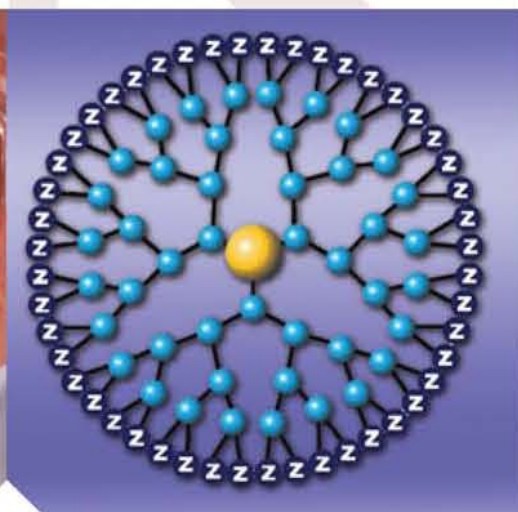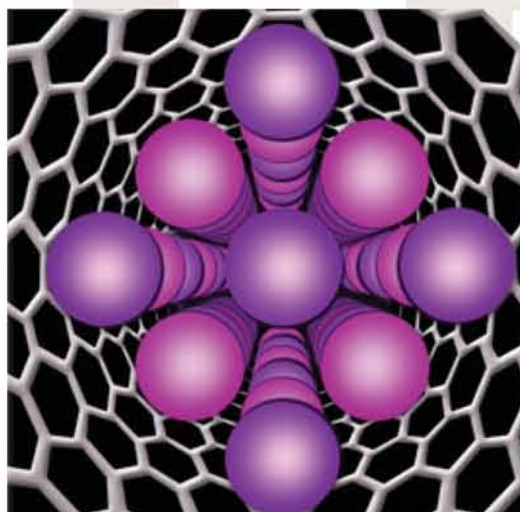# Nanomaterial Research Strategy

Nanomaterial Research Strategy

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Executive Summary

With the use of nanotechnology in the consumer and industrial sectors expected to increase significantly in the future, nanotechnology offers society the promise of major benefits. The challenge for environmental protection is to ensure that, as nanomaterials are developed and used, unintended consequences of exposures to humans and ecosystems are prevented or minimized. In addition, knowledge concerning how to sustainably apply nanotechnology to detect, monitor, prevent, control, and clean up pollution is needed.

The purpose of the Nanomaterial Research Strategy is to guide the EPA's Office of Research and Development's program in nanomaterial research. The strategy builds on and is consistent with the foundation of scientific needs identified by the Nanotechnology Environmental and Health Implications Working Group (NSTC, 2008), and in the EPA's *Nanotechnology White Paper* (EPA, 2007).

> The Nanomaterial Research Strategy (NRS) guides the nanotechnology research program within EPA's Office of Research and Development.

The purpose of EPA's nanotechnology research program is to conduct focused research to inform nanomaterial safety decisions that may be made under the various environmental statutes for which EPA is responsible. EPA recognizes that the information generated through its research program is also likely to have use in areas beyond the Agency's purview. EPA will collaborate across the government, industry, and the international community to implement this strategy. EPA's in-house research program will leverage results from EPA grant programs, as well as collaborate with grantees to address the many challenging research issues outlined in this strategy.

EPA's strategy focuses on four areas that take advantage of EPA's scientific expertise as well as fill gaps not addressed by other organizations. The four research themes are:

- Identifying sources, fate, transport, and exposure
- Understanding human health and ecological effects to inform risk assessments and test methods
- Developing risk assessment approaches
- Preventing and mitigating risks

EPA's Nanomaterial Research Program is designed to provide information to support nanomaterial safety decisions. The eight key science questions described in the strategy are intended to help decision makers answer the following questions:

- What nanomaterials, in what forms, are most likely to result in environmental exposure?
- What particular nanomaterial properties may raise toxicity concerns?
- Are nanomaterials with these properties likely to be present in environmental media or biological systems at concentrations of concern, and what does this mean for risk?
- If we think that the answer to the previous question is "yes," can we change properties or mitigate exposure?

Providing information to answer these questions will serve the public by enabling decisions that minimize potential averse environmental impacts, and thereby maximize the net societal benefit from the development and use of manufactured nanomaterials.

Major Acronym List

AA	Assistant Administrator
ADME	Absorption, distribution, metabolism, elimination
AML	Advanced Measurement Laboratory
BMPS	Best management practices
CAA	Clean Air Act
CEA	Comprehensive environmental assessment
CERCLA	Comprehensive Environmental Response Compensation and Liability Act
CR	Current Research
CREM	Council for Regulatory Environmental Modeling
CT	Committee on Technology
DAA	Deputy Assistant Administrator
DOD	Department of Defense
DOE	Department of Energy
DSSTOX	Distributed Structure-Searchable Toxicity
HPG	Hypothalamic-Pituitary-Gonadal
IRIS	Integrated Risk Information System
LCA	Life cycle Analysis
MOA	Mechanism of action
MOAS	Modes of Action
MR-CAT	Materials Research Collaborative Access Team
MYP	Multi-year plan
NAS	National Academy of Science
NCCT	National Center for Computational Toxicology
NCEA	National Center for Environmental Assessment
NCER	National Center for Environmental Research
NCI	National Cancer Institute
NCL	Nanotechnology Characterization Laboratory
NEHIWG	Nanotechnology Environmental and Health Implications Working Group
NERL	National Exposure Research Laboratory
NHEERL	National Health and Environmental Effects Laboratory
NGO	Non-Governmental Organization
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
NNCO	National Nanotechnology Coordination Office
NNI	National Nanotechnology Initiative
NPDS	National Program Directors
NRC	National Research Council
NRMRL	National Risk Management Research Laboratory
NRS	Nanomaterial Research Strategy
NSET	Nanoscale Science Engineering and Technology
NSF	National Science Foundation
NSTC	National Science and Technology Council
OECD	Organization for Economic Cooperation and Development
ORD	Office of Research Development

1.0
Introduction

Purpose. The Nanomaterial Research Strategy (NRS) describes the Environmental Protection Agency's (EPA) strategy for conducting and supporting research to understand the potential human health and ecological (henceforth referred to jointly as "environmental") implications from exposure to manufactured nanomaterials, and how nanotechnology can be used sustainably in environmental protection applications. EPA has written this document with three main purposes: (1) to guide its own researchers and managers as they conduct EPA's research program, (2) to assist scientists in other organizations as they plan research programs, and (3) to inform the public of how EPA intends to generate scientific information to guide environmental decisions related to nanomaterials.

The purpose of EPA's research program is to conduct focused research to address risk assessment and risk management needs for nanomaterials in support of the various environmental statutes for which EPA is responsible. This program will be coordinated with research conducted by other federal agencies, where EPA will lead selected research areas and coordinate and/or collaborate with its federal research partners in other research areas. EPA's in-house research program will leverage results from EPA grant programs, as well as collaborate with grantees to address the many challenging research issues outlined in this strategy.

Focus. The NRS focuses on developing scientific information for nanomaterial decision support. Because other entities also conduct research on nanomaterial safety, EPA is focusing on four areas that take advantage of EPA's scientific expertise as well as fill gaps not addressed by other organizations. The four research themes are:

- Identifying sources, fate, transport, and exposure

- Understanding human health and ecological effects to inform risk assessments and test methods

- Developing risk assessment approaches

- Preventing and mitigating risks

In addressing these themes, EPA's research program will focus on providing information that supports the type of decision logic outlined below in Figure 1-1.

Figure 1.1. Nanomaterials and Environmental Decision Making: Key Decision-Support Questions

What NMs, in what forms, are most likely to result in environmental exposure?

What particular NM properties may raise toxicity concerns?

Are NMs with these properties likely to be present in environmental media or biological systems at concentrations of concern?

If "yes," can we change properties or mitigate exposure?
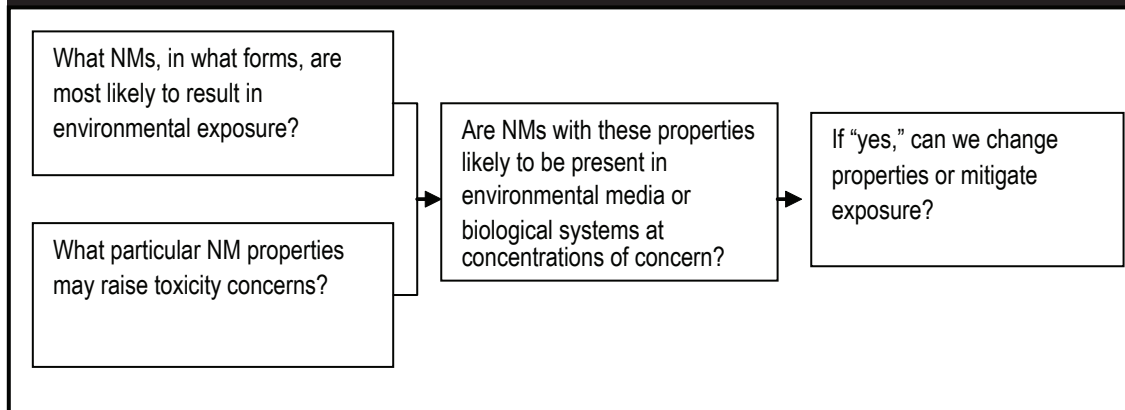
Objectives. EPA believes that its research should advance two key objectives: (1) the development of approaches for identifying and addressing any hazardous properties, while maintaining beneficial properties, before a nanomaterial enters the environment; and (2) identifying whether, once a nanomaterial enters the environment, it presents environmental risks. EPA will pursue these objectives from a life cycle perspective—i.e., by understanding where environmental impacts may occur and where benefits may be attained throughout a nanomaterial's existence; from its production, through its use in products and as it is disposed of or recycled.

Approach. The NRS will be implemented in EPA's Office of Research of Development (ORD), in two main ways: by funding grants through the Science to Achieve Results (STAR) and Small Business Innovation Research (SBIR) programs, and by EPA scientists within ORD's research laboratories and centers. Expertise needs will determine how resources are allocated between externally and internally conducted research.

Organization. The NRS is organized around the four research themes. Within each theme, research activities are identified along critical paths toward addressing science questions.

2.0
Context

EPA's NRS is one component of an international effort to generate information on nanomaterials and the environment. Other US federal agencies, national governments, industry, academic institutions, and non-governmental organizations are also involved. While the number of individuals and organizations generating information on the environmental impacts of nanomaterials is large and growing, for the purposes of placing the NRS within a larger context there are four major efforts underway:

- **Organization for Economic Cooperation and Development (OECD) Working Party on Manufactured Nanomaterials.** The OECD is coordinating a testing program on nanomaterials deemed by the Working Party to be representative of materials likely to enter commerce. Test plans are to be completed in mid-2009, with Phase 1 testing to be completed in approximately three years.

- **National Nanotechnology Initiative (NNI)** *Strategy For Nanotechnology-Related Environmental, Health, and Safety Research.* This interagency research strategy outlines the US federal research plans for approximately the next ten years. Figure 2-1, taken from the *Strategy,* illustrates the NEHI members' roles in implementing the interagency strategy. While coordinating agencies will play a leadership role in advancing interagency implementation of the NNI strategy, other agencies may play scientific leadership roles in particular areas.

- **EPA NRS.** The NRS was developed in concert with the NNI strategy.

- **EPA Nanomaterial Stewardship Program (NMSP).** EPA's office of Pollution Prevention and Toxic Substances has initiated a program for the voluntary submission of nanomaterials

Figure 2-1. Roles of NEHI Working Group Member Agencies with Regard to Nanotechnology –Related EHS Research Needs

Table 2. Roles of NEHI Working Group Member Agencies with Regard to Nanotechnology-Related EHS Research Needs

◆ - Coordinating agency   ● - Contributor   ■ - User

All coordinating agencies have roles as contributors to and users of the research from the respective categories, with the exception of FDA, which as the roles of coordinating agency and user.

Agency	Instrumentation, Metrology, and Analytical Methods	Nanomaterials and Human Health	Nanomaterials and the Environment	Human & Environmental Exposure Assessment	Risk Management Methods
NIH	●■	◆	■	■	
NIST	◆	●	●	●	●
EPA	●■	●■	◆	●■	◆
FDA	■	■	■	■	◆
NIOSH	●■	●■	●	◆	●■
NSF	●*	●*	●*	●*	●*
DOD	■	■	●■	■	●■
DOE	●■	■	●■	■	■
USDA	■	●■	●■	■	■
DOT		■	■	■	■
OSHA	■	■		■	■
CPSC	●■	■	■	●■	●■
USGS	●■		●■	●■	

*NSF is a contributor according to the mission of the agency covering the upstream, fundamental research on utilization, implications, and risk mitigation of nanotechnology, infrastructure and education.

environmental, health, and safety information from industry and others.

Collaboration for Decision Support. For the NRS to provide maximum scientific value and guide most efficient resource use, collaborating with and leveraging the work of others is crucial. Figure

2-2 illustrates the breadth of information needed to make decisions related to nanomaterials and the environment, as well as the number of federal entities involved in generating and using this information.

