials (ENMs) (materials containing engineered particles with at least 1 dimension between 1 and 100 nanometers [nm]) is predicted to exceed $1 trillion globally by 2015, whereas US federal funding for ENM EHS research grew 3-fold from 2005 to 2010 (Roco 2005; Youtie et al. 2011). The plethora of ENM applications and increasingly available data are spurring a number of efforts to carry out ENM risk assessments, but such efforts consistently point to a need for more data, and indeed new methodologies, to support robust conclusions about risks or benefits to human or ecological populations (Hansen et al. 2008; Savolainen et al. 2010; Aschberger et al. 2011; Yokel and Macphail 2011; Hendren et al. 2013). Progress has been made primarily in identifying acutely toxic materials and direct potential exposures (e.g., occupational exposures [Grieger et al. 2012]), but environmentally relevant scenarios remain difficult to predict or mitigate given the emergent status of mechanistic data combined with the interdisciplinary nature of ENM and the breadth of ENM types (Wiesner et al. 2009). Because not all scenarios can be investigated directly, reliable methods are needed to inform research planning in terms of priority data gaps and methods development to support subsequent risk assessment. Numerous reports and manuscripts on "ENM research gaps" exist (Tsuji et al. 2006; USEPA 2009c; NNI 2011; NRC 2012; von der Kammer et al. 2012), and similar efforts to identify new priority data gaps will likely continue as progress is made in addressing identified gaps. Yet,

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little discussion is found in the literature of methods for structuring a transparent, participatory process to identify such gaps in relation to future risk assessment and risk management of these materials (or other emerging technologies). A recent evaluation by the US National Research Council estimated that a minimum of $120 million in federal funding per year through 2017 is necessary to continue moving ENM EHS research forward in a timely manner (NRC 2012). Given the anticipated level of investment in ENM EHS research, a structured, strategic approach to engage stakeholders in identifying and prioritizing research and testing needs that are targeted to support future risk assessments is needed to maximize the impact of these investments on EHS (NRC 2013).

One such structured approach used by the US Environmental Protection Agency (USEPA) is Comprehensive Environmental Assessment (CEA) (Davis 2007; Powers et al. 2012). We applied CEA to inform research planning for 2 types of nanomaterials: nanoscale titanium dioxide (nano-TiO_2) and nanoscale silver (nano-Ag) (USEPA 2010b; 2012). Compared with most other efforts to identify research needs for ENM risk assessment purposes (e.g., Morgan 2005; Kandlikar et al. 2007; Wardak et al. 2008), the CEA approach offers several structural and methodological advantages for transparently reaching a collective goal with equal contribution from diverse participants (Powers et al. 2012; Davis 2013); transparency in the CEA approach refers primarily to an explicit process for making judgments and reaching conclusions that can be documented such that key facts, values, and an objective measure of the participants' collective judgment of priorities are recorded (e.g., in a summary report) (see Powers et al. 2012; Davis 2013). First, CEA provides a holistic framework (Figure 1) to organize complex information and facilitate the consideration of available data on a broad array of topics (e.g., product life cycle, environmental transport and transformation, ecological and human health impacts). Second, CEA applications have primarily used case studies on particular types of ENMs (e.g., nano-Ag) to facilitate identifying more specific research gaps than has been generally feasible in efforts thus far to evaluate data gaps for ENMs as a broad class of materials (USEPA 2010a; 2010b; ICF 2011; RTI International 2012; USEPA 2012; 2013). Despite progress in generating data on ENM effects in human and ecological populations, the use of these data in predicting ENM risks is constrained by diverse study designs that often preclude a direct comparison of outcomes from different studies (Schrurs and Lison 2012). Identifying more specific research gaps through the CEA approach can inform efforts to generate data in a better coordinated manner with the intention of supporting subsequent risk analyses. Finally, a key part of the CEA approach is the use of collective judgment methods to engage a group of individuals with diverse technical expertise and stakeholder perspectives in the process of identifying and prioritizing research needs that support future assessments and risk management efforts. This part of CEA is directly responsive to recent guidance to "foster engagement with stakeholders" in developing ENM research strategies (NRC 2013).

Collective judgment essentially refers to a process for reaching a decision that involves a group of individuals, but there are numerous ways of accomplishing this. As part of the CEA process for nano-TiO_2 and nano-Ag research planning, we employed a collective judgment method known as Nominal Group Technique (NGT) (Delbecq and Van de Ven 1971),

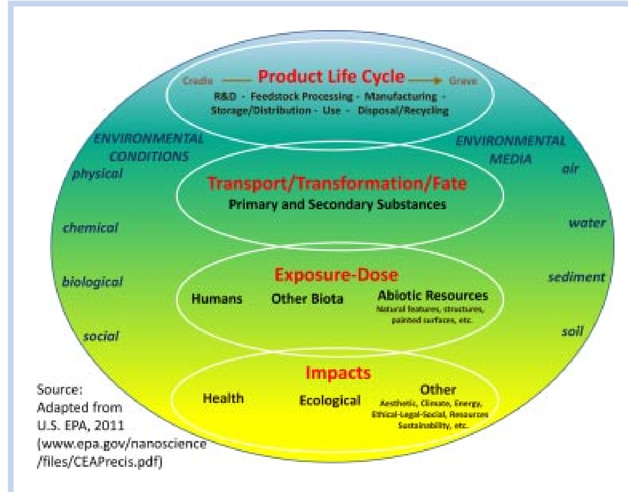

Figure 1. The CEA framework is used to structure available information for consideration by experts participating in the CEA process. Information considered is on 1 or more materials, technologies, or chemicals related to the product life cycle, environmental transport and fate, exposure and dose in receptors (i.e., humans, ecological populations, abiotic resources such as the built environment), and the impacts that such exposures might have in receptors. Notably, the potential influence of environmental conditions and media is considered throughout the framework. The font colors denote different components of the framework (e.g., main topic areas in red font, sub-areas in black font, and cross-topic area considerations in font). The gradual color change in the background symbolizes the related nature of each topic area within the CEA framework, and encourages participants in the CEA process to consider interactions between each topic area (e.g., environmental transport of a material leading to exposure and dose in human or ecological populations), rather than thinking of each topic separately.
CEA = Comprehensive Environmental Assessment.

which will be described in detail later. The objective of this paper is to present the outcomes of these CEA applications in the context of describing how our methodology can inform future efforts to identify collective goals in science (e.g., research priorities) through a structured decision support approach. This information will help inform research planning methods for nanomaterials, as well as other emerging technologies similarly characterized by rapid growth and pervasive uncertainty about potential impacts.

METHODS

ENM workshops

The fundamental objective of both EPA-sponsored workshops was to use a transparent, structured approach for recommending research that could support subsequent risk assessment and risk management. This objective was achieved through collective judgment workshops on nano-TiO_2 and nano-Ag that engaged a diverse group of individuals in: 1) identifying key research areas to inform future assessment and risk management efforts for these ENMs, and 2) prioritizing these research areas. Minimizing bias while maximizing the potential for participants to offer their independent view points was a key principle in developing the workshop process and accompanying materials. Accordingly, at each collective judgment workshop, NGT was used to structure input from participants on data needs, information gaps, and research priorities within the CEA framework (Figure 1). Participants for each workshop were selected to represent a balance of technical disciplines within the CEA framework (e.g., environmental fate, human exposure, ecological health) and organizational perspectives (e.g., academia, industry, nongovernmental organizations) (there was no overlap in participants between workshops). Each participant received a nominal monetary compensation for their time in preparing for and attending the workshop. More details on participant selection are available in workshop summary reports (USEPA 2010a; ICF 2011).

The "Nanomaterial Case Studies Workshop: Developing a Comprehensive Environmental Assessment Research Strategy for Nanoscale Titanium Dioxide" was held in Durham, NC, USA, 29–30 September, 2009. Forty-nine experts organized in 2 sub-groups identified 5 research topics and 18 research themes as top priorities (see USEPA 2010a for greater details on subgroup comparisons). The workshop culminated in a Workshop Summary Report, which contains additional details on the Nano-TiO_2 Workshop specifics (USEPA 2010a).