EPA is using several approaches to link the NRS to other efforts to develop scientific information in support of decision making. They include:

- **Coordinating and collaborating with other federal agencies.** As shown in Figure 2-1, EPA is the federal government's coordinating agency for the "Nanomaterials and the Environment" and "Risk Management Methods" areas of the NNI strategy. EPA also co-chairs the NEHI and is leading efforts, such as planning state-of-the-science workshops, to advance implementation of the interagency strategy. The NRS is also being implemented by EPA issuing joint grant requests for applications (RFA) with other federal agencies, including the National Science Foundation (NSF), the National Institute for Environmental Health Sciences (NIEHS), and the National Institute for Occupational Safety and Health (NIOSH). EPA's laboratories are also coordinating and collaborating with other agencies, such as with the National Toxicology Program and NIOSH on carbon nanotubes. Also, EPA is co-sponsoring with NSF new national Centers for the Environmental Implications of Nanomaterial

Figure 2-2. Federal Sources to Inform EPA's Nanotechnology Activities
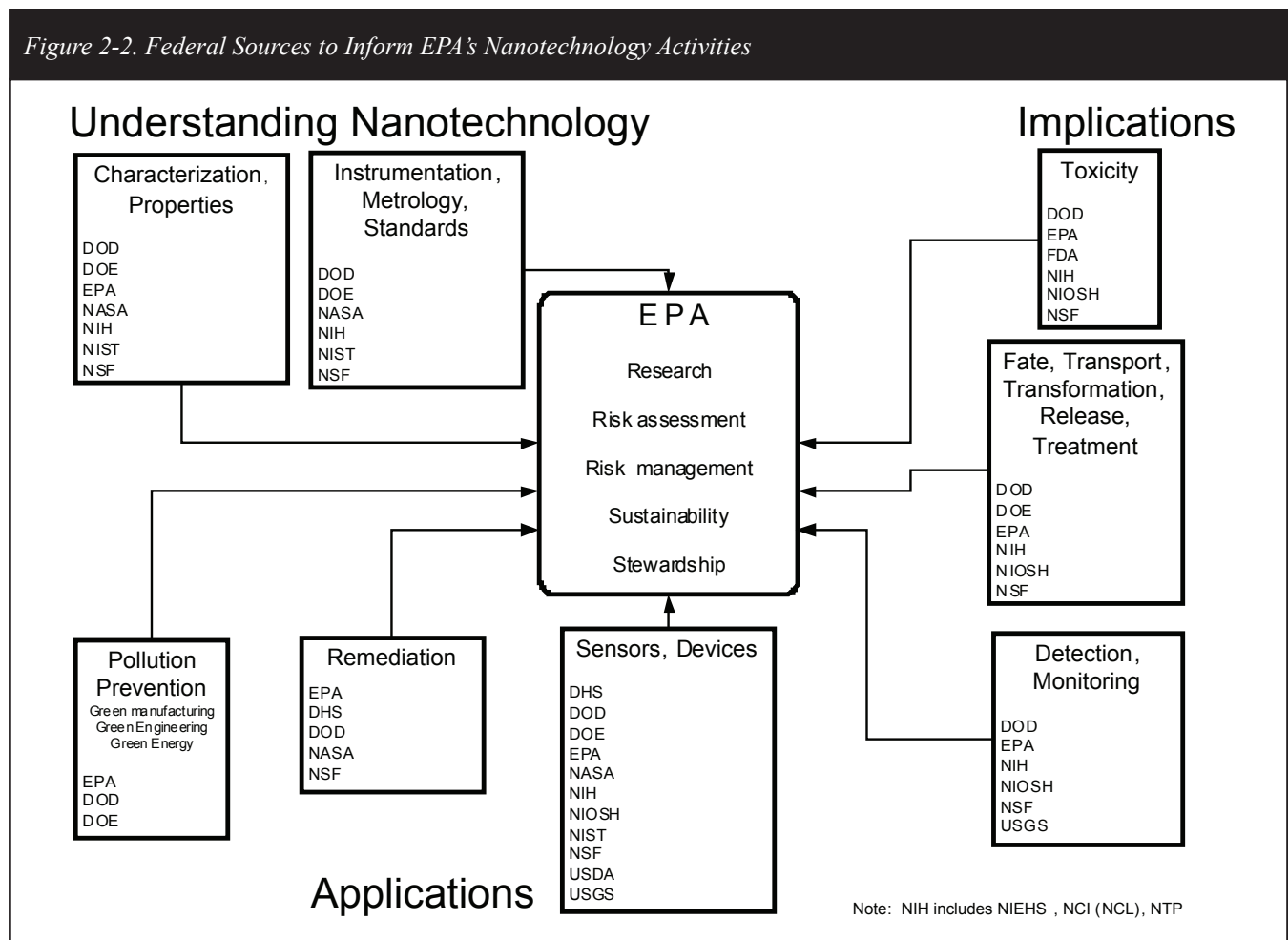
Figure 2-3 EPA's NRS Within The Decision-Support Context

Decision-Support & Institutional Context:
EPA-centric View

Other Agencies

NEHI   "Bi-lateral"

Academic Research   **EPA**   **OECD Testing Program**

Industry-sponsored Testing

Health and Environmental Decisions
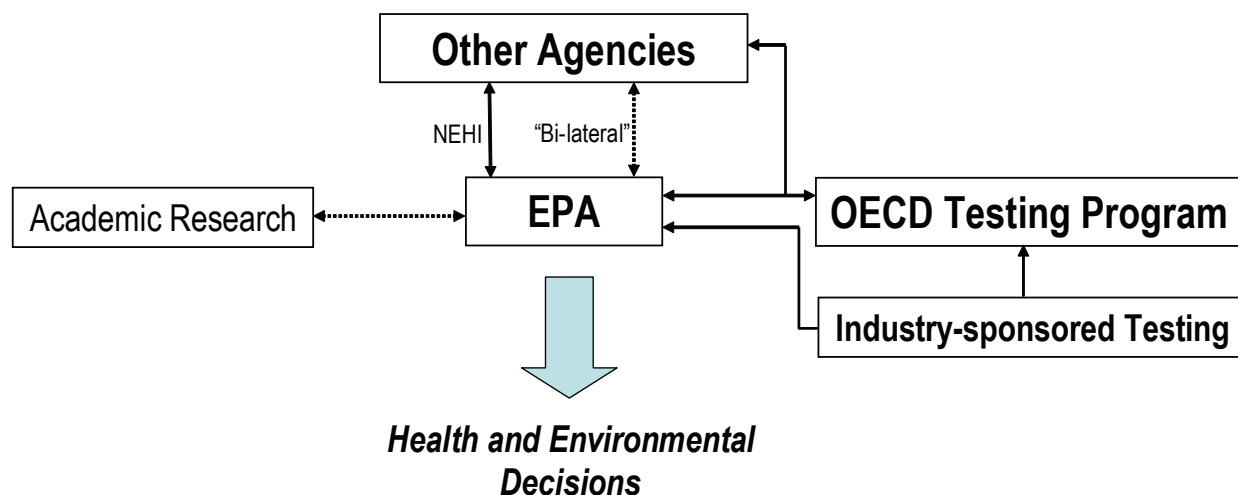
(CEINT) to conduct fundamental research and education on the implications of nanotechnology for the environment and living systems at all scales. The CEINTs will address interactions of naturally derived, incidental and manufactured nanomaterials with the living world.

- **Participating in the OECD Testing Program.** In implementing the NRS, EPA is co-sponsoring testing on a number of nanomaterials. EPA researchers will divide testing responsibilities and share test materials with the co-sponsoring organizations.

- Nanomaterial Stewardship Program. EPA believes that the NMSP will provide material-specific and general information that will be useful to advancing EPA's research program. Also, ORD researchers are collaborating with OPPT on identifying information gaps that the NMSP can address.

Figure 2-2 depicts how EPA fits within the larger information-gathering context to support decisions related to nanomaterials and the environment.

Integration. Successfully implementing the NRS within a larger scientific context will require EPA to integrate into its research program information from various sources. EPA is using the following means to enable such integration:

- Supporting and using the OECD's international database on nanomaterial environmental, health, and safety research.

- Holding joint meetings with EPA researchers and STAR grantees.

- Convening state-of-the-science workshops on each of the four NRS research themes.

- Leading and participating in NNI-sponsored workshops as part of implementing the interagency strategy.

Periodically, EPA will issue a research progress document describing EPA's overall advance in implementing the NRS.

ORD also recognizes that it must provide decision support in the near term, even as data are generated and methodologies developed for complete risk assessments. Therefore, ORD will provide scientific expertise in applying existing methods, models, and data to nanomaterial decision making, as well as investigating alternative decision-support tools in the absence of risk assessment information.

3.0
Key Considerations

This section outlines five key considerations that ORD took into account as it developed the NRS. These five considerations—selection of materials, research themes and science questions, informing risk assessment and risk management, setting priorities, and implementation—serve to bound the ORD nanomaterials research program. Putting bounds around the program is important, given resource limitations and acknowledging that the NRS fits within and should complement a larger national and international context of nanomaterial EHS research.

3.1 Selection of Materials

ORD is focusing its research on seven manufactured nanomaterial types: single-walled carbon nanotubes, multi-walled carbon nanotubes, fullerenes, cerium oxide, silver, titanium dioxide, zero-valent iron. Ultimately, ORD has as a goal, the development of predictive models and tools that will enable testing across these material types, since testing the many potential variations of materials within each of these seven material types would be very resource intensive.

ORD selected these seven material types based on the materials' current use in products, the near-term needs of EPA's program and regional offices, research underway at other federal agencies, and the materials selected for testing in the OECD's Working Party on Manufactured Nanomaterials. Over time, ORD expects to extend its efforts to other material types.

These materials are of interest to EPA either because of their potential use in cleaning up pollution (zero-valent iron) or because EPA may need to make safety decisions on the materials under its regulatory programs. EPA program offices that have already given consideration to some of these specific materials include the Office of Pollution Prevention and Toxics, the Office of Pesticide Programs, and the Office of Air and Radiation.

The United States, with EPA as a principal participant, is sponsoring or co-sponsoring the testing of all of the seven materials as part of the OECD's nanomaterial testing program. In particular, EPA is taking leadership roles in the testing of cerium, C-60 fullerenes, nanotubes, silver, and titanium dioxide. This program allows the ORD to leverage the work of other nations and organizations in advancing the Nanomaterial Research Strategy. For example, for the carbon materials Japan, Korea, and industry are conducting mammalian toxicity testing, while EPA will do environmental fate and ecological effects testing. Thus, the partnership for these materials cover all the endpoints under the OECD program.

There is no question that the types of, and variations on, nanomaterials is large and growing, and goes beyond the materials ORD has chosen for near-term study. However, these seven material types are a good starting point for the new ORD program, which will evolve together with state of nanoscience and as environmental decision-support needs change.

Figure 3-1. Relative Priority of Research Themes

NRS Research Themes

Sources, Fate, Transport, and Exposure

Human Health and Ecological Effects Research to Inform Risk Assessment and Test Methods

Risk Assessment Methods and Case Studies

Preventing and Mitigating Risks

3.2 Strategic Direction of Research Themes and Science Questions

EPA has identified four key research themes where it can support the National Nanotechnology Initiative and the science needs of EPA.

Key Science Questions. Under each of the four research themes, the EPA research program will address key science questions.

Theme 1. Sources, Fate, Transport, and Exposure

- What technologies exist, can be modified, or must be developed to detect and quantify manufactured nanomaterials in environmental media and biological samples?

- What are the major processes and/or properties that govern the environmental fate, transport, and transformation of manufactured nanomaterials, and how are these related to

the physical and chemical properties of those materials?

- What are the exposures that will result from releases of manufactured nanomaterials?

Theme 2. Human Health and Ecological Effects Research to Inform Risk Assessment and Test Methods

- What are the health effects of manufactured nanomaterials and their applications, and how can these effects be best quantified and predicted?

- What are the ecological effects of manufactured nanomaterials and their applications, and how can these effects be best quantified and predicted?

Theme 3. Risk Assessment Methods and Case Studies. In what ways, if at all, do risk assessment approaches need to be amended to incorporate special characteristics of manufactured nanomaterials?

Figure 3-2 Relationship of Key Science Questions to Support Risk Assessment and Management Decisions; Based on Comprehensive Environmental Assessment (Davis and Thomas, 2006)
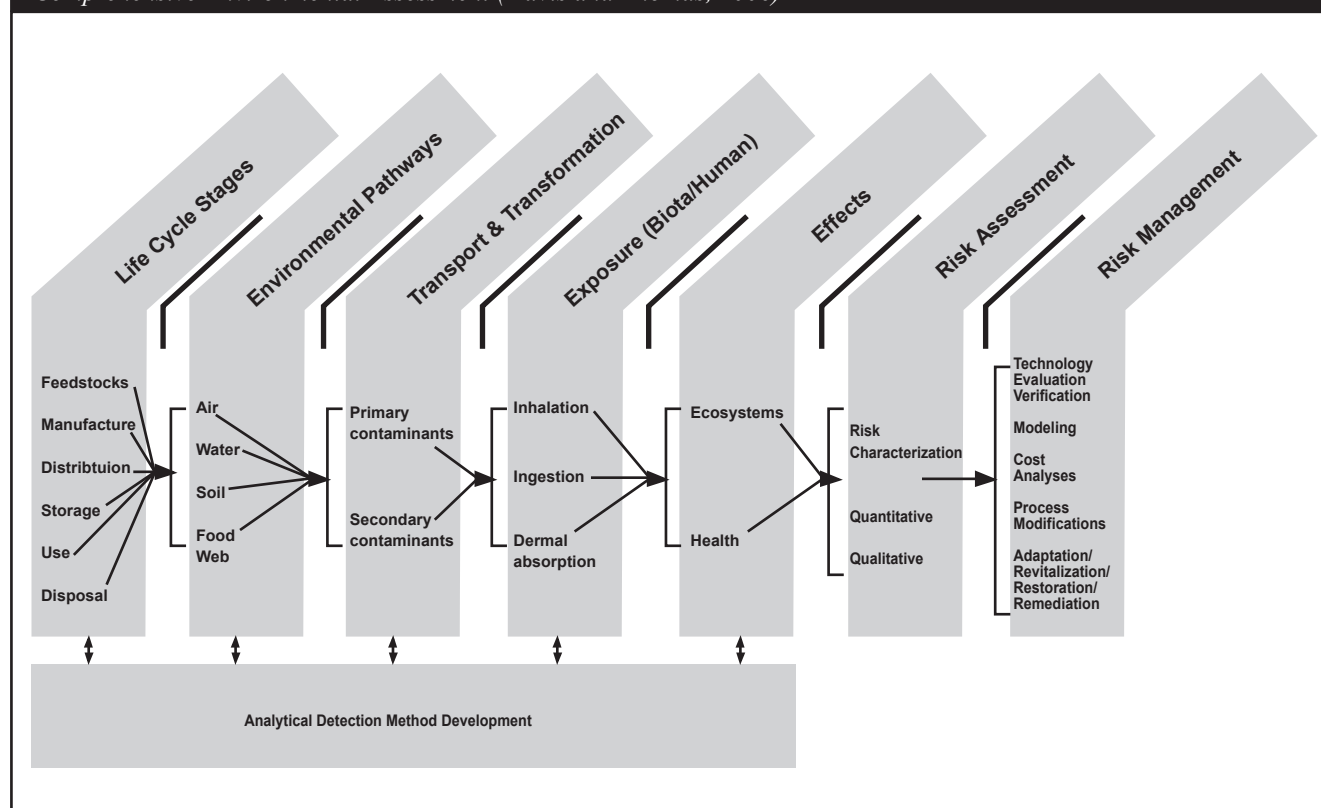
Theme 4. Preventing and Managing Risks

- Which manufactured nanomaterials have a high potential for release from a life cycle perspective and what decision-making methods and practices can be applied to minimize the risks of nanomaterials throughout their life cycle?

- How can manufactured nanomaterials be applied in a sustainable manner for treatment and remediation of contaminants?