The "Nanomaterial Case Study Workshop: Developing a Comprehensive Environmental Assessment Research Strategy for Nanoscale Silver" was held in Research Triangle Park, NC, USA, 4–7 January, 2011. Twenty-three participants consolidated individual research objectives into 23 research themes. Reports and summary presentations were integrated into a Workshop Summary Report (ICF 2011).

Workshop preparations

Specific applications of nano-TiO_2 and nano-Ag were selected to focus participants' attention on the potentially unique research needs of a given nanomaterial in a particular application. The first case study explored the specific use of nano-TiO_2 in sunscreen and drinking water treatment, and the second case study focused on the use of nano-Ag in spray disinfectants (See USEPA 2010b and USEPA 2012 for greater detail on the procedure used to select the nanomaterial applications). A draft case study summary document was prepared for each nanomaterial application before each workshop to provide participants with a common background on the specific type of nanomaterial and application being considered (USEPA 2009b; 2010c). Even for relatively new technologies such as ENMs, an extensive amount of information was compiled in these documents, which were structured by the CEA framework (i.e., chapters on information areas represented in Figure 1). Readers are encouraged to consult these documents both to gain a better understanding of the CEA approach and for more detailed background information that laid the foundation for the research priorities identified here.

The case study approach acknowledges the epistemological limitation that it is not possible to generate generalizable rules or conclusions about a class of materials that cannot yet be defined, measured, or even named in a standardized manner (Thomas et al. 2013). However, it is possible to point to a specific example of a known ENM in use and derive conclusions that may also prove useful in planning research for the ENM in a variety of applications, or even ENMs as a class of materials. The case study approach is taken here, because risk must be assessed and risk management decisions made regardless of whether such general, standardized definitions are available. As stated in the USEPA's 2007 *Nanotechnology White Paper*, a case study approach has proved useful in identifying information gaps and linking such gaps to the risk assessment process for other materials (e.g., airborne particulate matter) and thus could provide insight on similar needs for ENMs (USEPA 2007).

The extended, structured data sets represented in each draft case study document were reviewed by a group of experts with diverse technical expertise (e.g., manufacturing, environmental fate, exposure, ecological effects, health effects, risk management) and sector perspectives (e.g., academia, government, industry, and nongovernmental organizations) (Supplemental Data Figure 1). Expert participants were then asked to categorize research questions listed at the end of each chapter using a web form. They assigned research questions to 1 of 4 categories: i) one of the top 10 priority questions, ranked from most to least important; ii) 1 of 15 unranked, high-priority questions that are important but not included as a top 10 priority question; iii) 1 of 10 questions of lowest priority; or iv) all remaining, unranked questions. This categorization served to convey what they thought was the most important research to inform a future CEA of the nanomaterial (i.e., research that would support carrying out risk assessments, life cycle assessments, cost-benefit analyses, etc., which could then be complied into the CEA framework for evaluation of risk-related tradeoffs).

Participants were also encouraged to submit modifications to existing questions or add new questions. One week before the workshop, each participant received a rank-ordered list of the questions based on the input from all of the individuals, plus a compiled list of any revised and newly submitted questions. For more details on how the preworkshop rankings were compiled, see the Workshop Summary Reports (USEPA 2010a; ICF 2011).

NGT method to ascribe collective judgments

The NGT was first developed by Delbecq and Van de Ven (1971) as a way for individuals to identify and rank choices through collective engagement and structured sharing of perspectives. This technique is perhaps most associated with approaches for brainstorming ideas with groups of individuals, a concept not unlike the identification of priority research gaps for a particular topic. A broad discussion on the brainstorming literature is outside the scope of this paper; however, information on how others have previously used NGT to identify key research gaps or priority issues related to a specific topic (e.g., seawater desalination) is available (NWRI 2000; 2003a; 2003b), and details on how the technique was applied in the context of the two ENM workshops are provided in the following sections.

A number of alternatives to NGT were considered in planning the workshop, including various types of multi-criteria decision analysis (Stahl et al. 2002; Linkov et al. 2007; Seager and Linkov 2008) and expert elicitation techniques (Cooke and Goossens 2004; Cooke and Probst 2006; USEPA 2009a). The NGT process was selected for a number of reasons. For instance, NGT allows for the inclusion of both qualitative and quantitative information, which is important because very little quantitative data related to risk analysis was available for either nano-TiO_2 or nano-Ag. In addition, compared with other approaches, NGT required a relatively low investment of time and other resources. Another potential benefit of NGT is the presentation of individual perspectives reflecting a mix of technical backgrounds and sector affiliations. Participants discussed the importance of particular research questions through a structured round-robin procedure. The participants voted for research priorities independently, simultaneously, and anonymously at the end of the process. This ensured that the final ranking represented each group member's input equally through a transparent process. This aspect of NGT may facilitate greater transparency in, and understanding of, the final ranking of research priorities.

We employed the NGT method in 5 steps. The steps are described in general terms here, with information specific to each workshop detailed in Workshop Summary Reports (USEPA 2010a; ICF 2011).

Step 1. Preworkshop exercises. Before the workshop, participants reviewed the information presented in the case study documents and ranked potential research questions listed at the end of each chapter. Participants reviewed the rankings as the first activity in the workshop, reflecting on emerging research objectives.

Step 2. Workshop round robins. Each participant was in turn allowed up to 3 minutes to present the research question that they thought was most important to pursue to support a future CEA of the nanomaterial. The objective of using this structured round-robin format for participant presentations was to encourage clear justifications or arguments for each proposed priority area. Although participants varied in how clearly they articulated an argument or justification, the format nonetheless provided an explicit opportunity for each individual to include their perspectives in the group's consideration of research priorities.

Step 3. Workshop consolidations. Research questions were consolidated via facilitated discussion with the participant group into a common research theme to reach a manageable number of topics for them to explore during breakout group sessions. Consolidation facilitated participants' focused consideration of potential ENM research directions through group dialog about the specific types of research identified. This focused consideration also helped support an improved understanding of each potential research direction.

Step 4. Workshop votings. Participants independently prioritized research themes through a multivoting process in which each participant assigned 10 points to the top priority theme, 9 points to the second most important, and so on down to 1 point.

Step 5. Workshop prioritizations. Points were tallied for each research theme to generate a prioritized list of research themes.

Subsequently, participants were assigned to breakout groups that developed a report highlighting the underlying individual research questions and discussing how such research would inform future assessment efforts. The breakout groups shared their report with all workshop attendees to foster additional input on each research theme.

Evaluating workshop results

To analyze the workshop outcomes in terms of the described goals, we compiled the research priorities from both workshops using data collected during the workshops. To evaluate whether and the extent to which the workshop process produced novel research questions, we analyzed the origin (i.e., case study document, preworkshop exercises, or the workshop itself) of all questions in the final priority list of research themes that resulted from each workshop. This analysis was done by tabulating the questions put forward in each respective case study, the corresponding preworkshop exercises, and the workshop of interest. Variability surrounding the order of prioritization for nano-Ag research themes was evaluated by graphing the median points allocated by participants versus the sum of points for each research theme in the nano-Ag workshop. Various trend or regression types (exponential, linear, logarithmic, polynomial, power) were evaluated, and the one with the best fit (i.e., highest R^2) was selected.

RESULTS AND DISCUSSION

The CEA approach was used to provide input into research planning for 2 types of ENMs: nanoscale titanium dioxide and nanoscale silver. In these applications of CEA, we employed a collective judgment method known as NGT in 2 workshops sponsored by the USEPA. We expect the results and discussion of these applications to inform future applications of structured, strategic approaches for research planning that support improved linkages between current ENM research planning and risk assessments, thereby maximizing time and financial resources for testing ENMs.

Results from applying the CEA approach to research planning for nano-TiO_2 and nano-Ag show 2 main findings: 1) the NGT workshop method engaged diverse perspectives in a systematic manner to provide each individual equal input in the outcome (Supplemental Data Figure 1), and 2) each workshop resulted in a clear list of priority research themes that integrated established themes of research needs with previously unidentified data gaps (Figure 2, Table 1). These results demonstrate that the CEA approach supports many of the factors recognized by the NRC and others as critical for assessing and managing potential risks of environmental contaminants such as ENM, namely: stakeholder engagement, transparency, and integrated, transdisciplinary research (NRC 2011; Anastas 2012). As discussed in the following sections, however, the approach had limitations that provide opportunities for improvement in future applications.

Systematically engaging diverse perspectives

The value of engaging diverse perspectives in CEA and science in general is not a novel concept (Rapport 1997), and indeed data indicate that environments that cultivate cross-disciplinary work generate more novel findings or outcomes than more homogenous environments (NAS 2004; Uzzi and Spiro 2005; Page 2007). However, implementing the integration and coalescing of diverse perspectives is not a simple task (National Academy of Sciences 2004; Harris et al. 2012), and thus many efforts are underway to improve integrative efforts in a variety of sectors, including research related to environmental and human health impacts (Anastas 2012) and merging of risk assessment and life cycle assessment methods (Linkov and Seager 2011). In the field of nanotechnology in particular, engaging as many relevant perspectives as possible early in the development of research to support decision making seems prudent given the multitude of disciplines in the field of nanotechnology (e.g., chemistry, physics, toxicology, engineering, ecology). For example, while engineers might understand certain parameters that must be included in designing ENM, toxicologists can provide valuable perspective on how such design choices might impact environmental and human health.

A distinction must be drawn between having multiple perspectives in a free form discussion about potential risks and benefits of certain design features or types of nanomaterials, versus engaging diverse perspective in a structured manner. Both demonstrate a commitment to including diverse stakeholders in the decision at hand (e.g., determining research priorities, policy making), yet a less structured discussion

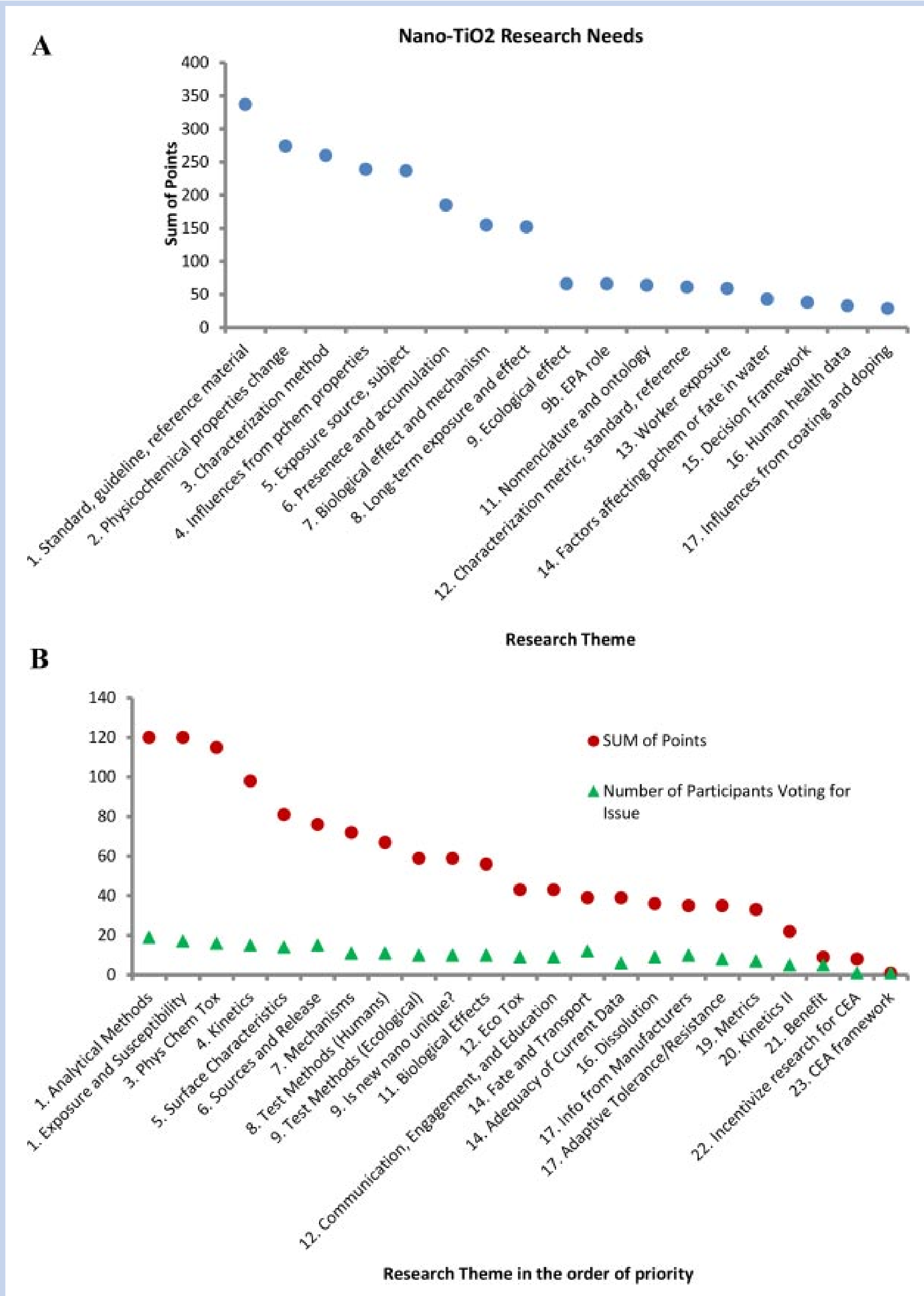

Figure 2. The sum of points (circles) and number of votes (triangles) of top priority research themes (*x*-axis) identified in the nano-TiO_2 workshop (**A**) and nano-Ag workshop (**B**). Participants in the nano-Ag workshop identified each research area with a name (e.g., "Analytical Methods"), whereas participants in the nano-TiO_2 workshop simply identified areas by number. For the nano-TiO_2 workshop, we developed short names for each numbered area to simplify the review of the topics in the figure (see Table 1 and Supplemental Data Table 1 for complete listing of all priority questions from each workshop). In the nano-Ag workshop (Figure 2B), there was general agreement between the sum of points (circles) allotted to each theme by all participants and the number of participants voting for each theme (triangles) (i.e., the larger the sum of the points, the larger the number of participants that voted for the theme, whereas the lower the sum of points, the smaller the number of participants that voted for the theme; indicating agreement between either measure of priority order). In the nano-TiO_2 workshop, the number of participants voting for each theme was not collected, and therefore the numbers of participants voting for each theme are not plotted.

approach can lead to a situation in which the outcome is driven by a subset of particularly vocal individuals. Furthermore, the direction that the group as a whole provides to decision makers might be left to interpretation by those developing a summary report. In contrast, a structured stakeholder engagement method, such as an NGT workshop, helps ensure that each individual is allowed both equal time to present their views to other stakeholders and equal input in the final outcome (e.g., a prioritized list of research gaps). As summarized in *Methods*, our process provided a method to structure interaction within a group of individuals with diverse perspectives. In addition, through a multivoting procedure, NGT facilitated each individual's having equal input in an outcome composed of all of their viewpoints.

Table 1. Top research priorities identified in CEA workshops for nano-TiO_2 and nano-Ag