3.3. Informing Risk Assessment and Risk Management

Figure 3-2 illustrates the interrelationship of the research activities and research products that inform risk assessment and risk management issues. While the basic paradigms of health and ecological risk assessment are still relevant, they are expanded in the comprehensive environmental assessment (CEA) approach to encompass the product life cycle of nanomaterials. By taking a broad view of the potential for releases of both primary and secondary materials to multiple environmental media, the evaluation of the environmental and health risks of nanomaterials is seen as an issue that cuts across EPA programmatic domains and is not simply categorized as solely an air, water, toxics, or solid waste issue. The CEA approach (Davis and Thomas, 2006; Davis, 2007) starts with a qualitative life cycle framework. It takes into consideration multiple environmental pathways, transport and transformation processes, cumulative and aggregate exposure by various routes, and ecological as well as human health effects. Depending on the availability of data, both quantitative and qualitative characterizations of risks may result. However, given the limited information currently available on nanomaterials, the CEA approach is being used to identify where key data gaps exist with respect to selected case studies of specific applications of nanomaterials.

3.4 Prioritization of Research

ORD evaluated several key issues and activities to identify priorities for its research program. Research recommendations from the EPA *Nanotechnology White Paper* and research coordination leadership in the NNI Strategy (2008) were important considerations. Defining questions for establishing priorities were:

- Does the research support EPA's mission to protect human health and the environment?

- Is the research important to support EPA regulatory decisions on nanomaterials?

- What role does EPA play in leading/ coordinating this research topic under the NNI EHS strategy (2008)?

- Is the research part of an international agreement to collaborate and leverage research activities?

- What research is important to support Agency risk assessment and management activities?

- How do partnerships with federal, academic, and industry researchers enhance research activities?

Having considered these questions within the context of resource constraints and research being conducted by other organizations, ORD has focused its nanotechnology research program on the areas described in Section 4 of this strategy.

3.5 Implementation

The research described in this NRS will be implemented through multi-year plans (MYP). The Office of Research and Development's research multi-year plans present the long-term strategic vision of EPA's research programs. The MYPs serve as a planning and communication tool to describe the scope of research addressing EPA's priority science questions. The MYPs are also used to help (1) demonstrate how ORD's research programs contribute to Agency outcomes and strategic goals; (2) provide information to aid in and support decisions during budget formulation; and (3) assist in managing performance and accountability reporting.

ORD is forming a Nanomaterial Research Coordination Team, which is a cross-EPA research planning group, to communicate program office and regional research needs to ORD and for ORD to communicate its research activities and products under the strategic research themes. This approach promotes ORD's focus on the highest priority issues and provides a roadmap to achieving long-term research goals while allowing the flexibility for ORD to address emerging nanotechnology issues that are affecting specific programmatic areas.

This section discusses the research themes and associated key science questions. For each science question, text addresses the topic background and program relevance, describes the proposed research activities, and discusses the anticipated outcomes.

<u>Critical Paths</u>. For each key science question, the NRS presents a critical-path diagram for addressing the question. The boxes within each diagram represent the sequencing of key deliverables, and the arrows indicate how one deliverable informs another. The critical-path diagrams do not reflect when specific research activities begin or end: in general, work will be initiated far in advance of the deliverable, and may continue in some form once a deliverable has been completed.

4.0
Research Themes

4.1 Research Theme: Sources, Fate, Transport, and Exposure

4.1.1 Key Science Question 1. *What technologies exist, can be modified, or must be developed to detect and quantify manufactured nanomaterials in environmental media and biological samples?*

4.1.1.1 Background/ Program Relevance

The detection of manufactured nanomaterials in various environmental media presents a significant challenge. This is due in part to potential confounding by the presence of anthropogenic and natural nanomaterials. Challenges arise because many different manufactured nanomaterials currently exist and their numbers are increasing; for certain types of nanomaterials, such as nanotubes, many thousands of different structures are possible. In addition, the fate, transformation, and mobility of these materials are only beginning to be understood. Consequently, scientific understanding of the reactions these materials undergo, how they age in various environmental media, how they interact with other compounds present in the environment, and whether and to what extent they form agglomerates or aggregates is limited. These issues compound the complexity of detecting and quantifying nanomaterials in environmental media.

The development of effective methods for measuring manufactured nanomaterials in environmental media at concentrations relevant to potential exposure scenarios is critical to understanding the environmental impacts of these materials. Such methods would also enable the more rapid achievement of the safe development of nanotechnology-related products. ORD-sponsored research will ultimately seek to develop remote, *in situ*, and continuous monitoring devices that yield real-time information and that can detect manufactured nanomaterials at very low concentrations.

Risk assessments of nanomaterials will require the ability to measure their environmental concentration in the workplace, home, biota (including human tissues), and ecosystems of interest. Analytical methods needed to characterize and analyze nanomaterials will require the modification of existing analytical tools and the development of completely new tools and approaches to meet these challenges. The same properties that make nanomaterials a significant challenge to analyze in any matrix (such as high binding capacities) may also provide unique opportunities for developing new analytical methods (e.g., tagging with fluorophores) for their analysis in complex biological and environmental systems. Obviously, studies will be necessary to determine how such tagging techniques will alter the physciochemical properties of the nanomaterials. ORD will integrate fundamental research on detection method development from NSF, NIST, DoD, and others with its own focused methods research effort to inform this research question.

4.1.1.2 Research Activities

Measurement science (based on analytical chemistry and physical properties) will have multiple roles in nanomaterials assessment and will require different types of analytical methods. There are several major areas of investigation with nanomaterials that require the application of a wide array of measurement and characterization techniques for characterization, detection, identification, or quantification.

Characterization of nanomaterials: ORD will undertake studies to characterize the physical and chemical properties of bulk nanomaterials to assess and quantify their unique features and characteristics (e.g., surface-to-volume ratio, 3-dimensional structure, size, size distribution, relative dimensions (aspect ratio), chirality, electrical/magnetic properties, and microstructure). Access to the equipment needed for these studies will require the formation of partnerships with other federal agencies, such as the National Institute of Standards and Technology (NIST), the National Cancer Institute (NCI) and the Department of Energy (DOE). Each of these agencies has or is in the process of establishing nanomaterial research facilities, such as the Advanced Measurement Laboratory (AML) at NIST and the Nanotechnology Characterization Laboratory (NCL) at NCI. These research facilities provide access to a wide variety of measurement and characterization tools.

Analytical methods supporting EF&T studies: ORD will take advantage of existing analytical methods for nanomaterials to support the initial focus on lab-based studies. An ever increasing number of papers in the literature have reported on the application of analytical methods for the measurement of nanomaterials for monitoring lab-based studies to model environmental processes under controlled conditions (e.g., soil leaching and subsurface transport) and concentrations. Examples include the analysis of fullerenes by liquid chromatography coupled to a photodiode array detector, the tracking of ^{14}C in radio-labeled carbon-based nanotubes, and the analysis of quantum dots by fluorescence spectroscopy.

Detection in environmental matrices: The published literature on the use of existing analytical tools for detecting or monitoring manufactured nanomaterials in the environment (especially in matrices other than the vapor phase) is very limited. Perhaps the first publication that borders on being a review of this literature is that of Nowack and Bucheli (2007). The lack of methodologies for analyzing environmental samples likely results from two major factors: (1) only in the last couple of years has any need for environmental analysis been contemplated, and (2) the challenges facing the detection and quantification of manufactured nanomaterials (especially those based solely on carbon) in environmental samples far exceed those associated with conventional pollutants, even those pollutants that comprise complex mixtures of many congeners (e.g., toxaphene).

To make unambiguous and quantitative determinations of manufactured nanomaterials in environmental samples, ORD will develop a combination of ensemble techniques (e.g., hyphenated methods coupling separation with spectroscopic detection, that measure collectively a number of particles) and single-particle techniques (e.g., methods, such as imaging, that measure individual particles). The separation method employed may be size exclusion chromatography, sedimentation field flow fractionation, or capillary electrophoresis. Determination could then be made, for example, by the coupling of ICPMS or a spectrofluorometer for fluorescent quantum dots. Ensemble methods can be developed for at least some classes of nanomaterials that provide screening assays to confirm the absence of detectable levels of nanomaterials or to provide an upper limit concentration estimate.

To develop analytical methods suitable for environmental monitoring, ORD will work with NIST to contribute to the development of standardized reference materials in a variety of representative matrices. Methods for environmental analysis or routine monitoring must account for the extraordinarily wide array of potential parent materials and transformation products. In contrast to methods for the other roles described above, approaches to environmental measurement must include non-target analysis, where the type(s) of nanomaterials that need to be detected are not known in advance (the entire spectrum of parent materials must be amenable to analysis). The problems that traditionally plague environmental analysis, such as the wide array of matrix interferences that limit detectability, make environmental monitoring of nanomaterials even more challenging. Examples of this type of application do not yet exist, and are an additional research need. Once suitable analytical methods have been developed in the laboratory, sites will be selected for monitoring of various media (i.e., air, water, soil, sediment and sludge) where environmental concentrations would be expected to be greatest, such as production sites for nanomaterials and manufacturing sites of products containing nanomaterials.

4.1.1.3 Anticipated Outcomes

- Development of methods for characterizing nanomaterials, through partnerships with NIST, NCI and/or DOE

- Development of analytical methods for the detection of carbon-based nanomaterials in environmental matrices

- Development of analytical methods for the detection of non-carbon-based nanomaterials in environmental matrices

- In cooperation with other federal agencies, development of standardized test materials for a variety of representative environmental matrices

Critical Path for Research on Detection

Key Science Question 1: What technologies exist, can be modified, or must be developed to detect and quantify manufactured nanomaterials in environmental media and biological samples?

2009

Report on the state-of-the-science for sampling and measurement in environmental media.

2010

Extend multimedia modeling capabilities to address NM exposure and risk issues/applications

Develop methods for measuring selected NM in environmental matrices

Evaluate physical and chemical properties that influence exposure to nanomaterials in environmental media.

Provide approaches for detection of NM in the environmental media

Modified or developed methodologies to detect and quantify NM in environmental media and biological samples

4.1.2 Key Science Question 2. *What are the major processes and/or properties that govern the environmental fate, transport, and transformation of manufactured nanomaterials, and how are these related to the physical and chemical properties of those materials?*

4.1.2.1 Background/Program Relevance

Given the current scientific uncertainty surrounding fate, transport, detection and modeling of manufactured nanomaterials, it is difficult to accurately assess the environmental disposition of nanomaterials or the potential exposure pathways to human and ecological receptors. Ultimately predictive models for estimating the environmental fate and transport of nanomaterials are needed.

Nanotechnology research for fate, transport, detection and modeling of manufactured nanomaterials is needed to identify the most critical parameters and uncertainties associated with these materials. This research will characterize the environmental fate and transport (EF&T) of nanomaterials from sources to human and ecological receptors. The research

will support risk assessments of manufactured nanomaterials and ways to manage their potential releases. Initially the research will provide a fundamental understanding of the physical and chemical properties of nanomaterials and their impact on fate and transport pathways. In order to address this fundamental understanding, research to provide specific analytical detection techniques for nanomaterials also will be necessary. Research collaborations with agencies such as NIST, academia, and industry are planned to advance the understanding of the limitations and capabilities of identified analytical techniques. Finally, existing predictive models that may be used for nanomaterial fate and transport will be modified, and if necessary, new models will be developed. These efforts will involve collaborations with other federal agencies, consortiums, international partners and academia.

Because of the introduction and increased production of nanomaterials, it is necessary to better understand the fate, transport, detection and modeling of these materials. Quantitative as well as qualitative research is necessary to reduce the uncertainty surrounding the introduction and existence of nanomaterials in the environment and to identify the exposure pathways of concern to receptors. Quantitative research such as identifying the speciation of silver nano particles and the impact of speciation on the mobility of the silver particles in sediments as well as the bioavailability to surrounding receptors is an example of one ORD research project. Qualitative research such as assessment of existing chemistry methods for measuring nanometal oxides in ambient air is another project. Research on these and other issues will assist the Agency in risk assessment and risk management of engineered nanomaterials. ORD will conduct the following broad research activities as described below.

4.1.2.2 Research Activities
- Understand the processes that govern the fate and transport of manufactured nanomaterials
- Understand the chemical and physical properties of manufactured nanomaterials and how they influence fate and transport processes
- Develop predictive models for transport of manufactured nanomaterials

ORD has initiated a research program to study nanotechnology fate and transport research; the primary objectives will be to determine the physciochemical properties controlling the mobility of nanomaterials through ecosystems and develop predictive models for estimating their mobility. Research questions include the identification of system parameters that alter the surface characteristics of nanomaterials through aggregation (e.g., pH effects), complexation (e.g., surface complexation by dissolved organic carbon) or changes in oxidation state (e.g., chemical- or biological-mediated electron transfer). This work will provide the basis for prioritizing potential ecological exposure pathways that warrant further exploration.

Understand the processes that govern the fate and transport of manufactured nanomaterials
The potential for the occurrence of manufactured NMs in sediments, soils, air and aqueous environments, necessitates the understanding of the processes controlling the fate and transport of these materials in each of these environmental matrices. The unique challenges to understanding the EF&T of nanomaterials is based on knowledge that:

- Nanomaterials exist as particles, and thus their surface chemical and physical properties will determine their environmental fate and transport

- The chemical and surface properties of nanomaterials will be modified by interaction with naturally occurring constituents such as dissolved organic matter, biota (e.g., bacteria, and biomolecules (e.g., polysaccharides)

- Changes in surface properties with naturally occurring constituents will significantly alter the mobility of nanomaterials in aquatic ecosystems

The wealth of information currently in the environmental literature concerning the fate and transport of chemical contaminants results from the study of chemicals that are soluble to some extent in aquatic ecosystems. Much of the existing work will have little value for predicting the EF&T of nanomaterials. The body of work concerning the movement and stability of colloidal material, which range in size from 1 nm to 1 μM, in aquatic ecosystems, however, is already providing insight into the processes controlling the transport of

nanomaterials in the environment (Loux and Savage, 2008). The EF&T processes most likely to control the transport of nanomateials in the environment will include dispersion, agglomeration, and surface complexation with natural organic matter and biological constituents.

ORD will conduct controlled laboratory studies to understand these fate and transport processes and the factors that control them. Initial work will focus on understanding their transport in porous and compacted media; the tendencies of nanomaterials to aggregate, sorb or agglomerate in ecosystems; and the factors that influence the mobility of the nanomaterials. ORD has also identified research questions surrounding the impact of nanomaterials in groundwater, surface water, drinking water, wastewater and solid waste. In addition to laboratory studies, ORD will collect data from field systems to understand large-scale fate and transport processes and the factors that influence them.