Rank	Nano-TiO_2 questions	Nano-Ag questions
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 (commercial use)?	***Analytical Methods***
	• Are the current EPA harmonized health test guidelines for assessing toxicity adequate to determine the health effects/toxicity of nano-TiO_2?	• Do adequate analytical methods exist to detect and characterize exposure to nano-Ag via soil, water, and air?
	• What criteria, especially associated with an inert colloid particle, should the EPA use when evaluating harmonized test protocols?	• Do adequate analytical methods exist to detect and characterize nano-Ag in environmental compartments and in biota?
	• 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?	• Are there standard nano-Ag reference materials that can be used in exposure and effects testing to aid in comparison of results among investigators?
		• Are available methods adequate to characterize nano-Ag concentrations and associated exposure via relevant matrices such as:
		a. air?
		b. water?
		c. food?
		• At a minimum, what assays could be considered in a harmonized test guideline for determination of the human health effects of nano-Ag?
2	• How do TiO_2 properties change from the manufacturing stage, on its incorporation into products, during its use, during storage, on release to the environment, on environmental aging, and in different compartments?	***Exposure and Susceptibility***
	• How do various manufacturing processes for nano-TiO_2 affect their physicochemical properties?	• How do the following parameters affect [dose and exposure] (1) physiological characteristics, (2) behavior, (3) lifestages, and (4) susceptibility factors?
	• 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?	• What are the relevant susceptibility factors in terms of exposure?
	• Do we have sufficient information to differentiate decision-critical characteristics across the various nanoscale TiO_2 sunscreens or water-formulations?	• What kinds of exposure do these populations have, including physicochemical characteristics?
	• Have the life cycle flows (intentional and unintentional) and properties of nano-TiO_2 in different applications been adequately characterized?	• Do particular species of biota and particular human populations have greater potential for exposure to nano-Ag through the life cycle?
		• Which sources, pathways, and routes offer the greatest exposure potential to nano-Ag for humans?
		• What is the distribution of exposure intensities and frequencies of such exposures among homemakers, children, and maintenance personnel, and are these of concern for acute or chronic health effects?
3	• 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?	***Physical and Chemical Toxicity***
	• Do adequate methods exist to characterize nano-TiO_2 in relevant environmental matrices such as soil, sediment, or biofilms and living organisms?	• What physicochemical properties of nano-Ag can be used to predict toxicity to humans or biota?
		• How does surface coating affect toxicity to humans or biota?
		• To what extent do particle properties (e.g., size, shape, chemical composition, surface treatments) determine biological responses to nano-Ag?
		• Which physicochemical properties of nano-Ag are most essential to characterize before, during, and after toxicity experiments?

Table 1. (*Continued*)

Rank	Nano-TiO_2 questions	Nano-Ag questions
4	• How do surface coatings and physical and chemical properties 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?	***Kinetics and Dissolution***
	• 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? How can species be described as they move from source to sink?	• What is the half-life of nano-Ag in the environment?
	• 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-TiO_2 occurs?	
	• What is 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?	
5	• Which sources, pathways, and routes pose the greatest exposure potential to nano-TiO_2 for biota? For humans? At what concentrations? And for children?	***Surface Characteristics***
	• Do particular species of biota and populations of humans have greater exposure potential (e.g., high-end exposures because of unusual conditions or atypical consumption)? In particular, do children get a higher exposure or dose?	• How does surface coating affect the physicochemical properties of nano-Ag?
	• 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-TiO_2 and associated contaminants in air, water, and soil?	• *Do explosion risks exist for dried nano-Ag powders or nano-Ag powders modified with certain types of surface coatings?*
		• What effect, if any, do surface treatments of nano-Ag particles have on:
		• uptake?
		• biopersistence?
		• bioaccumulation?
		• biomagnification?
		• What effect, if any, do surface treatments of nano-Ag particles have on human exposures and uptake?
6	• *What is the global environmental content of nano-TiO_2 now and in the future?*	***Sources and Release***
	• *Ecologically is TiO_2 a point source or regional exposure problem? If a regional distribution issue, what are concentration gradients in key media?*	• How effectively is nano-Ag removed from sewage and industrial process water by wastewater treatment technology, and can information on the removal of conventional silver be applied to nano-Ag removal?
	• *By region and environmental segment (soil, water, etc.), what is known about the background concentration and characteristics of nano-TiO_2 due to natural or non anthropogenic processes?*	
	• Where does nano-TiO_2 accumulate in the environment and in humans? What is the current background level in humans?	• What are the potential exposure vectors by which nano-Ag or nano-Ag by-products could be released to the environment at the various life-cycle stages?
	• Does nano-TiO_2 bioaccumulate in humans?	
		• What are the associated feedstocks and by-products; of these feedstocks and by-products, which might be released, in what quantities, and via which pathways?
		• What are the release rates of all sources of nano-Ag into the environment?
7	• What might be the primary mechanism(s) of action and dose of toxic effects in different species or in different materials?	***Mechanisms of Nanoscale Silver Toxicity***
	• Do nano and conventional TiO_2 have different toxicological mechanisms of action or do the two materials simply have a surface-area or surface-coating dependent difference in potency?	• What are the fundamental biological responses to and associated mechanisms of nano-Ag exposure at the cell, organ, and whole-animal levels?

Table 1. (*Continued*)

Rank	Nano-TiO_2 questions	Nano-Ag questions
	• Is the available biological effects evidence adequate to support ecological risk assessment for nano-TiO_2? If not, what is needed?	
	• What are the fundamental biological responses of nano-TiO_2 interactions at the cellular level (as dictated by its physical and chemical characteristics)? (Dose interactions)	• Are the effects observed for exposure to nano-Ag due to silver ion release or the presence of nanoparticles? Can this be distinguished?
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.	***Test Methods—Mammals/Humans***
	• How do you prioritize to get specific health effects data on specific TiO_2s of concern, based on levels in the environment or based on short-term effect data? (Think PCBs)	• At a minimum, what assays could be considered in a harmonized test guideline for determination of the human health effects of nano-Ag?
	• What are the chronic, long-term effects of nano-TiO_2 (eco and human effects)?	
		• What standardized test methods or characterization protocols are necessary to ensure that research results generated in multiple laboratories are consistent, reproducible, and reliable?
		• Are the current tests for regulatory acceptance relevant to nano-Ag?
		• Can nano-Ag have impacts on the F-1 (next) generation via changes in gene expression patterns?
9	*See Supplemental Data Table 1*	***Ecotoxicity Test Methods***
		• At a minimum, what assays could be considered in a harmonized test guideline for determination of the ecological effects of nano-Ag?
		• What standardized test methods or characterization protocols are necessary to ensure that research results generated in multiple laboratories are consistent, reproducible, and reliable?
		• Are the current tests for regulatory acceptance relevant to nano-Ag?
		• Can nano-Ag have impacts on the F-1 (next) generation via changes in gene expression patterns?
10	*See Supplemental Data Table 1*	**Is New Nano Unique?**
		• Does nano-Ag form the same strong complexes with anions as conventional silver, and if so, is it also effectively mobilized in aquatic environments?
		• What are the physical–chemical properties of currently available and historic silver products?
		• *Do nano-Ag products actually offer more efficacy than products currently on the market?*
		• Do the properties of nano-Ag that differ from those of well-characterized colloidal silver, if any, cause them to behave differently in aquatic, terrestrial, and atmospheric environmental compartments?
		• If they do differ, how do they differ?
		• Can information about how colloidal silver behaves in these environments be used to understand how nano-Ag behaves?
11	*See Supplemental Data Table 1*	**Biological Effects**
		• What are the most sensitive ecological endpoints to nano-Ag exposure?
		• What are relevant susceptibility factors (for biological response)?
		• What are the short-term and long-term biological responses observed at current nano-Ag occupational exposure levels as well as consumer exposure levels?

Table 1. (*Continued*)

Rank	Nano-TiO_2 questions	Nano-Ag questions
		• Many effects of emerging substances are not known until many years after their introduction and use in commerce. What are the chronic and subchronic effects of nano-Ag, and how can we accelerate our understanding of them? Can nano-Ag have impact on F-1 (next) generation via changes in gene expression patterns?

Priorities from both workshops are presented in rank order based on the number of points participants allocated each area. Only top priorities are presented here, which were identified by a natural break in the amount of points allocated to 2 areas (i.e., 156 and 66 points were allocated to Priorities 8 and 9, respectively, in the nano-TiO_2 workshop [See Figure 2], so only the first 8 priorities are presented here). Lower priorities are included in Supplemental Data. *Italics, underlined* text denotes priorities identified in the CEA process that are less commonly recognized as research gaps in other efforts to inform research planning for ENM (e.g., NNI 2011; NRC 2012).
WWTP = wastewater treatment plant.

Identifying clear priorities

The outcome of each workshop, a list with clearly prioritized research areas, demonstrates how the approach used here allows decision makers to clearly delineate between research priorities (Figure 2, Table 1). By culminating in a list of prioritized research areas, rather than a generalized description of research directions, the process does not leave decision makers to decipher which area might be more important from the perspective of the diverse group of stakeholders engaged.

Participants reached the relatively small list of priorities (<25) by combining individual questions into groups of questions that were similar or closely related. Such consolidation makes sense for a variety of reasons. One is that little or no meaningful difference may exist between some questions, particularly in terms of their implications for an assessment or subsequent risk management decision. Another reason is the practical difficulty of prioritizing almost a hundred individual questions versus fewer than 25 research themes. Moreover, consolidating individual questions into broader priority areas might facilitate implementing the research by allowing those developing research plans to focus more deeply on one or a handful of themes. Nevertheless, several limitations are present to this consolidation approach, as discussed in the following sections.

Novelty and origin of research priorities

Many of the research priorities identified in the CEA process for nano-TiO_2 and nano-Ag align with those identified through other efforts to guide ENM research planning in general (e.g., analytical methods, harmonized test methods, influence of surface coatings on environmental behavior) (NNI 2011; NRC 2012). Such alignment demonstrates that the CEA approach can successfully guide research planning for emerging areas of science. In addition, several priorities identified through the CEA approach stand out as less commonly recognized research gaps (e.g., developing a decision tree framework for nano-TiO_2 assessment, determining whether nano-Ag products are more effective than currently available antimicrobial products; see Table 1 and Supplemental Data Table 1). Pursuing more novel questions such as these might be particularly useful in generating information that could support future decision making about unintended consequences of emerging materials, such as nanomaterials.

Within each list of consolidated research areas, most questions originated from the draft case study documents (Figure 3). Although the workshops were not designed to explicitly test the impact of listing potential research priorities in the draft case study document, our observations suggest that such lists may prime participants' thinking. The lists of initial research questions for participants to consider in developing priorities were provided to support thinking about potential priorities that were outside their particular expertise area. The lists supplemented explicit encouragement to participants to think broadly about potential research areas. Nevertheless, the lists might have unintentionally discouraged some participants from developing more novel research questions. As discussed further, potential limitations of providing an initial set of specific research questions are being addressed in ongoing efforts to apply the CEA approach.

Despite most research priorities originating from the case study documents, 25% to 30% of research questions included in the final priority lists were identified by participants during the workshops (Figure 3A). Indeed, most (56%–100%) of the questions identified in each workshop were included in the final list of research priorities (Figure 3B). The preference to include these newly identified questions likely stems from a variety of reasons, but our data are consistent with a strong influence of face-to-face, group interaction on how participants subsequently prioritize research areas when voting individually. The Social Presence Theory suggests that the physical presence of an individual influences how others interpret a message (Short et al. 1976, as cited by Lowry et al. 2006), implying that the preference to include questions generated in a face-to-face setting in a final priority list might stem from having those questions discussed in person versus submitted in writing before a workshop. In fact, data suggest that for complex tasks, such as predicting research priorities to support future decision making, greater social presence can be particularly important (Lowry et al. 2006).

Data also indicate, however, that particularly with increasing group size, face-to-face interaction can result in fewer ideas generated per individual, decreased commitment to the group goal, and less time to evaluate ideas, while at the same time increasing anonymity (Lowry et al. 2006). Indeed, lower commitment to the group goal may be reflected in participants' generating and subsequently voting for a question developed during the workshop simply because it uses their own wording, as opposed to a the wording of a question in the draft case study documents. Nevertheless, the structured NGT approach employed in these workshops may offset other potential pitfalls of in-person group dynamics by ensuring that each participant has equal time to generate ideas and clear input into the final research priorities through a voting procedure.

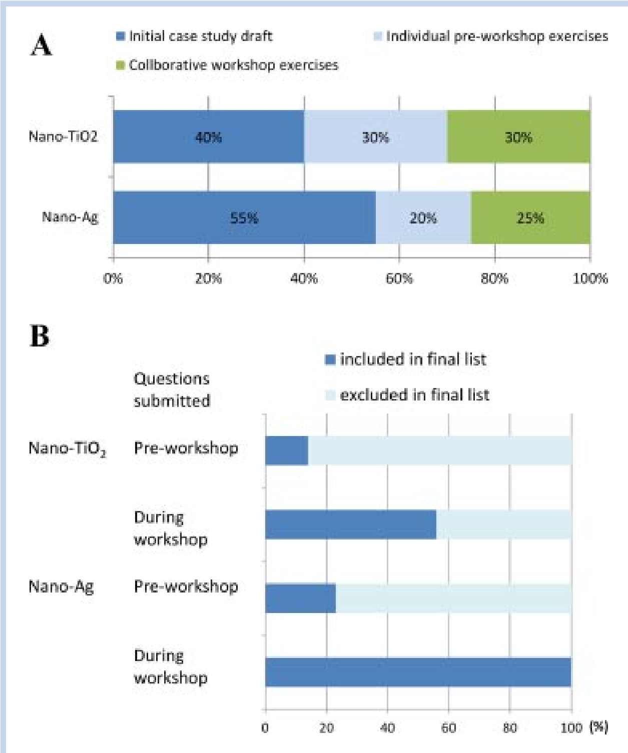

Figure 3. Origin of questions included in the final consolidated list of priority research themes for nano-TiO_2 and nano-Ag (**A**). The percentage of individual questions generated during pre-workshop exercises or during the workshop, and included in the final consolidated priority list of research themes for nano-TiO_2 and nano-Ag (**B**). Data show that although most identified research priorities originated from the draft case study documents, participants also generated 25% to 30% of the priority questions during the workshop. Participants were more likely to include, rather than exclude, questions generated during a workshop in a final list of priorities.

Notably, findings by Lowry et al. (2006) also suggest that supplementing face-to-face interactions with virtual communication (e.g., via a web interface) can improve the quality of communication, which we are currently exploring in ongoing applications of CEA.

Transparent representation of variability in perspectives on research priorities

A key factor in implementing the research priorities identified in each workshop is the confidence that those planning and funding research have in the method used to identify research priorities. An advantage of the multivoting approach employed here is the ability for individuals planning research in organizations across the scientific community to clearly see the variability in how individuals prioritized research areas compared with the group as a whole (Figure 4). Our data suggest some variation in the relative order of priority areas between individuals and the group, which is expected, given the diverse backgrounds and affiliations of the participants (Figure 4; Supplemental Data Figure 1). Compared with approaches that generate a group consensus decision or determine priorities based on the interpretation of the group's discussion by those organizing the process, the approach employed here provides greater transparency by using a multivoting procedure to document how different experts prioritize different research areas. Moreover, by having a record of all of the specific issues identified throughout the process, both before and after consolidation and multivoting, research managers or other interested decision makers are free to examine lower-ranked topics either as possible questions to pursue in their own right or as stimulants to further ideas or considerations.

Increased transparency in differences between stakeholders is expected to provide research managers with greater confidence in developing strategies to address the gaps brought out in this process. Increased confidence may stem from a better understanding of variability between experts in identified priorities and of how expert views parallel the different needs of their individual research institution(s), which will be associated with their own particular areas of focus and resources (e.g., ecological testing or human health). Other conceptual tools such as Value of Information (Linkov et al. 2011) could also be of potential utility in conjunction with CEA in supporting decisions by research managers.

Lessons learned

Although the collective judgment process described in this work was successful in transparently engaging diverse stakeholders and identifying a clear list of research priorities, several limitations provide "lessons learned" for future applications.

Cap workshop participant number at 25. The research themes identified by the 2 smaller NGT groups in the nano-TiO_2 workshop were largely similar, particularly for those at the top of the priority list (USEPA 2010a); thus, a single group of approximately 25 participants seemed sufficient to develop a comprehensive, prioritized list of research objectives in the Nano-Ag workshop. Given the outcomes of the nano-Ag workshop, our data suggest that approximately 25 participants can effectively identify a set of technically diverse research priorities. Although others have suggested that fewer participants (i.e., 8–15) are sufficient (Aspinall 2010), the breadth of the CEA framework suggests that a larger number is useful to adequately represent the many technical expertise areas considered in this approach. Twenty-five or fewer participants also corresponds well with previous findings on the optimal group size for expert engagement efforts (Aspinall 2010). Ultimately, our observations suggest that selecting a group size requires balancing 2 factors: 1) larger groups can provide a greater diversity of technical and sector perspectives than smaller ones, and 2) smaller groups can facilitate more fluid working relationships and involvement from all participants than large ones. The best balance between these 2 factors will likely depend on the objectives of the workshop and available resources (e.g., time to organize, travel money), but outcomes from our workshops suggest that a size of 20 to 25 individuals works well. Notably, there may be key differences between the optimal size of a stakeholder group for face-to-face and more remote meetings that facilitate indirect interaction (e.g., online discussion forums or webinar tools). We are currently exploring the utility of engaging a larger group of expert stakeholders remotely, before bringing a subset face-to-face, to ensure greater representation of diverse perspectives while minimizing financial and environmental costs of travel to a face-to-face meeting.