Understand the physical and chemical properties of manufactured nanomaterials and how they influence fate and transport processes
Processes that control movement (i.e., sorption, dispersion, agglomeration, degradation) will be strongly affected by the chemical and physical properties of nanomaterials, such as surface charge, pH, ionic strength, redox conditions, and ambient air conditions such as temperature and humidity. Consequently, typical chemical parameters for predicting chemical fate and transport such as water solubility, octanol-water partition coefficient and vapor pressure will be substituted with parameters such as particle size, surface charge and surface potential. Obtaining information on the chemical and physical properties of specific nanomaterials and classes of materials is necessary to understand their effect on fate and transport processes. For example, a specific ORD research project is characterizing the surface reactivity of silver, iron, titanium dioxide and cerium oxide and determining the impact of this reactivity on mobility and toxicity of the nanomaterials. Another example is ORD's investigation of processes controlling the mobility of carbon-based nanomaterials in porous media. The mobility of these materials largely depends on the degree and type of functionalization (elements or other functional groups at the surface of the nanostructures), which affect solubility and surface charge.

Clearly, the determination of how transport of nanomaterials through soils, the vadose zone, and groundwater is affected by solution chemistry and colloid surface properties is critical for understanding the fate of nanomaterials. These are important questions for understanding the fate of nanoiron particles purposely placed in the ecosystem for source control of DNAPL plumes. Previous metals research has shown that chemical speciation of inorganic engineered nanomaterials is an important factor to understand for the fate and transport and ultimate bioavailability of the materials. Initial research by ORD on nanosilver particles impregnated in clothing and washed indicates potential pathways for human exposure and introduction of nanosilver to the environment. Silver is impregnated in fabrics and other materials as an anti-fungal/anti-microbial agent, but little is known about how the properties of the nanosilver particles impact their fate and transport in the environment. Initial research indicates that the presence of oxidants in the wash water likely limit the bioavailability of the nanosilver particles. ORD continues to assess the chemical transformation and speciation of inorganics such as silver.

Develop predictive models for transport of manufactured nanomaterials
The successful development of EF&T models for nanomaterials will depend on understanding of the processes controlling the EF&T of engineered nanomaterials and the ability to determine the chemical and physical properties needed to predict such processes. ORD will study the applicability of existing environmental fate and transport models and to develop new predictive EF&T models that are tailored specifically to nanomaterials. Early analysis of the Estimation Programs Interface Suite (EPI Suite) models, the primary set of predictive tools the Agency uses for calculating the fate and transport of soluble organic chemicals, indicates that they will have little or no applicability to predicting the EF&T of nanomaterials. Models do exist for predicting the transport of natural colloidal materials and they are being investigated for application to nanomaterials. As such, traditional DLVO (Derjaguin, Landau, Verwey and Overbeek) theory is already lending insight into environmental fate and mobility trends of nanomaterials (Loux and Savage, 2008). Basic colloid models will have to be modified. Likiewise, a modified version of EPA's MINTEQA2 model used for calculating metal speciation could provide surface

potentials for nanomaterials. Surface complexation models are also finding use for determining the effect of surface complexation on nanomaterial stability in aquatic ecosystems (Fukushi and Sato, 2005).

4.1.2.3 Anticipated Outcomes

Results from this research will provide an improved understanding of the EF&T of manufactured nanomaterials in the environment. This will allow EPA to develop a set of predictive tools.

Researchers will:

- Develop a scientific understanding of the processes that govern the fate and transport of manufactured nanomaterials

- Measure the chemical and physical properties of manufactured nanomaterials and determine how these properties influence and impact fate and transport

- Identify the exposure pathways associated with production, end-use, and recycling or disposal of manufactured nanomaterials in different environmental matrices

- Improve the scientific understanding of detection methodologies for quantifying manufactured nanomaterials

- Develop multiple predictive models for understanding and measuring the transport of manufactured nanomaterials

Figure 4-2 Critical Path for Research on Sources, Fate, and Transport
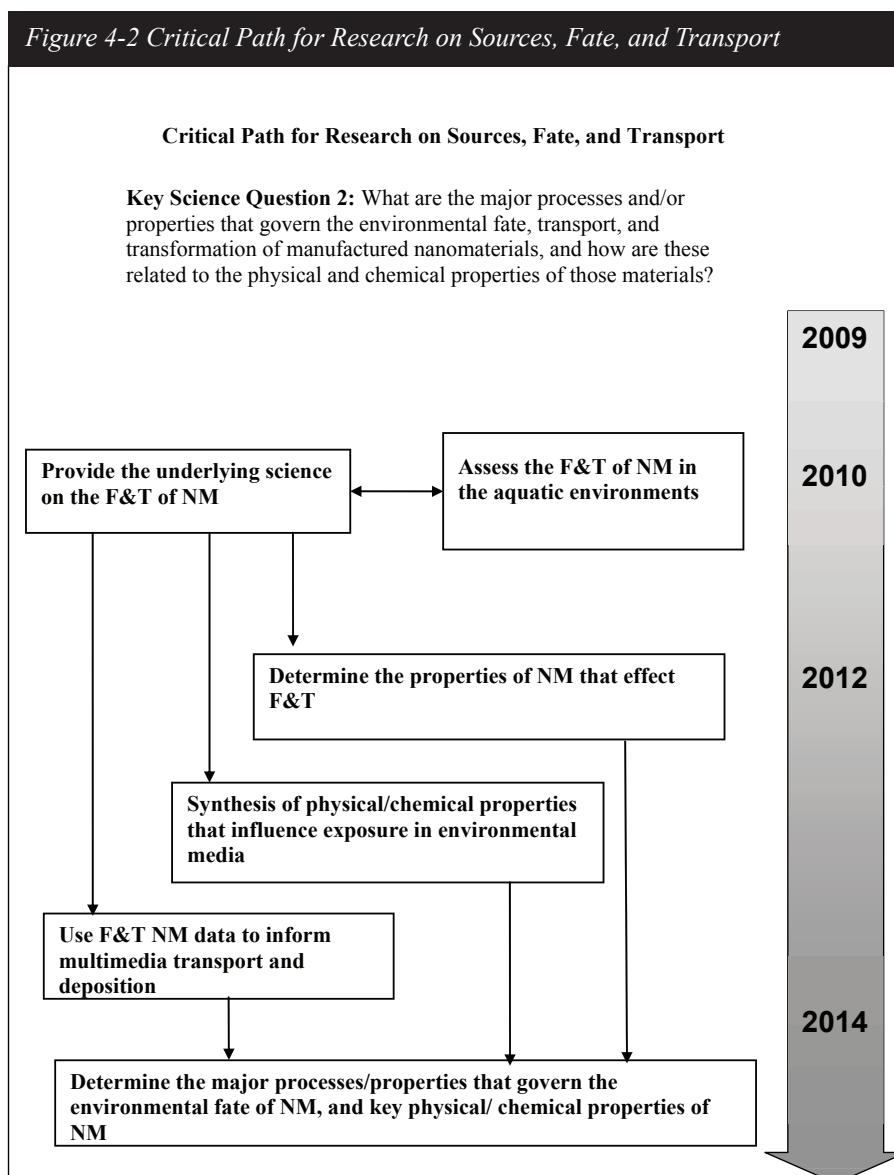
4.1.3 Key Science Question 3. *What are the exposures that will result from releases of manufactured nanomaterials?*

4.1.3.1 Background/ Program Relevance

Research is needed to provide insight into the type, extent, and timing of exposures to nanomaterials in all relevant environmental media and through all relevant exposure pathways. Cumulative exposures, both with other manufactured nanomaterials as well as with bulk-scale pollutants, also need to be explored. The information provided through this exposure research can be linked with other exposure and biological impact data to improve the scientific basis of risk assessment for manufactured nanomaterials. General population exposure may occur from environmental releases from the production and use of nanomaterials and from direct use of products (e.g., cosmetics) containing nanomaterials. The rapid growth of products that contain nanomaterials could result in their presence in soil and aquatic ecosystems. This presence will result from effluents of manufacturing plants, and the recycling or disposal of nano-based consumer products into landfills and surface/ground water. An exposure assessment attempts to answer the following questions for a particular substance or chemical:

- Who or what is exposed (e.g., people, ecosystems)?

- What are the pathways for exposure (air, water, land)?

- How much exposure occurs?

- How often and for how long does exposure occur; that is, what is its frequency and duration?

4.1.3.2 Research Activities

EPA uses a number of models to conduct chemical exposure assessments. Descriptions and links to these models can be found at the websites for the Council for Regulatory Environmental Modeling (CREM: http://cfpub.epa.gov/crem/) and the Center for Exposure Assessment Modeling (CEAM: http://www.epa.gov/ceampubl/). Table 4-1 provides a listing of several of the models/tools used by the program offices for exposure assessment and each model's general application and applicability to nanomaterials in its current form. With the exception of the EPI-Suite™ calculators, all of the exposure assessment models need the user to provide input data on the physical and chemical properties for the chemical of interest. The EPI Suite™ calculators are based on a single input, a Simplified Molecular Identification and Line Entry System (SMILES) string that is a typographical method for representing unique chemical structures. The other models in Table 1 were developed primarily for exposure assessments of synthetic organic chemicals, and thus require input such as water solubility, octanol-water partition coefficients and Henry's Law constants to predict fate and transport.

	Table 4-1 Models/Tools to Conduct Chemical Exposure			
	Several of the primary models/tools used by the Program Offices for exposure assessment and each model's general application and applicability to nanomaterials in their current form			
Acronym	Model Name	Primary Program Office	Application	Applicability to NMs
E-FAST	Assessment Screening Tool Version 2.0	OPPT	Estimates concentrations of chemicals in multimedia from multiple release activities	Modification Required
EPI-Suite™	Estimation Programs Interface Suite	OPPT	Estimates physical & chemical properties for organic chemicals	Not Applicable
EXAMS	Exposure Analysis Modeling System	OPP	Estimates fate, transport, and exposure concentrations of chemicals in aquatic ecosystems	Modification Required
Trim Expo	Total Risk Integrated Methodology Exposure-Event Module	OAQPS	Estimates human exposure to criteria and hazardous air pollutants	Modification Required

Exposure models will require modification to allow the input of molecular parameters and physical and chemical data specific to nanomaterials (e.g., particle size, surface charge, distribution or sticky coefficients, and agglomeration tendencies). OPPT has recently requested the assistance of ORD to review the E-FAST model, which supports EPA's New Chemicals and Existing Chemicals Programs, for its applicability to nanomaterials. Specifically, ORD will:

- Focus on the physical, chemical, and other properties currently required as user provided/default inputs

- Determine whether these inputs are appropriate for nanomaterials when assessing exposures related to industrial releases to surface water, air, and/or landfills

- Identify other properties as potential inputs that might be more appropriate for assessing general population and environmental exposure to nanomaterials

The challenges in identifying and measuring the concentration of manufactured nanomaterials in environmental and biological systems will present significant obstacles to providing the data necessary to conduct exposure assessments of these materials for both ecological and human receptors. Such assessments will require the development of alternative methods for determining the source and the environmental concentrations of nanomaterials in aquatic and terrestrial ecosystems. The interest in nanomaterials is driven by their unique properties and activities at different scales; these same properties provide the opportunity for developing indicators of exposure by measuring changes in structures and functions of biological organisms in contact with nanomaterials. By identifying indicators of exposure resulting from exposure to nanomaterials, it will be possible to reconstruct the exposure pathway and ultimately the source and the environmental concentration of the nanomaterial of interest. This ability to move from an internal biological response to external environmental concentration represents a growing area of exposure science referred to as *exposure reconstruction.*

ORD's research in this area focuses on the linkage of responses across endpoints at multiple biological levels of organization, from molecular alterations to populations. These linkages can serve as a basis for identifying and validating mechanistic indicators of exposure and effects, informing ecological risk assessments of nanomaterials. Currently, a systems-based approach is being used to assess exposures and define toxicity pathways for model chemicals with well-defined modes/mechanisms of action (MOA) within the hypothalamic-pituitary-gonadal (HPG) axis. These pathways serve as a basis for understanding responses of small fish across biological levels of organization, ranging from molecular responses to adverse effects in individuals to, ultimately, changes in population status. The studies employ a combination of state-of-the-art molecular biology, bioinformatic, and modeling approaches, in conjunction with whole animal testing. As such, the project will enable a unique opportunity to interface empirical toxicology with computational biology in the exposure assessment of nanomaterials.

The molecular biological tools for this research will focus on the application of the 'omic' tools (i.e., genomics, proteomics and metabolomics) to identify indicators of exposure. These tools provide the ability to identify indicators of exposure by measuring gene regulation, protein formation, and changes in an organism's metabolome in response to exposure to a chemical or mixture of chemicals. By elucidating the kinetics of the marker's response, it is also possible to provide an understanding of the temporal and spatial aspects of exposure.

Currently, no information is available in the literature concerning the identification of indicators of exposure for nanomaterials. However, ongoing research with pesticides exhibiting estrogenic activity is demonstrating the feasibility of this approach. ORD has developed molecular indicators of exposure (based on genomic responses) of aquatic organisms (water flea, *Daphnia magna* and fathead minnow, *Pimephales promelas*) to estrogenic compounds and is using advanced genomic methods to develop androgenic indicators. The Nuclear Magnetic Resonance (NMR)-based metabolomics research program being conducted at ORD's NMR research facility is demonstrating the use of high-resolution NMR to identify changes in the profiles of endogenous metabolites (i.e., the metabolome) in the serum and urine of fathead minnows exposed to estrogenic

compounds. The literature also provides examples of the use of genomics to identify indicators of exposure in humans. Microarray analysis of blood samples taken from benzene-exposed workers has identified peripheral blood mononuclear gene expression as an indicator of exposure for benzene (Forest et. al, 2005).

Collaboration to further identify the exposure pathways of manufactured nanomaterials
ORD will work in collaboration with other agencies and academia to study and identify the most common exposure pathways for manufactured nanomaterials. ORD will seek to establish international collaborations through the development of collaborative or coordinated calls for proposals. These research proposals will also engage ORD scientists in the study of exposure routes and pathways, relevant

exposure doses, and critical exposure concentrations. Research will also identify potential subpopulations of organisms that are more susceptible to manufactured nanomaterial exposure than others.

4.1.3.3 Anticipated Outcomes

- Identification of the dominant exposure pathways to ecological receptors of interest

- Assessment of the applicability of EPA's current exposure models to nanomaterials

- Identification of the physical and chemical properties required to inform exposure

- Identification of indicators of exposure through the application of genomics, proteomics and metabolomics

Figure 4-3 Critical Path for Research on Exposure Pathways

Critical Path for Research on Exposure Pathways

Key Science Question 3: What are the exposures that will result from releases of manufactured nanomaterials?

2009

Provide the underlying science on the exposure pathways of NMs

An assessment of the applicability of EPA's current exposure models to nanomaterials

2010

Identify the exposure pathways associated with production, end-use, and recycling or disposal of manufactured nanomaterials in different environmental matrices

2012

Synthesis of physical/chemical properties that influence exposure in environmental media

Identification of indicators of exposure through the application of genomics, proteomics and metabolomics

2014

Modification of current exposure model and development of new exposure models to predict exposure pathways for nanomaterials in environmental media

4.2 Research Theme: Human Health and Ecological Effects Research to Inform Risk Assessments and Test Methods

4.2.1 Background and Program Relevance

As described in EPA's *Nanotechnology White Paper,* nanomaterials could have health and ecological implications arising from new routes of exposure and/or toxicities associated with exposure to these novel materials, by-products associated with their applications, or their interactions with various environmental media.

By characterizing nanomaterials' health and ecological effects and identifying the physical and chemical properties that regulate their toxicity and biokinetics, ORD will address a lack of information required for nanomaterials risk assessment.

ORD's research will provide EPA offices with information on the health and ecological effects of specific nanomaterials and applications impacting EPA's mission, as well as guidance on best practices, approaches and test methods for assessing/predicting their health and ecological effects. ORD will also be addressing key immediate priority effects research needs identified in the US EPA *Nanotechnology White Paper,* such as, adequacy of test methods, characterization of the health and ecological effects of nanomaterials (nanotoxicology), hazard identification, dosimetry and biological fate.

ORD's nanomaterials health and ecological effects research builds upon its ongoing risk assessment-based research within the Air, Water, and Safe Products/Safe Pesticides programs. These research activities provide the facilities and expertise that are directly applicable to addressing nanomaterial health and ecological effects resulting from various potential routes of exposure and environmental interactions. ORD's research is conducted within a risk assessment paradigm. ORD's nanomaterials health and ecological effects program will conduct research to:

- Evaluate current test methods to assess their adequacy to determine the toxicity of nanomaterials, and modify or develop toxicity test methods, as required

- Determine the acute and chronic health and ecological effects of selected nanomaterials, including their local and systemic toxicities

- Determine the health and ecological effects associated with nanomaterial applications and their interactions with environmental media

- Determine the physical and chemical properties responsible for nanomaterial health and ecological toxicities, mode(s) of action, and mechanism(s) of injury in order to identify the appropriate exposure-response metric(s), e.g., surface area, particle size, etc. relative to traditional, concentration-based metrics

- Identify the physical and chemical properties of nanomaterials that regulate their deposition, uptake, and fate, as well as host susceptibility and sensitivity factors (e.g., gender, age, life stage, disease conditions) that may influence their toxicity and biokinetics

- Identify ecological systems that contain especially susceptible organisms, life stages, or populations

- Identify and develop alternative testing approaches, technologies, and models to screen, rank, and predict the *in vivo* toxicity of nanomaterials and their applications

4.2.2 Key Science Question 4. *What are the health effects of manufactured nanomaterials and their applications, and how can these effects be best quantified and predicted?*

4.2.2.1 Human Health Effects Research Activities

ORD will examine the health effects of nanomaterials that are relevant to EPA's mission and mandated regulatory responsibilities by addressing the health effects research needs identified in EPA's *Nanotechnology White Paper* and the NNI's, *Environmental, Health and Safety Research Needs for Engineered Nanoscale Materials.* However, there exist significant challenges associated with addressing nanomaterials health effects; these include:

1)The significant diversity of manufactured nanomaterials as well as their potential to produce health effects due to their novel properties, new routes of exposure associated with their use, by-products associated with their applications, or their interactions with various environmental media

2) The need to provide nanomaterials health effects information in a timely manner to Agency offices to address their immediate needs

3) The need to address the 3Rs of toxicity testing (reduce, refine and replace the use of animals) in research and regulatory programs

Opportunities do exist to address these challenges associated with assessing nanomaterials health effects and include:

1) Employing the vision and recommendations of the National Academy of Sciences, National Research Council report, *Toxicity Testing in the 21st Century:*

A Vision and a Strategy that provides a direction to identify alternative toxicity testing approaches, assays, and methods to ultimately predict *in vivo* health effects of nanomaterials and their applications as well as means to address the 3Rs of toxicity testing

2) Leveraging ORD nanomaterials health effects research with similar activities at the national (NNI and other federal programs including: NIOSH, National Toxicology Program, etc.) and international levels (Organization for Economic Cooperation and Development, OECD)

3) The existence of validated alternative testing methods and ORD's airborne particulate matter health effects program that has demonstrated the ability of *in vitro* test methods to provide consistent results reported for *in vivo* studies, including clinical and epidemiology studies, associated with examining the pulmonary toxicity of particles

Figure 4-4 An Integrated Testing Strategy for ORD's Nanomaterials Health Effects Research
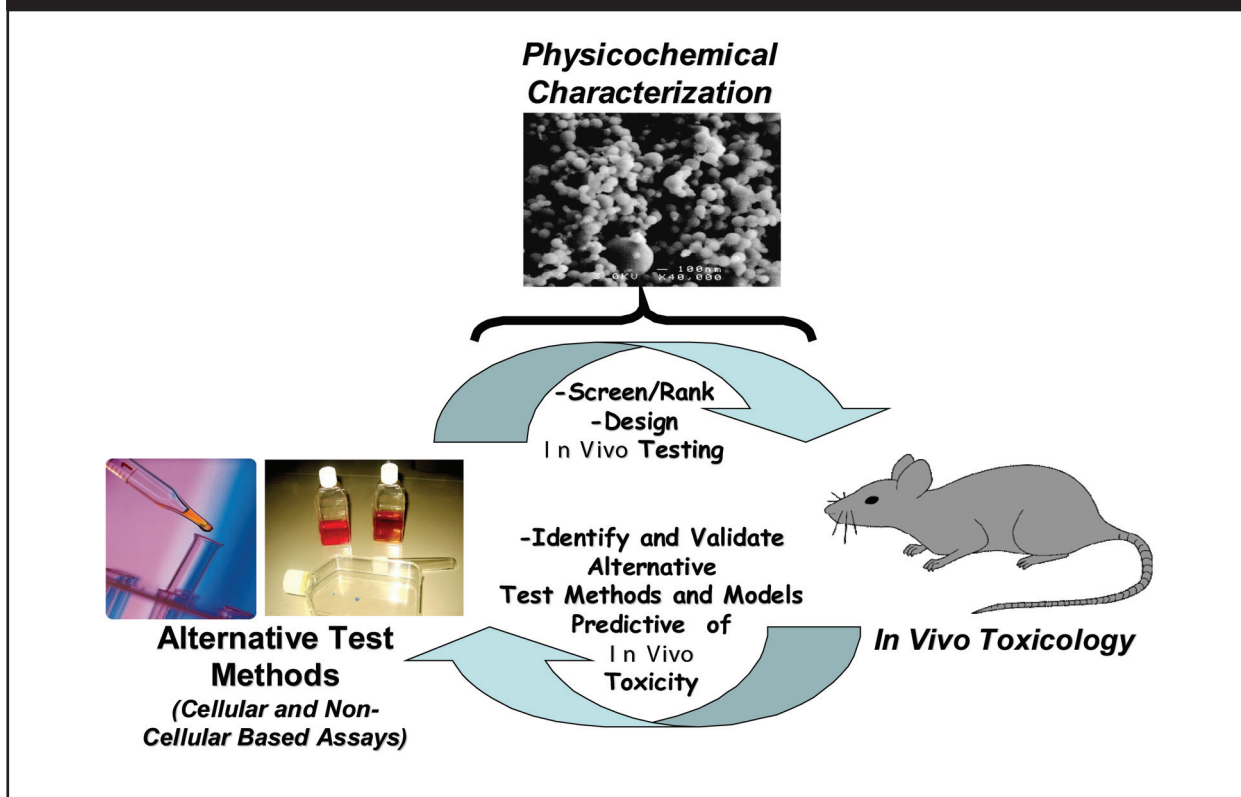
An integrated multi-disciplinary testing strategy for nanomaterials health effects research: ORD will employ an integrated testing strategy as shown in Figure 4-4 to address nanomaterials health effects research described under Key Science Question 4. The strategy will integrate and coordinate the expertise of toxicologists, material scientists, and exposure assessment scientists to examine the health effects of nanomaterials and their applications. An integrated testing strategy to assess nanomaterials health effects is consistent with numerous nanomaterials health effects workshop reports (G. Oberdorster et al, Particle and Fibre Toxicology 2:8, 2005; D.B. Warheit et al., Inhalation Toxicology 19(8):631-643, 2007; John Balbus, et al., Enviorn. Health Perspect. 115:1664-1659, 2007; J.G. Ayres et al, Inhalation Toxicology 20(1):75-99, 2008).

ORD's nanomaterials integrated testing approach consists of three key components:

1. Nanomaterials Physical and Chemical Characterization: Nanomaterials that are relevant to EPA will undergo recommended physical and chemical characterization. This will require integrating the expertise of nanoscale material scientists into ORD health effects research, since physical and chemical information is critical to: 1) ensure the purity and confirm/validate the properties of nanomaterials before initiating research to assess their health effects; 2) detect and quantifying nanomaterials in cells and tissues in order to determine nanomaterial biokinetic or ADME; and 3) provide information for the identification of nanomaterials properties regulating their toxicity (hazard identification) and exposure-response metrics.

2. Alternative Test Methods: ORD will employ cellular and non-cellular test methods to assess the toxicity of nanomaterials that are relevant to EPA. *In vitro* toxicity testing will use a variety of cell types reflecting different routes of exposure (dermal, inhalation, ingestion) and health effects that may arise due to the ability of nanomaterials to translocate from their initial site of deposition to other organs within the body. Nanomaterials *in vitro* toxicity testing will assess the mutagenic, intestinal, pulmonary, dermal, immunological, neurological, reproductive, cardiovascular, and developmental toxicities using cellular models reflective of these

toxicities. Alternative testing methods will also employ non-cellular assays to examine the surface properties of nanomaterials by assessing their reactivity and molecular interactions with proteins as well as other biological constituents; e.g. antioxidants and second messengers. Non-cellular interactions and surface properties may play a key role in regulating nanomaterial cellular uptake and toxicity.

Alternative toxicity testing methods provide a means to: 1) rapidly screen and rank the relative toxicities of various nanomaterials for *in vivo* toxicity testing; 2) provide key information (e.g., exposure dose and health endpoints) to assist in designing *in vivo* toxicity testing that will potentially refine/reduce the number of animals needed for *in vivo* studies; 3) determine mechanism(s) of injury and mode of action of nanomaterials; 4) rapidly perform comparative toxicity studies between chemically identical nano vs. micro-size materials; 5) perform nanomaterials interactions, uptake, and distribution at the biochemical, cellular, and intracellular levels; and 6) correlate nanoparticle surface properties with their biological and cellular interactions, and toxicity.

ORD's ToxCast program (http://epa.gov/comptox/toxcast/news.html) will assist in extending ORD's efforts to develop alternative test methods to evaluate nanomaterials toxicity. ToxCast offers an approach to address the extreme diversity of nanomaterials by applying high-throughput platforms and computational approaches to screen a large number of materials. The ToxCast program will assist in ORD's efforts to rank the toxicity of nanomaterials as well as develop models to identify physical and chemical properties that determine the toxicity of nanomaterials.

3. Nanomaterials *In Vivo* Toxicity Testing: ORD's nanomaterial health effects research strategy will assess the toxicity of nanomaterials in animals; i.e., *in vivo* toxicity. These studies will examine cancer, pulmonary, dermal, and gastrointestinal toxicities associated with initial site of deposition of nanomaterials by various routes of exposure (dermal, inhalation, ingestion) as well as immunological, neurological, reproductive, cardiovascular, and developmental toxicities to assess their potential systemic toxicities. *In vivo* toxicity studies will examine the deposition and fate of nanomaterials following various routes of exposure, as well as

identify host susceptibility and sensitivity factors (e.g., gender, age, life stage, and disease conditions) that may influence their toxicity and biokinetics

Coordinating and Leveraging ORD's integrated testing strategy to assess nanomaterials health effects:
As depicted in Figure 4-4 and as previously described, physical and chemical characterization of nanomaterials will be conducted prior to assessing their health effects. Also as depicted in Figure 4-4, it is anticipated that ORD's integrated testing strategy to assess nanomaterials health effects will be a coordinated, iterative process providing: 1) an approach to rank nanomaterials for *in vivo* toxicity testing; 2) assist in designing nanomaterial *in vivo*

toxicity testing studies; and 3) allow for shallow and in-depth parallel toxicity testing in order to identify those alternative approaches and *in vitro* assays/responses that correlate with *in vivo* nanomaterial toxicity. This information will be critical in order to ultimately identify the physicochemical properties of nanomaterials and alternative test methods that predict their *in vivo* toxicity. Opportunities exist for ORD's integrated nanomaterials health effects testing strategy to progress at a rapid rate by leveraging its efforts with similar activities at the national (other federal programs under the NNI; for instance, those of NIOSH and the National Toxicology Program) and international levels (Organization for Economic Co-operation and Development, OECD).