Rely on diverse expertise to develop research details. We extended the length of the nano-Ag workshop by 1 day based on an observation from the previous workshop on nano-TiO_2 that additional time for breakout groups to discuss priority areas

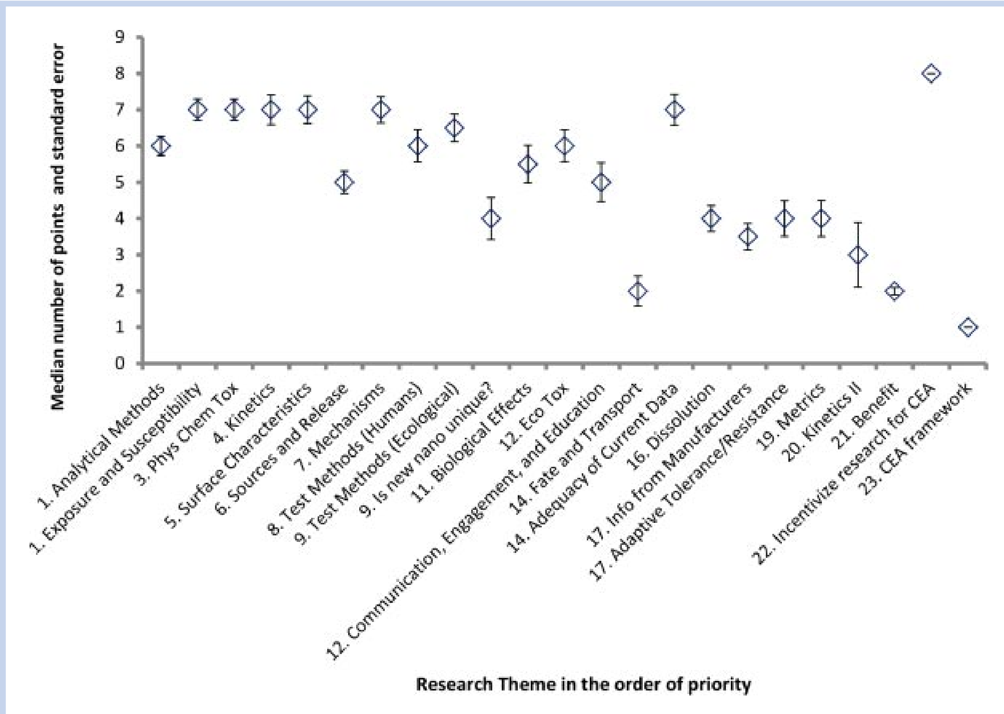

Figure 4. The variability in the number of points that participants allotted to each priority research theme in the nano-Ag workshop. Variability is displayed as the median and standard error of the number of points each research theme received (*y*-axis). Themes are plotted in the rank order of (*x*-axis). Relatively small error bars denote general agreement between participants in the rank order; however, larger error bars for some themes (e.g., the theme ranked 9th ["Is new nano unique?"] and the theme 20th ranked ["Kinetics II"]) indicate areas of greater variability in the participants' views on the priority of particular topics.

would enhance the workshop outcome (i.e., more of the identified research areas could be addressed in breakout groups, thereby providing more information for decision makers who might use the priorities to develop research plans). Interdisciplinary and transdisciplinary research is increasingly encouraged, although barriers (e.g., time, funding, culture) remain in actually conducting such research (National Academy of Sciences 2004; Harris et al. 2012). As such, workshops that bring together expert stakeholders representing diverse technical and sector perspectives present an important opportunity to draw on such a spectrum of insights. Breakout groups allow experts to develop a greater understanding of details surrounding the interfaces of their disciplines with others, which in turn can inform the scientific community in planning and promoting interdisciplinary and transdisciplinary research.

Identify broad priority research areas before developing specific questions. The use of specific questions in the draft case study documents and preworkshop exercises provided a useful starting point for participants, but it has possible limitations. First, it may have primed participants to develop priority research questions in areas identified in the draft documents. Although not inherently a problem, priming could narrow the scope of participants' thought processes and thus lead to instances in which "known unknowns" are overlooked. Second, it might have resulted in some participants focusing closely on the specific wording of the question, or particular aspects of narrow research topics, rather than looking for broader priority areas. Finally, after identifying specific research topics, some participants struggled to agree on how to consolidate them and, based on informal feedback, seemed somewhat frustrated by the process because it appeared to de-emphasize the importance of each individual topic. Although asking a diverse group to consolidate research topics into common themes can lead to difficult discussions on how to best combine individual topics, such difficult discussions were necessary to make the ranking of separate priorities a feasible goal within a time-limited workshop. Nevertheless, the effort to consolidate research topics was a particularly important challenge in conducting a transparent and structured process. The consolidated list of questions, though inclusive of all participants' input, hinged on the guidance and judgment of the facilitators who conducted the discussion sessions. This process by nature includes a nonlinear collection of disparate opinions from a group and the development of a general consensus on the consolidation opinions. Although these activities were subsequently ratified with a quantifiable voting system, such an open discussion forum could compromise to some extent the repeatability and transparency that are guiding principles of CEA. This aspect of the process highlighted the importance of balancing the guiding principles for the workshops (i.e., transparency, structure, and protection from bias) with the needs for feasibility and flexibility.

Based on these observations, in a more recent effort to apply the CEA approach to multiwalled carbon nanotubes (MWCNTs), the participants first identified priority research areas and then developed specific research questions. This revised approach is intended to allow participants to generate specific research questions de novo after prioritizing broader areas of the CEA framework (Figure 1), which might also avoid the issue of potentially constraining participants' thinking with questions in the draft case study document they initially review. Outcomes of this alternative approach are discussed elsewhere and are the subject of manuscripts in preparation (RTI International 2012).

Provide guidance on developing research questions. Although many of the individual research questions identified through this work are expected to inform research planning, some of the questions posed by participants were matters of opinion or answerable with "it depends." Such statements are difficult to translate directly into actionable research. We are actively addressing this in ongoing efforts by providing a list of criteria for research questions (e.g., "be of spatial and temporal scope that reasonably could be addressed by a research team," "have a factual answer that does not depend on value judgments"), which we adapted from Sutherland et al. (2011). Although any 1 participant may not have complete knowledge of each criterion (e.g., responsible spatial and temporal scope for a research team), by bringing together individuals with diverse experiences the group as a whole can reach an understanding of effective research questions to inform future assessment and risk management efforts. For example, a laboratory researcher may not have a clear understanding of the type of data a risk assessor is looking for, whereas a risk assessor may have less of an appreciation of what is reasonable for a single research team to accomplish, but by working together they could generate a research question relevant to risk assessors and within a reasonable spatial and temporal scope for a laboratory.

Rate rather than rank research questions or themes. Before the nano-TiO_2 and nano-Ag workshops, participants ranked a subset of questions (i.e., top 10) and rated the remaining questions (i.e., high priority, low priority). A similar ranking system was used at the workshop to finalize the research priorities. One reason to only rank a subset of questions or themes is the observation that ranking a large number of individual questions would likely be time consuming, and evaluating each question in a consistent manner could be a difficult task. Rating individual questions or research themes, however, could provide a way to evaluate a relatively large number of questions or research areas in a consistent manner. Rating questions or themes allows participants to consider each one separately in the context of constant criteria (e.g., cost of conducting research, importance of data for minimizing exposure), rather than attempting to compare it with all of the others under consideration. Notably, a key part of this lesson is the critical nature of clearly stating the goal of the rating process; the distinction between prioritizing research for the sake of furthering the science versus prioritizing research to inform future risk assessments and hence risk management efforts is perhaps easy to overlook, but the latter goal is important to make clear to participants. Rating potential research questions or themes offers the opportunity for participants to consistently think of risk assessment and risk management by asking them to rate each area on parameters related to risk assessment and management (e.g., importance of information for conducting risk assessment, confidence in data for risk management). Accordingly, in efforts to apply CEA to MWCNTs, participants were asked to rate potential research areas based on aspects related to risk assessment and risk management.