Figure 4-5 Critical Path for Conducting ORD's Nanomaterial Human Health Effects Research
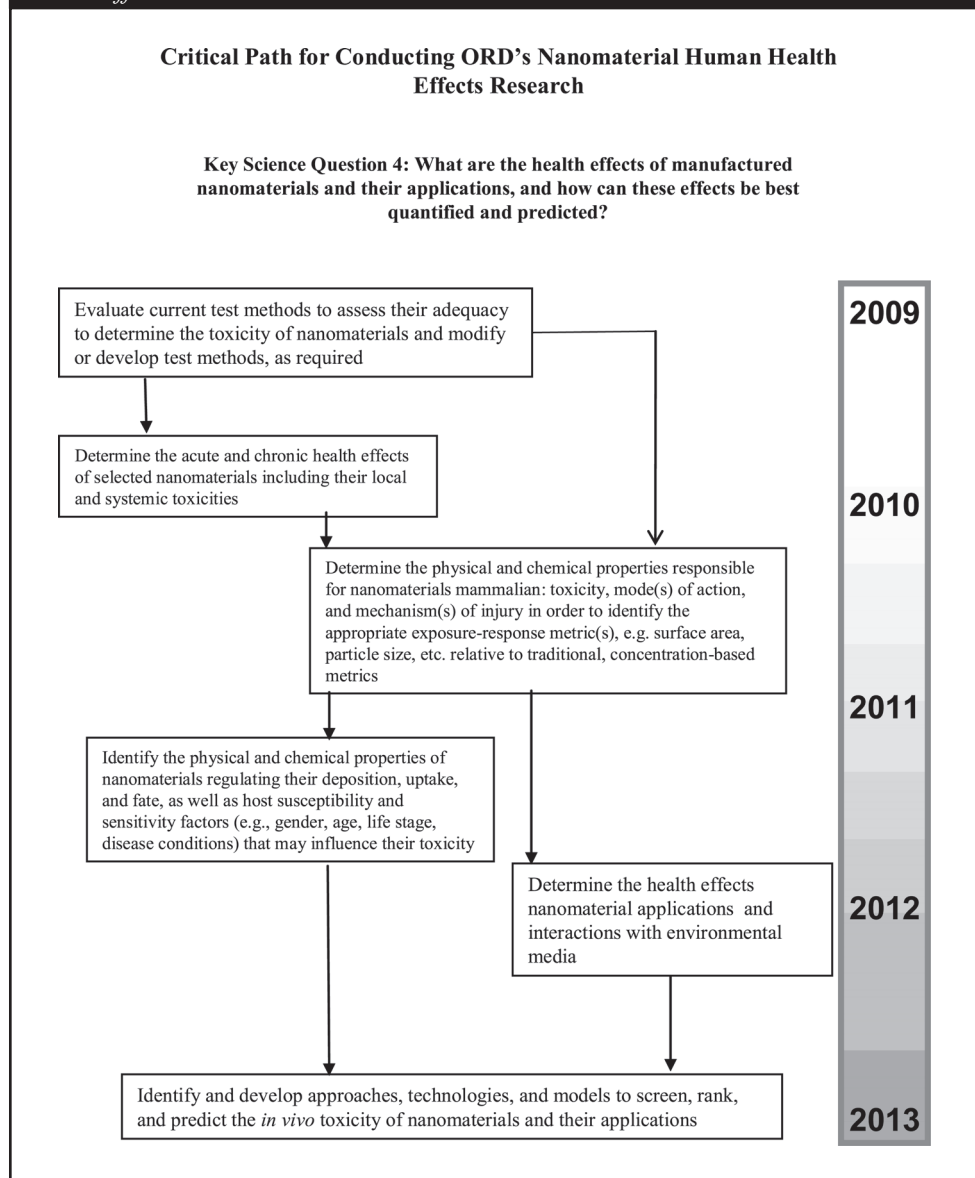
4.2.3 Key Science Question 5. *What are the ecological effects of manufactured nanomaterials and their applications, and how can these effects be best quantified and predicted?*

4.2.3.1 Ecological Effects Research Activities
ORD's nanomaterials ecological effects strategy will address the ecological effects research needs identified in EPA's *Nanotechnology White Paper* and the NNI's *Environmental, Health and Safety Research Needs for Engineered Nanoscale Materials*, and is intended to be responsive to EPA's regulatory needs. The ecological effects research strategy focuses on the physical and chemical factors unique to nanomaterials that may influence their toxicity, determine rates of uptake and disposition in ecological matrices, and require novel approaches for quantifying exposure-response relationships. The strategy is organized into chronological tasks, beginning with the need to evaluate methods used in traditional toxicity for their adequacy or applicability to nanomaterials. The tasks are broadly defined and it is expected that research will advance in an iterative manner; it is likely that initial tasks will need to be revisited depending on results of subsequent research efforts, and as new nanomaterials are developed.

Task 1 - Evaluate the suitability of existing test methods for assessing the hazards of manufactured nanomaterials: nanomaterials, or products containing nanomaterials, are already being submitted for approval under Agency programs such as TSCA and FIFRA. These and other Agency programs have existing protocols for evaluating hazards to ecological receptors in both aquatic and terrestrial systems, but the appropriateness of these methods for nanomaterials has yet to be evaluated. Key concerns include how to expose organisms to nanomaterials in ways that have relevance to exposures that may occur in the environment, and whether these standardized assays address the organisms, life stages, and bioavailability considerations that are most important for understanding the potential ecological risks of nanomaterials. In addition to direct toxicity testing, emphasis will be placed on measurements of exposure, uptake, and dose.

Task 2 - Understand the mechanisms underlying the ecological effects of nanomaterials and identify potential gaps in hazard assessment procedures: Building on results of exposures using standard (or appropriately modified) test methods, further research will explore the specific mechanisms of nanomaterials toxicity and ecological effects. Understanding the mechanisms of effects is key to determining novel risks that may be created by nanomaterials, defining the appropriate organisms and endpoints for nanomaterials risk assessments, and providing the basis for future predictive models. Parameters that govern adsorption, distribution, metabolism, and excretion (ADME) will be evaluated, as will means of expressing toxicological dose. Other studies will evaluate the interaction of nanomaterials with physical, chemical, and biological components of ecological systems to determine if there are effects of nanomaterials not captured by single organism toxicity testing, such as altering the relationships among ecosystem components and thereby affecting overall ecosystem function. Throughout Task 2, emphasis will be given to determining whether nanomaterials exert effects through mechanisms that would not be well addressed by existing ecological hazard and risk screening tools.

Task 3 - Develop methods and models to predict the hazard or ecological risk of nanomaterials: Due to the diversity of nanomaterials expected to enter the marketplace in the coming years, EPA will need predictive tools that can be used to prioritize newly developed nanomaterials for testing and further evaluation. For example, quantitative structure/activity relationships (QSARs) may be developed to predict the toxicity of untested materials based on their chemical structure and an understanding of the mechanisms underlying dose and toxicity. Likewise, ecological effects models may be important predictive tools if research in Task 2 indicates that ecological processes above the organismal level are being uniquely affected by nanomaterials. This work will build directly from Tasks 1 and 2 and associated research conducted by the Computational Toxicology Program.

Leveraging research with ORD laboratories, centers and other federal programs: ORD's nanomaterials health and ecological risk assessment research will leverage work with other federal programs and international efforts where similar nanomaterials are being monitored, studied, and characterized. For example, ORD laboratories are jointly addressing nano-cerium dioxide to assess potential environmental exposures, and associated
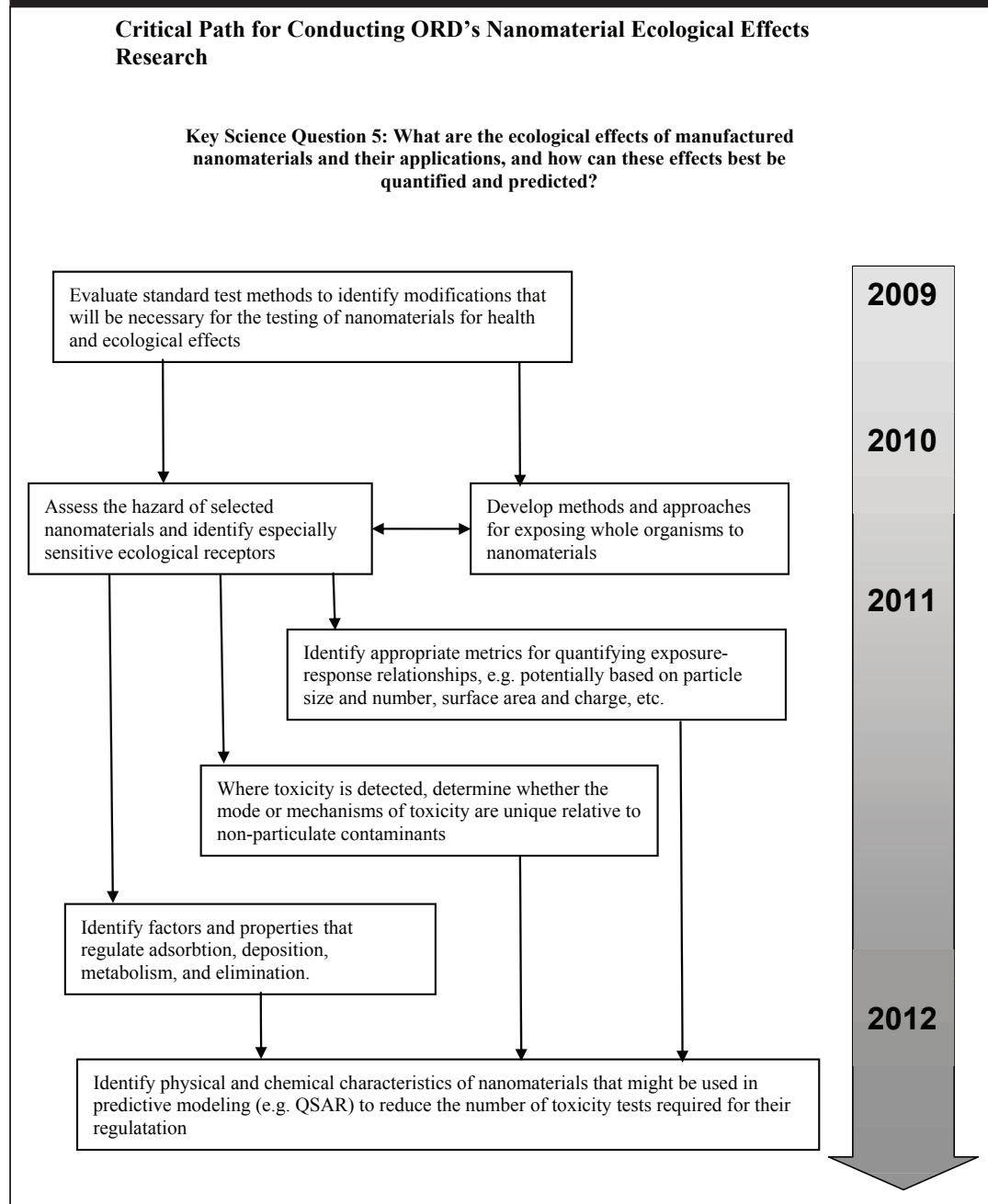
health effects. Research to examine the health and ecological effects of nanomaterials following their release into or interactions with environmental media will require the combined expertise of ORD's health and exposure scientists. ORD's nanomaterials health effects multi-tier strategy allows a means to interface with national and international nanomaterials *in vivo* toxicity efforts as a means to allow for the identification of alternative methods, approaches, and biological responses that are consistent with those generated in nanomaterials animal toxicity testing studies. Finally, the physical and chemical characterization of nanomaterials and their detection in biological systems will require a multidisciplinary approach with close interactions across ORD as well as with other organizations such as the Department of Energy's National Laboratories.

4.2.4 Anticipated Outcomes

ORD's human health and ecological effects research programs will provide key information regarding the health and ecological implications from exposures to nanomaterials, and their applications, in order to identify and manage potential adverse impacts and inform program offices and regions regulatory and other policy decisions. Specifically, ORD's nanomaterials effects research will provide Agency offices with information on the health and ecological effects of specific nanomaterials and their applications, as well as guidance on best practices and approaches/test methods for assessing/predicting health and ecological effects. ORD's nanotechnology health and ecological effects research activities will provide publications in peer-reviewed scientific journals on the:

- Characterization of nanomaterials health and ecological effects; identification of physical and chemical properties and host/sensitivity factors that regulate nanomaterials dosimetry, fate, and toxicity (information for both risk assessment and development of "greener" nanomaterials and a sustainable nanotechnology)

- Identification of testing methods/approaches to predict *in vivo* toxicity of nanomaterials; characterization of molecular expression profiles that may provide biomarkers of nanomaterial exposure and/or toxicity (exposure assessment and predictive nanotoxicology)

- Provision of necessary counsel and guidance that will assist in the review of premanufacture notice applications and assess the adequacy of harmonized nanomaterial test guidelines to assist OPPTS and internationally, the OECD (regulatory assistance/support and leveraging nanomaterials effects research)

- Addressing the gap in knowledge regarding the toxicity of nanomaterials, which has impeded the ability to conduct accurate life cycle analysis

Critical Path for Conducting ORD's Nanomaterial Ecological Effects Research

Key Science Question 5: What are the ecological effects of manufactured nanomaterials and their applications, and how can these effects best be quantified and predicted?

2009

2010

2011

2012

Evaluate standard test methods to identify modifications that will be necessary for the testing of nanomaterials for health and ecological effects

Assess the hazard of selected nanomaterials and identify especially sensitive ecological receptors

Develop methods and approaches for exposing whole organisms to nanomaterials

Identify appropriate metrics for quantifying exposure-response relationships, e.g. potentially based on particle size and number, surface area and charge, etc.

Where toxicity is detected, determine whether the mode or mechanisms of toxicity are unique relative to non-particulate contaminants

Identify factors and properties that regulate adsorbtion, deposition, metabolism, and elimination.

Identify physical and chemical characteristics of nanomaterials that might be used in predictive modeling (e.g. QSAR) to reduce the number of toxicity tests required for their regulatation

4.3 Research Theme: Developing Risk Assessment Methods

4.3.1 Key Science Question 6. *How may risk assessment approaches need to be amended to incorporate special characteristics of manufactured nanomaterials?*

4.3.2 Background/Program Relevance

Nanomaterials may have special properties that may influence their environmental behavior and effects on human health and ecosystems. These unusual features introduce complications for basic aspects of risk assessment such as characterization of exposure and dose-response relationships. For example, is particle count or one or more measures of surface properties (area, charge, etc.) a better metric than mass for describing dose-response relationships? Although nanomaterials pose significant new and possibly unique challenges for the practice of risk assessment, features of the basic paradigm for risk

assessment and risk management (NRC, 1983) are presumed to apply to these materials. Hazard identification determines qualitatively whether the nanomaterial will cause an adverse health effect. Dose-response assessments establish the quantitative relationship between dose and incidence of health effects. Exposure assessment is performed and the incidence of an adverse effect (risk) in a particular population is determined by combining exposure and dose-response. The effects of nanomaterials on the environment must also be assessed in order to protect and restore ecosystem functions, goods, and services. Ecological risk assessment entails the evaluation of goals and selection of assessment endpoints in a problem formulation step, followed by analysis of exposure to stressors and determining the relationship between stressor levels and ecological effects. The next step is estimating risk through the combination of exposure and stressor-response profiles, description of risk by discussing lines of evidence, and determination of ecological adversity (U.S. EPA, 1998). Interfacing among risk assessors, risk managers, and interested parties during the initial planning of a risk assessment and communication of risk at the end of the risk assessment are critical to ensuring that the results of the assessment can be used to support a management decision. The importance of communication and stakeholder involvement in both human health and ecological risk assessment and risk management has also been noted by the Presidential/ Congressional Commission on Risk Assessment and Risk Management (1997: (see Figure 2-1) and recently affirmed in the National Academy of Sciences "Science and Decisions: Advancing Risk Assessment" (NAS, 2008).

While basic features of the health and ecological risk assessment paradigms may still be relevant to nanomaterials, this emerging technology nevertheless warrants careful systematic evaluation such as that of the comprehensive environmental assessment (CEA) approach (Davis and Thomas, 2006; Davis, 2007), which treats the evaluation of the environmental and health risks of nanomaterials as an issue that cuts across EPA programmatic domains and is not simply categorized as solely an air, water, toxics, or solid waste issue. The CEA approach starts with a qualitative life cycle framework, as shown in Figure 4-7. It takes into consideration multiple environmental pathways, transport and transformation processes, cumulative and aggregate exposure by various

routes, and ecological as well as human health effects. Depending on the availability of data, both quantitative and qualitative characterizations of risks may result. However, given the limited information available on nanomaterials, the CEA approach is currently being used to identify where key data gaps exist with respect to selected case studies of specific applications of nanomaterials.

Case studies are recommended in the EPA *Nanotechnology White Paper* as a means to further inform research supporting the risk assessment process. The term "case study" is used to refer to specific examples of nanomaterials and the types of issues that would be need to be considered to assess their respective environmental and health risks. By focusing on specific examples of nanomaterials in realistic applications, it is possible to identify and prioritize research needs to assess the real world impacts of these materials. Given the striking differences in toxicological and physicochemical properties of nanomaterials, generalizations across nanomaterials need to be considered cautiously.

4.3.3   Research Activities

The role of ORD's nanomaterial risk assessment research is (1) to help guide overall research efforts toward generating the information needed to conduct future comprehensive environmental assessments of nanomaterials and (2) to carry out such assessments in coordination with all of ORD and the program offices. The research question ORD will address is, "How may risk assessment approaches need to be amended to incorporate special characteristics of manufactured nanomaterials?" To address this question, ORD will identify and prioritize information gaps by developing a series of case studies and workshops to further refine research needs for specific nanomaterials, as recommended in the EPA *Nanotechnology White Paper*.

In order to develop case studies of particular nanomaterials and their specific applications, appropriate nanomaterials must be selected. The collective judgment of an internal workgroup representing all relevant program offices was used for this purpose. The workgroup was given a summary of available information on the chemistry, human health, toxicology, exposure, and release of various

nanomaterials. Workgroup members were then asked to select two nanomaterials based upon five criteria: potential for biota/human exposure; apparent potential for both health and ecological effects; a reasonable amount of information with which to develop a case study; relevance of the nanomaterial to programmatic or regulatory needs; and "nanoness," e.g., having at least one dimension less than 100 nm. Using these criteria, nanoscale titanium dioxide and single walled carbon nanotubes (SWCNTs) were initially selected; subsequently, SWCNTs were replaced with nanoscale silver (nano-Ag) due to difficulties in obtaining adequate information on applications of SWCNTs that had presumptive exposure potential for the general population. Two applications of nanoscale titanium dioxide are under development, for water treatment and for sunscreen. The choice of a nano-Ag application is currently under evaluation. These selected classes of nanomaterials also serve as a common focus and point of coordination for near-term studies by the various ORD laboratories.

The case studies present available information for specific nanomaterials using the CEA approach as an organizing structure. These documents are intended to be used as part of a process to systematically identify and prioritize information gaps where additional research is needed. Draft case studies will be the focus for a series of workshops involving invited technical experts and stakeholders. Workshops will be conducted in a formal, structured manner using expert judgment techniques (e.g., multi-criteria decision analysis, expert elicitation). A detailed summary of the discussions and views expressed during the workshop will be used in refining the current research strategy document. The workshop summary will highlight areas of work that will be needed to support comprehensive environmental assessments of nanomaterials. This refined statement of research priorities will provide longer-term guidance for both ORD and the broader scientific community. This approach is consistent with a recent NAS review of the NNI's nanotechnology EHS research strategy (National Academy of Sciences, 2008).
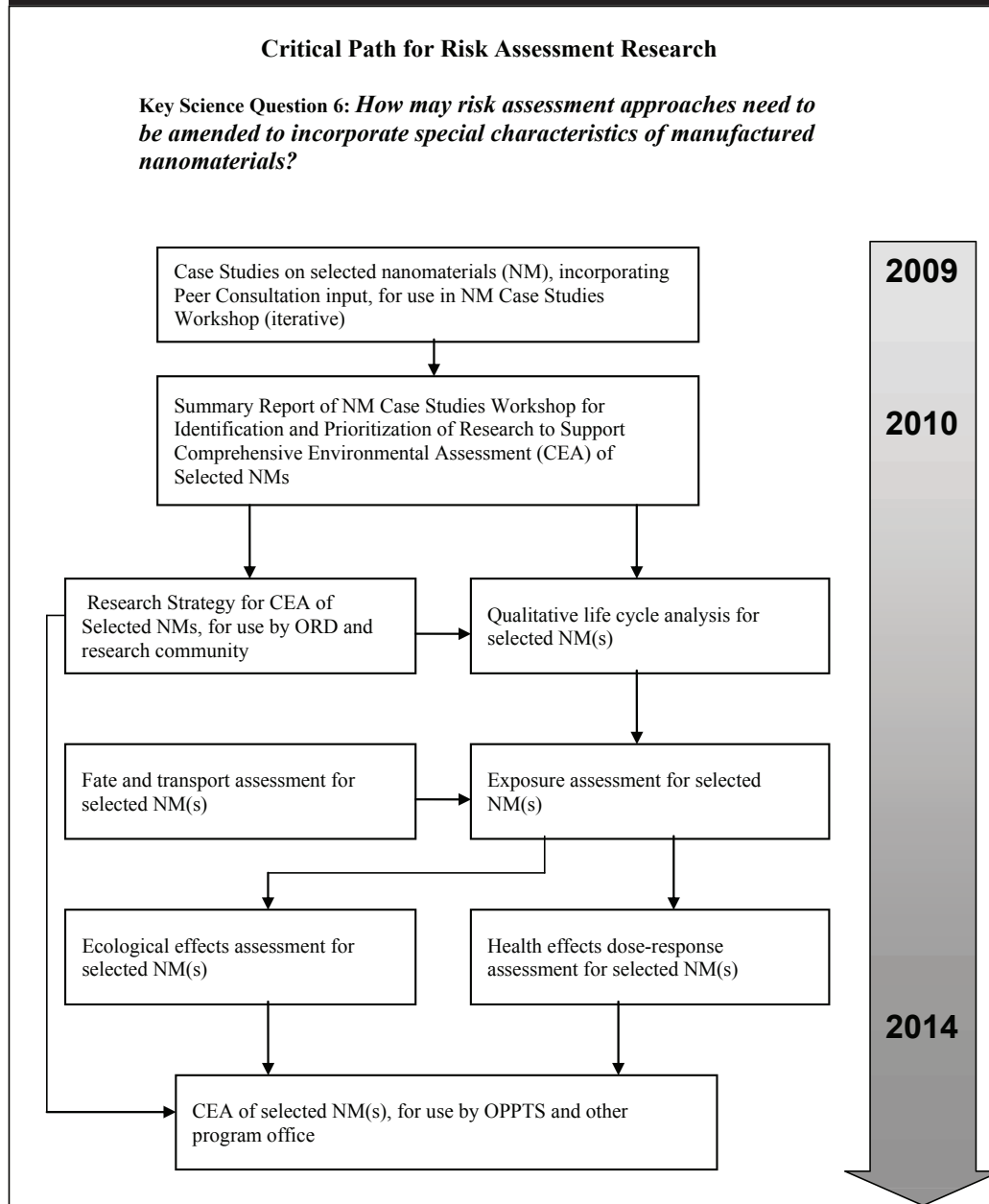
Concurrent with these longer range CEA-oriented activities will be more immediate and more narrowly focused assessment efforts in accordance with programmatic needs and data availability. Assessments of this type cannot be specified at present but are anticipated, contingent on progress in addressing scientific issues such as those identified throughout this document.

4.3.4   Anticipated Outcomes

Note that the outcomes listed here and in the Critical Path for Risk Assessment Research (see Figure 4-7) are intended to be representative of an iterative process that will involve the creation of a series of additional case studies and periodic reevaluation of earlier case studies as new information becomes available. The timeframe for the outcomes shown in the Critical Path figure is conservatively estimated but highly uncertain because of the many scientific uncertainties currently associated with nanomaterials. As indicated above, limited assessments (more narrowly focused than a CEA) may be attempted as data become more available, and such assessments could occur at any point within the overall timeframe shown in the Critical Path figure.

- Initially, two draft case studies for different applications of nano-titanium dioxide, to be followed by additional case studies and periodic iterative evaluation of earlier case studies as new information becomes available

- Workshop(s) for invited experts and stakeholders and public observers, using formal expert judgment methods to identify and prioritize research needed to support comprehensive environmental assessments of nanomaterials
- Using input from the workshop discussions, a document that lays out long range research directions for obtaining information needed for nanomaterial CEAs

Figure 4-7 Critical Path for Risk Assessment Research

Critical Path for Risk Assessment Research

Key Science Question 6: *How may risk assessment approaches need to be amended to incorporate special characteristics of manufactured nanomaterials?*

Case Studies on selected nanomaterials (NM), incorporating Peer Consultation input, for use in NM Case Studies Workshop (iterative)

Summary Report of NM Case Studies Workshop for Identification and Prioritization of Research to Support Comprehensive Environmental Assessment (CEA) of Selected NMs

Research Strategy for CEA of Selected NMs, for use by ORD and research community

Qualitative life cycle analysis for selected NM(s)

Fate and transport assessment for selected NM(s)

Exposure assessment for selected NM(s)

Ecological effects assessment for selected NM(s)

Health effects dose-response assessment for selected NM(s)

CEA of selected NM(s), for use by OPPTS and other program office

2009

2010

2014

4.4 Research Theme: Preventing and Managing Risks

4.4.1 Key Science Question 7. *Which manufactured nanomaterials have a high potential for release from a life cycle perspective, and what decision-making methods and practices can be applied to minimize the risks of nanomaterials throughout their life cycle?*

4.4.1.1 Background/Program Relevance

To understand the potential environmental implications of nanomaterials and to identify potential approaches to manage emissions/releases, it is critical to understand potential entry points of nanomaterials into the environment. Under this question, ORD will conduct research to understand emissions/releases that can occur either during production, use, recycling, or disposal of nanomaterials. Examples of points of entry into the environment include:

- **Manufacturing Waste Streams:** During the manufacture of nanomaterials, the inevitable by-product and waste streams will need to be evaluated. Pollution prevention (e.g., green chemistry) research may be very helpful in

the development of environmentally friendly manufacturing processes for nanomaterials.

- **Air Treatment:** Manufactured nanomaterials can be emitted along with other conventional pollutants during production processes. In addition, there are products that use manufactured nanomaterials where during their use nanomaterials can be emitted to the air, (e.g., brakes and fuel additives).

- **Water Treatment:** Some nanomaterials are intended to be biocides and may enter DW treatment facilities. Personal care products and pharmaceuticals containing nanomaterials will eventually be washed down the drain and transported to wastewater treatment plants. There they will either be removed from the wastewater and end up in the biosolids residuals or they will remain in the wastewater and be discharged into surface water as part of the treatment plant's effluent.

- **Disposal of Used Material:** At the end of its useful life, each of the consumer products and equipment items created using nanomaterials will enter the waste stream. It is critical to understand where these products end up (e.g., landfill, incinerator) in order to provide guidance on possible emissions/releases of nanomaterials.

- **Product Usage:** As products incorporating manufactured nanomaterials enter the consumer market place, material release may occur during the normal intended usage or conversely during unintended usage. Releases may occur through abrasion, adsorption/absorption, or volatilization, among other processes. For instance, if veterinary pharmaceuticals are administered using nanomaterials, these materials may be excreted and released into the environment when manure is land applied as fertilizer.

In addition to human and ecological exposure, there is a need to better understand how the manufacture, use, and waste management of nanomaterials will contribute to other environmental problems, including climate changes due to global warming and stratospheric ozone depletion; land use leading to acidification, eutrophication, and photo-oxidation; odor, noise, waste heat, radiation, and casualties. To

address these issues, researchers are implementing more comprehensive assessment tools, such as life- cycle assessment (LCA), that can establish comparative impacts of products and processes in terms of well-defined impact categories. Such an assessment can be applied across the entire life cycle [materials acquisition (cradle) to disposal (grave)] or along any desired part there-of (gate-to-gate). Hence within a single assessment, LCA for nanomaterials has the potential to address both the toxicological and environmental questions associated with these materials.

LCA experts worldwide agree that existing LCA tools are capable of supporting the development of decision frameworks for nanomaterials and nanoproducts.[1],[2] A number of cradle-to-gate and gate-to-gate LCAs have recently appeared in open literature, helping researchers to identify the key concerns that must be addressed if the goal of a full-scale LCA is to be realized. The proper life cycle boundaries, particularly the "grave," must be defined for a given material. This can be confusing when considering nanomaterials because they have the ability to permeate much smaller regions, passing throughout the environment. Data gaps concerning the transport, persistence, and toxicity of nanomaterials must be filled. This is challenging, because the diverse properties of nanomaterials (i.e., surface charge, size, shape, chemical composition) that can be synthesized will strongly impact how these materials disperse and react within the body and the environment. Thus, either a large amount of research or the development of accurate predictive models is needed to acquire the missing data. Additionally, issues such as the treatment of nanomaterials incorporated into larger composite materials and the recycle of nanomaterials must be addressed. The complexity of choices associated with the use of nanomaterials that can influence the LCA categories defined above is summarized in Figure 4-8.

The value of any assessment is not only the data it generates, but how the data are applied. Are there acceptable tradeoffs associated with nanomaterials? Is the large-scale production of an environmentally taxing material justified if it has medical applications

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1 Maynard, A.D., 2006. Nanotechnology: A Research Strategy for Addressing Risk. Woodrow Wilson International Center for Scholars, Washington, DC.

2 Kloepffer, W., M. A. Curran, et al. (2007). Nanotechnology and Life Cycle Assessment: Synthesis of Results Obtained at a Workshop in Washington, DC, 2-3 October 2006.

or can reduce costs or enhance performance? Questions such as these illustrate the ultimate need for a valuation system with suitable metrics. To this end, research is needed to develop an easily applied, LCA-based framework that can be used with other pertinent factors such as cost and societal benefit to provide a comprehensive evaluation of nanomaterials throughout their life cycle.

Figure 4-8 Characterization of a Selected Nanotechnology for Life Cycle Assessment

Characterization of nanotechnologies for life cycle assessment is challenging because of the various aspects of the material that can significantly influence the traditional impact categories.