CONCLUSIONS

Through structured case study documents and workshops, a diverse group of expert stakeholders identified and ranked research gaps for 2 types of ENMs. The CEA framework was used to organize information on specific applications of ENMs, namely, nano-TiO_2 used for water treatment and topical sunscreens and nano-Ag used for disinfectant sprays. As part of the CEA process, collective judgment workshops were used to structure stakeholder engagement such that stakeholders with diverse technical expertise and sector perspectives had equal input in the outcome of the workshop. Outcomes of each workshop are expected to move the field of nanomaterial research forward by presenting clear priorities, which include less commonly identified and yet important areas of research. We also identified lessons learned regarding the benefits of using 25 or fewer workshop participants, emphasizing breakout group interactions, identifying broad priorities before detailed elaboration (i.e., specific research questions), providing clear guidelines for research question development, and choosing suitable prioritization methods. These lessons can inform future research planning efforts for various emerging materials, including ENMs, across the scientific community.

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Disclaimer—The views expressed in this article are those of the authors and do not necessarily represent the views or policies of the US Environmental Protection Agency.

SUPPLEMENTAL DATA

Supplemental Figure S1. Technical and sector characteristics of workshop participants.

Supplemental Figure S2. Distribution of votes for research priorities in nano-Ag workshop.

Supplemental Info. Lower research priorities identified in CEA workshops for nano-TiO_2 and nano-Ag.

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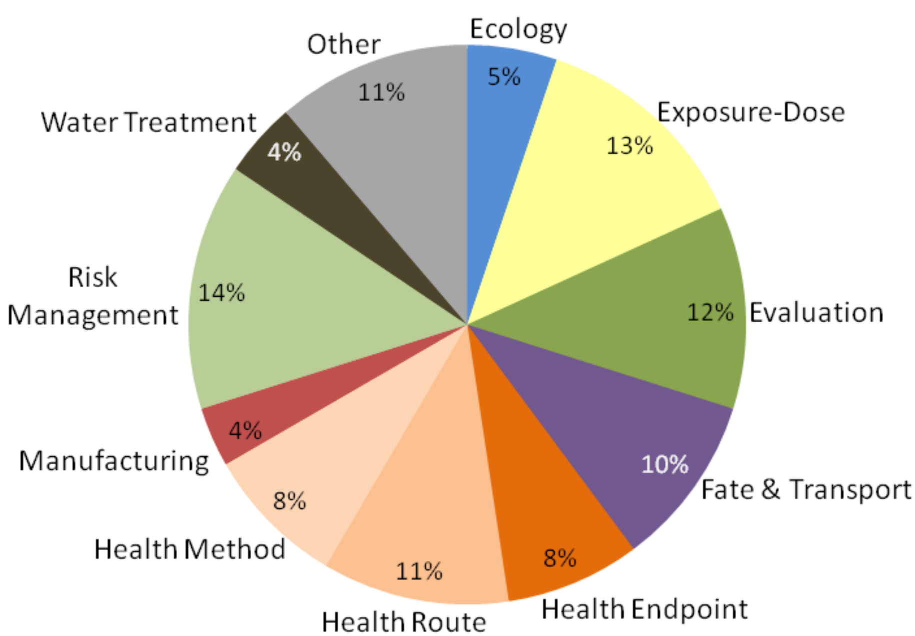
Supplementary Figure Legend

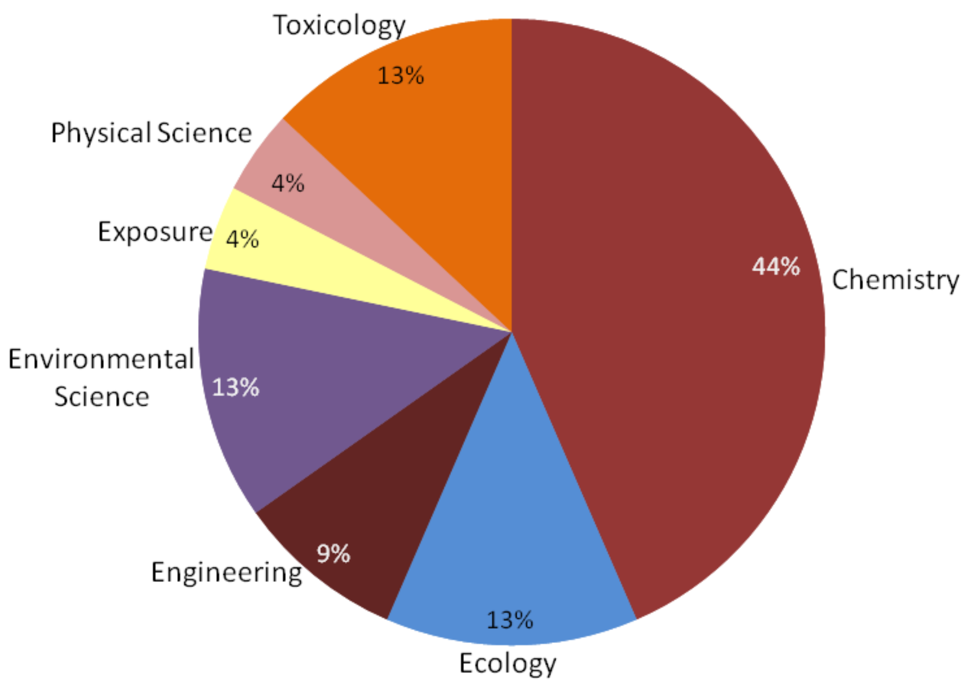
SI Figure 1: Workshops Engaged Stakeholders with Diverse Technical and Sector Perspectives

Technical Expertise areas represented at the (A) Nano-TiO_2 (n =49 participants) and (B) Nano-Ag (n= 23 participants) Workshops. See Workshop Summary Report for details on specific expertise falling into each area (e.g., animal toxicology, epidemiology, human clinical in "Health Method" of panel A). Sector affiliations of participants in each workshop are shown in Panel C.

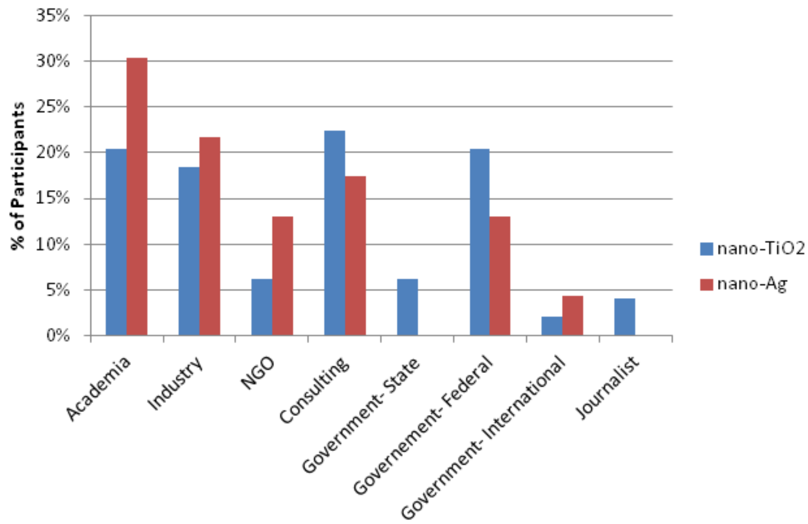
Supplemental Figure S1a. Technical and sector characteristics of workshop participants.



Supplemental Figure S1b.



Supplemental Figure S1c.



SI Figure 2: Number of Participants Voting in Each Point Category for the Nano-Ag Workshop

The number of participants who allocated a particular number of points (i.e., 10-points, 9-points, etc.) in their weighted votes for each research theme in the nano-Ag workshop. The point categories for votes are represented on the y-axis and research themes are represented in priority order on the x-axis. Numbers in each cell represent the number of participants who voted in the point category (y-axis) for the theme (x-axis). Darker blue boxes correspond to a higher number of participant votes in the point category while lighter blue to yellow boxes correspond lower numbers of participant votes. See Methods in main text for more details on the voting process.

Supplemental Figure S2. Distribution of votes for research priorities in nano-Ag workshop.

Topic	Analytical Methods	Phys Chem Tox	Kinetics	Surface Characteristics	Sources and Release	Mechanisms	Test Methods (Humans)	Biological Effects	Is new nano unique?	Test Methods (Ecological)	Fate and Transport	Dissolution	Eco Tox	Metrics	Communication, Engagement, and Education	Info from Manufacturers	Adequacy of Current Data	Adaptive Tolerance/Resistance	Kinetics II	Incentivize research for CEA	Benefit	CEA framework
Topic ranking	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
10-point votes	3	3	4	0	0	0	1	1	4	0	0	0	0	0	0	0	0	0	1	0	0	0
9-point votes	1	3	1	1	2	3	1	2	0	2	2	0	0	1	1	0	0	0	0	0	0	0
8-point votes	1	1	2	6	2	2	0	1	0	0	0	1	1	0	0	0	1	1	0	1	0	0
7-point votes	3	4	1	0	0	1	2	0	0	3	0	0	1	1	0	2	2	0	1	0	0	0
6-point votes	5	2	3	1	0	2	2	1	0	0	0	1	2	0	1	0	0	1	0	0	0	0
5-point votes	0	0	0	2	5	0	1	1	0	1	0	1	0	1	2	1	0	1	0	0	0	0
4-point votes	2	1	0	1	1	2	0	0	3	1	2	2	1	2	1	1	2	0	0	0	0	0
3-point votes	3	2	0	0	4	0	2	2	1	1	0	2	1	1	0	1	0	1	1	0	0	0
2-point votes	0	0	4	1	0	1	0	1	0	1	5	1	0	0	1	1	0	1	0	0	3	0
1-point votes	0	0	0	2	1	0	1	1	1	0	3	1	2	1	2	3	0	1	2	0	1	1

Supplementary Table 1: Lower Research Priorities Identified in CEA Workshops for nano-TiO_2 and nano-Ag

Priorities from both workshops are presented in rank order based on the number of points participants allocated to each area. Lower priorities are presented here, which were identified by a natural break in the number of points allocated to two areas (i.e., 156 and 66 points were allocated to Priorities 8 and 9 respectively in the nano-TiO_2 workshop [See Figure 3] so priorities 9 and below are presented here); see Table 1 in main text for priorities that participants allocated more points to in each workshop (i.e., higher ranked priorities). ***Italics, underlined*** text denotes priorities identified in the CEA process that are less commonly recognized as research gaps in other efforts to inform research planning for ENM (e.g., (NNI 2011, NRC 2012)).

Rank[a]	Nano-TiO_2 Questions	Nano-Ag Questions
9a	• Is the available ecotoxicity evidence adequate to support ecological risk assessment for nano-TiO_2? 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-TiO_2 and its ecological effects?	See Table 1
9b	• 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 TiO_2 data in the open literature as applied to nano-TiO_2 and other particles?	
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-TiO_2? Is the definition of less than 100 nm adequate? Or, should a dimension be derived based on the toxicological properties?	

12	• What are the important metrics and standards that we need to use to characterize nano-TiO_2? • What is the role of standard reference materials for integrating the results of different investigators regarding particle characterization and particle toxicology? What is needed?	***Ecological Effects Required for Risk Assessment*** • What are the most sensitive ecological endpoints to nano-Ag exposure? Are there sufficient data/analytical techniques to determine how sensitive specific endpoints and organisms are to nano-Ag exposure, including: a. Benthic invertebrates; b. Marine invertebrates; and c. Freshwater invertebrates? • Is the available ecological effects evidence adequate to support ecological risk assessment for nano-Ag? If no, what research is needed to make an assessment possible? ***Communication, Engagement, and Education*** • *How do we effectively communicate risk/benefit information for nano-Ag to the general public?* • *How do we engage citizens and workers in discussions about how nano-Ag sprays are being used?* • *How do we educate people about the risks, benefits, and safety related to nano products?* • *We need an integrated holistic approach to nano risk assessment. How can we do this?*
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)?	

14	• 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 humid acids or other common constituents or contaminants in water undergoing treatment affect the fate, including agglomeration/aggregation properties, of TiO_2? •	***Fate and Transport of Nano-Ag*** • What physicochemical properties of nano-Ag can be used to predict fate and transport in environmental media? • How could existing models applicable to conventional silver be used to adequately predict the transport and fate of nano-Ag through environmental compartments, or how could they be modified to do so? ***Adequacy of Current Data*** • Do current publications describing the health effects of nano-Ag particles and laboratory-generated nano-Ag particles accurately depict the toxicity of commercially available nano-Ag materials? • Are there any parallels between health effects of conventional silver and those in emerging studies on nanosilver?
15	• *Can we develop a decision-tree framework and best practices to facilitate environmental assessment of individual nanomaterials?* • *Would a toxicity – application – exposure – LCA – order in a decision tree be workable for conducting a CEA for nano-TiO_2?* • *How do we integrate analytical methods used to characterize risk (mass flow, life cycle) to evaluate and compare environmental trade-offs?*	
16	• 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? • What kind of studies would provide the most suitable data to understand dose-response of occupational exposure to nanomaterials and health effects in humans?	***Dissolution*** • What information exists on the temporal changes in the release of ionic silver by nanoparticles physicochemical and environmental characteristics? • What are the rates of dissolution of nano-Ag into the environment? • Does particle size of nano-Ag affect the rate of release of silver ions in environmental compartments?

17	• What effect, if any, do coatings, dopings, carriers, dispersants, and emulsion types have on biopersistence and bioaccumulation? (3-8) • Should TiO_2 particles with coatings and strongly chemisorbed species be evaluated separately for the purposes of environmental transport, ecotoxicity, and toxicity? N/A	***Information from Manufacturers*** • Has the database and risk assessment methodology used by FDA during approval of nano-Ag medical devices been integrated with EPA's database and risk assessment processes? • What are realistic strategies for collecting data on production quantities and product characteristics given that much of this information is proprietary? ***Adaptive Tolerance / Resistance*** • The majority of toxicity studies with conventional silver were conducted over a decade ago. Are more studies needed that utilize state-of-the-art technology for comparing its mode of toxicity to that of nano-Ag? In other words, can we accurately say that nano-Ag and conventional silver have different modes of toxicity if most of the studies available for conventional silver were not conducted using current methods? • Is the nano-Ag harmful to the beneficial organisms in wastewater treatment?
19	N/A	***Metrics*** • How should dose and exposure be characterized for human exposures? • For the purpose of assessing potential risk, what metrics are most informative for quantifying exposure and dose of nano-Ag?
20	N/A	***Kinetics II*** • Does nano-Ag react with materials (i.e., organic matter, other metals, polymers) and alter properties such as REDOX potential or leached metal ion rates? • What changes occur to the physicochemical properties of nano-Ag throughout the life-cycle stages, either as a function of process and product engineering or as a function of incidental encounters with other substances and the environment? • *Does the release of nano-Ag contribute to climate change?*
21	N/A	***Benefits*** • *Do nano-Ag products actually offer more efficacy than products on the market?*
22	N/A	***Incentivize Research for CEA*** • *How can we incentivize researchers to focus in on the most critical questions and best methods for CEA?*

		• *<u>How urgent is the need for the benefits offered by the candidate application/material?</u>*
23	N/A	***CEA Framework*** • How can CEA framework be improved to ensure passive or active consumer/occupational exposure research is completed for nano-Ag and for other nanomaterials?

[a]Note: In the nano-TiO_2 workshop research themes that received the same number of points in the multi-voting procedure were numbered using an "a" and "b" (e.g., 9a and 9b). In the nano-Ag workshop, research themes receiving the same number of points were numbered by assigning the same number to both themes (e.g., both "Ecological Effects Required for Risk Assessment" and "Communication, Engagement, and Education" received 43 points and thus are both numbered "12"). In these instances the next theme was numbered to maintain the correct total number of themes (e.g., "Fate and Transport of Nano-Ag" is number 14 rather than number 13).