Characterization of a Selected Nanotechnology for Life Cycle Assessment
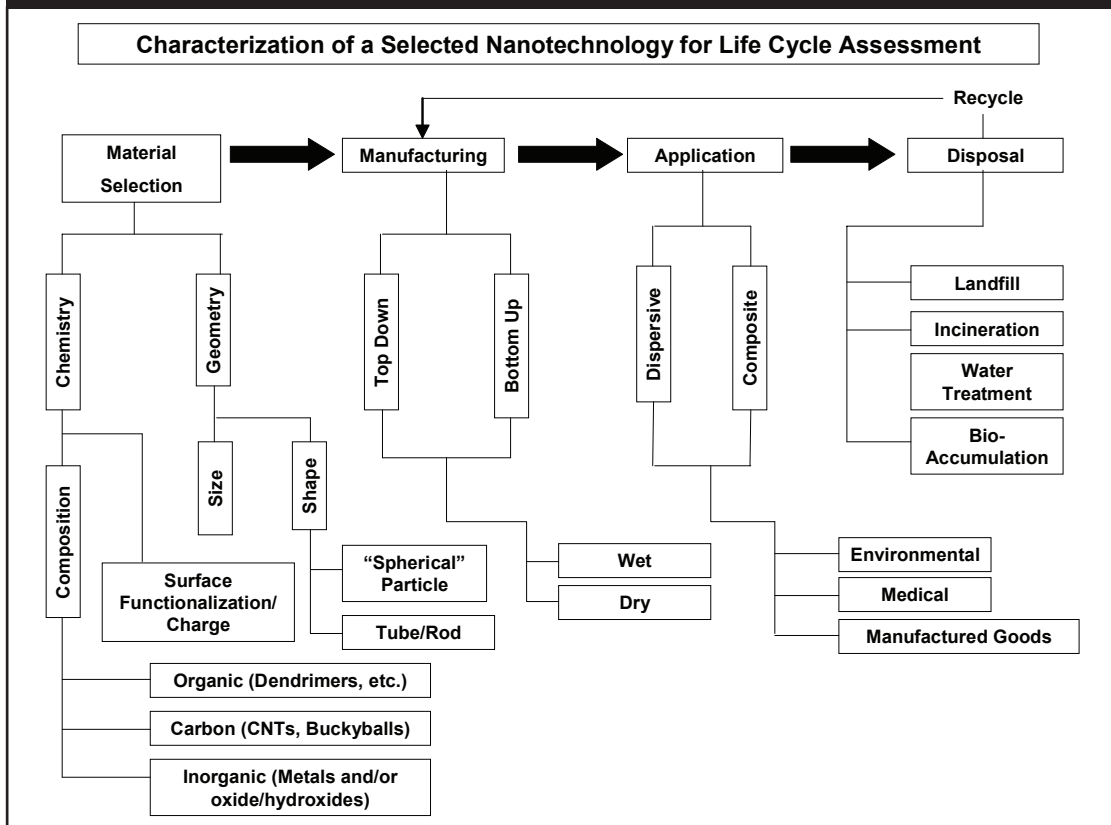
4.4.1.2 Research Activities

ORD will identify industries, processes, and products that have relatively high potential to release manufactured nanomaterials into the environment. Existing literature will be evaluated to better understand the industries of importance and identify where gaps in information preclude a full assessment of emission/release points of concern. ORD will perform a systematic assessment of the production, use, and ultimate fate of nanomaterials to understand the potential for emissions/releases into the environment. A modified tool using life cycle principles will be developed to better understand which industries pose the greatest potential to emit/release nanomaterials of concern and to inform decision makers about the overall impact of manufactured nanomaterials. This effort will also include a series of assessments for the highest priority industry categories. Results from ORD workshops will be used to guide industry and nanomaterial selection for assessment. Comparative assessments will be produced to help inform decision-makers at what stage in the lifecycle of nanomaterials interventions could be used to avoid future environmental pollution. The ORD effort will be closely coordinated with other organizations, particularly EPA's Office of Pollution Prevention and Toxics, which is also generating data on nanotechnology industries.

This research can be used to inform EPA, industry, and academia about potential proactive and "greener" approaches for manufacturing nanomaterials that

are designed to prevent nanomaterial release into the environment. It could also be used as input for future thorough LCAs. The development of a robust assessment tool can support decisions in the development of appropriate nanotechnologies. Such a tool is highly needed and has yet to be fully developed. In addition, the necessity for specific data will help with the design of fate, transport, and toxicity studies that are necessary to better understand the use and release of nanomaterials. The goal is to develop a decision-support framework available to stakeholders that is easy to apply and can accommodate a wide variety of nanomaterials and nanoproducts.

High-potential industries/processes
ORD will draw upon the latest literature, hold workshops, and interact directly with industry representatives to identify market trends for nanotechnology industries that utilize the priority manufactured nanomaterials indicated earlier in this document. This research will attempt to quantify the amounts of nanomaterials expected to be produced and used by existing industries, identify key processes used to manufacture these nanomaterials, and project future industries where significant releases may occur.

Identification/characterization of potentially released materials
Once we know where the manufactured nanomaterials may be released, it will be important to understand something about the characteristics of these materials to inform future transport, transformation, exposure, and health studies. The research will focus on whether the nanomaterial emissions/releases have the same characteristics (size, chemical composition) as the original material or have been modified before release to the environment. This area of research will be highly dependent upon the availability of technology to identify and characterize manufactured nanomaterials. Unfortunately, the ability to make these measurements is also highly uncertain and will require extensive research. Efforts to identify, develop, test, and verify detection technologies will be critical to the success of this research activity.

Entry point into the environment
Given that during the manufacture, use, and recycling or disposal of conventional products there are always emissions/releases of pollutants, it is reasonable to presume that some form of manufactured

nanomaterials will follow similar entry points into the environment. One of the primary goals of this research is to generate the data and tools needed to quantify and project these points of entry, so they can evaluate potential risks and possible approaches to manage those risks. One of the key issues to investigate is whether the nanomaterial compounds will be emitted/released in their original form or whether they will be physically or chemically bound with other compounds. This will directly impact transport and transformation and will influence potential exposures and health risks. For instance nanomaterials that are introduced to the environment in solution may be more likely than other nanomaterials to remain in their original form and become bioavailable. Nanomaterials that are chemically cross-linked in a matrix are less likely to be released in their original form and size, although uncertainties remain. Because of their exceptional properties and characteristics, some manufactured nanomaterials are being intentionally released to serve as catalytic agents for remediation or filtration purposes or as instruments for detection of pollution. This research will summarize the latest uses and provide available information on the characteristics of the materials released.

Materials modification to support green manufacturing of nanomaterials
Research on greener synthesis approaches will identify opportunities to reduce the environmental implications of nanomaterial production. Since basic nanotechnology production processes are still under development, EPA is well placed to work with others to design production processes that minimize or eliminate any emissions/releases. One area of research is producing nanomaterials using benign agents such as phenolics from tea extract, vitamins B1, B2, and C, or even sugars and carbohydrates which have been demonstrated to generate a wide variety of nanomaterials for various applications. These alternative synthesis methods use these benign materials which act as capping agents (e.g., ensures that nanoparticles do not agglomerate) creating and allowing the nanomaterials to maintain their properties and benefits. In addition to the addressing the key science question above, this research will be designed to answer the following question: how can energy consumption be minimized and waste/pollution prevented in the manufacturing of nanomaterials and products? The general approach will be to develop a

strategy that allows the greener preparation of these materials. Three of the main green chemistry areas that will be investigated include: 1) the choice of solvent, 2) the reducing agent employed, and 3) the capping or dispersing agent. For example, ORD is using a flame and furnace reactor combination to produce single-walled and multi-walled carbon nanotubes. We are using a common feed-stock (e.g., propane), as opposed to mixtures of carbon monoxide and hydrogen, and a metallic catalyst to initiate nanotube formation.

The goal of this research question is to perform the key initial step to inform additional research on transport, transformation, and subsequent exposure and health studies. In addition, by identifying potential release points, this research will provide key data required to inform how best to manage any potential risks.

Risk Management
ORD will conduct research on the feasibility of using conventional technology to manage the emissions/releases of manufactured nanomaterials or degradation by-products to all media. This research will inform regulatory officials and industry about the viability of various risk management alternatives and potential improvements to ensure the safe manufacturing, use, and disposal of nanomaterials. This research has the potential to influence decisions regarding manufacturing, storage, handling, use, and disposal of selected nanomaterials. The results of the research will be provided in the form of reports and computer-based systems that can be used to address the unique issues associated with various industrial operations.

To support the research activities below, ORD will conduct various workshops with industry, academia, and other parts of EPA to discuss potential environmental liabilities associated with manufacturing, using, recycling, and disposing of nanomaterials. The parties will exchange information and ideas about where releases are more likely to pose the greatest risks and what alternatives (e.g., preferred manufacturing approaches via green chemistry) are available that could minimize environmental liabilities. These workshops will help all participants consider how nanotechnology products can be designed in the most environmentally sustainable manner possible.

ORD will conduct parametric studies to determine if conventional operating conditions used to

incinerate traditional waste streams will effectively destroy nanomaterials present in waste, interfere with the effective destruction of traditional waste material, and/or create new hazardous products of incomplete combustion (PICs). In addition, since nanomaterials are for the most part long-lasting and not biodegradable, ORD will investigate their leaching potential to water bodies. Also, nanomaterials could serve as a means to concentrate other toxic pollutants present in various types of landfills, making them more bioavailable. This concern will also be investigated.

4.4.1.3 Anticipated Outcomes

- Identification of industries, processes, and products that have relatively high potential to release manufactured nanomaterials into the environment by working collaboratively with other organizations to inform decision-makers about the overall impact of manufactured nanomaterials

- Improved understanding of the industries of importance and identification where information gaps that preclude a full assessment of emission/release points of concern

- A systematic assessment of the production, use, and ultimate fate of nanomaterials that will improve understanding of the potential for emissions/releases into the environment

- Development of a modified tool using life cycle principles to: (a) better understand which industries pose the greatest potential to emit/release nanomaterials of concern and (b) inform decision-makers about the overall impact of manufactured nanomaterials

- A series of assessments for the highest priority industry categories, the results of which will be used to guide industry and nanomaterial selection for assessment

- Development of comparative assessments to help inform decision-makers at what stage in the lifecycle of manufactured nanomaterials interventions could be used to avoid future environmental impacts

- Design of production processes that minimize or eliminate any emissions/releases and reduce energy consumption during the manufacturing of nanomaterials and products

- An evaluation of the efficacy of existing pollution control approaches and technologies to manage releases of manufactured nanomaterials to all media during their production

- ORD will collaborate with others to report on opportunities to reduce the environmental implications of nanomaterial production by employing greener synthesis approaches
- Comprehensive evaluation of the impact nanomaterials could have on conventional thermal destruction and land disposal practices

- ORD will identify design production processes that minimize or eliminate any emissions/releases and reduce energy consumption during the manufacturing of nanomaterials and products

4.4.2   Key Science Question 8. *How can manufactured nanomaterials be applied in a sustainable manner for treatment and remediation of contaminants?*

While it is critical to understand the potential environmental implications of nanotechnology, it is also important to investigate how various nanomaterials can be used to prevent, control or remediate environmental contaminants that have up to now been difficult to manage with conventional technology.

Nanotechnology will be used to both create new technologies and improve the performance of conventional technologies. There are several avenues to obtain environmental benefits from nanotechnology.

- Use nanoscale materials in a synthesis process as a substitute for more toxic components or as a process mediator that reduces the mass of potentially toxic materials employed in the chemical process (e.g., catalysts)

- Incorporate nanoscale materials into a part of the production process used to treat noxious chemicals prior to final discharge

- Employ nanoscale materials to treat emissions/releases from power production and industrial processes waste streams

- Treat contaminated environmental media (i.e., air, water, sediments, or soil)

ORD's initial emphasis will be to address key pollutants of concern to EPA program and regional offices that have historically been difficult to manage, including sources that emit low concentrations of air pollutants and remediation of hazardous materials in complex heterogeneous environments.

In addition to supporting the recommendations of outside experts, this research will be valuable to EPA program and regional offices and outside stakeholders such as industry and states who are constantly looking for innovative solutions to address intractable pollution problems. Many of these needs have already been identified.

4.4.2.1 Research Activities
This area is primarily driven by the need to address existing environmental problems through the application of nanotechnologies. Only where nanotechnologies potentially offer superior solutions to high priority problems do they become viable candidates for ORD environmental applications research. Two key technical areas are identified below where benefits can be anticipated either directly through the development of nanotechnology-based materials and processes and/or indirectly through the development of technologies used to characterize nanomaterials that may subsequently be applied in support of environmental restoration efforts.

Waste/byproduct minimization
The use of nanotechnology in industrial processes has many potential advantages. One potentially significant environmental benefit is reducing the amount of material sent to the waste stream. Under this research area, ORD will work with its partners in industry and academia to investigate advanced approaches that have the potential to reduce waste products in those industrial sectors with high volumes of waste. Waste minimization benefits to be realized through nanotechnology applications will result either through the substitution of less-toxic chemical components in the manufacturing process or through the reduction in the required mass of toxic chemical components via enhanced reaction rates or efficiencies. An example of the first scenario includes the use of nanomaterials to improve material characteristics of bio-based, nanocomposite products.

These products are being developed as substitutes for more traditional petroleum-derived materials, resulting in a reduction of the mass of toxic components that could potentially be released into the environment. There are also numerous examples of the development of nanomaterials for use as catalysts in chemical manufacturing processes. The use of nanoscale catalysts results in an overall enhancement of process efficiency, thus reducing the required mass of toxic chemical components used in the manufacturing process.

Application of nanomaterials to reduce environmental risks
Under this research area, ORD will investigate the potential for various nanomaterials to minimize the release of toxic chemical constituents. Similar to the use of nanoscale catalysts in the manufacturing process, the use of nanomaterials to treat process waste streams (gas, liquid, or solid phases) provides enhancements in removal rates and/or efficiencies. One key activity will include the application of nano catalysis for the reduction of air pollutants and a better understanding of how these catalysts can be used in various environmental applications. Inorganic nanoscale materials, including metallic iron nanomaterials and aluminosilicate-based zeolites, have been synthesized for removal or degradation of metals and organic contaminants from air and water effluents generated as a result of manufacturing and power-generation operations. Similar to the case described above for the manufacturing process, the use of nanomaterials in end-of-pipe treatments affords the opportunity for regeneration or controlled disposal of treatment by-products. In addition, this research will study the use of nano-scale iron particles to remediate aqueous streams contaminated with chlorinated-organics, pesticides, PCBs, heavy metals and such inorganics like $Cr+6$, arsenates, perchlorates, and nitrates. If these treatment and remediation processes are successful, they can be incorporated into existing treatment systems to further reduce contaminant loading.

Another area of emphasis within this program will be to investigate the ability to physically and chemically tailor substances, surfaces, and pores at the nano-scale to improve selectivity and efficiency of membrane filtration, adsorption, and c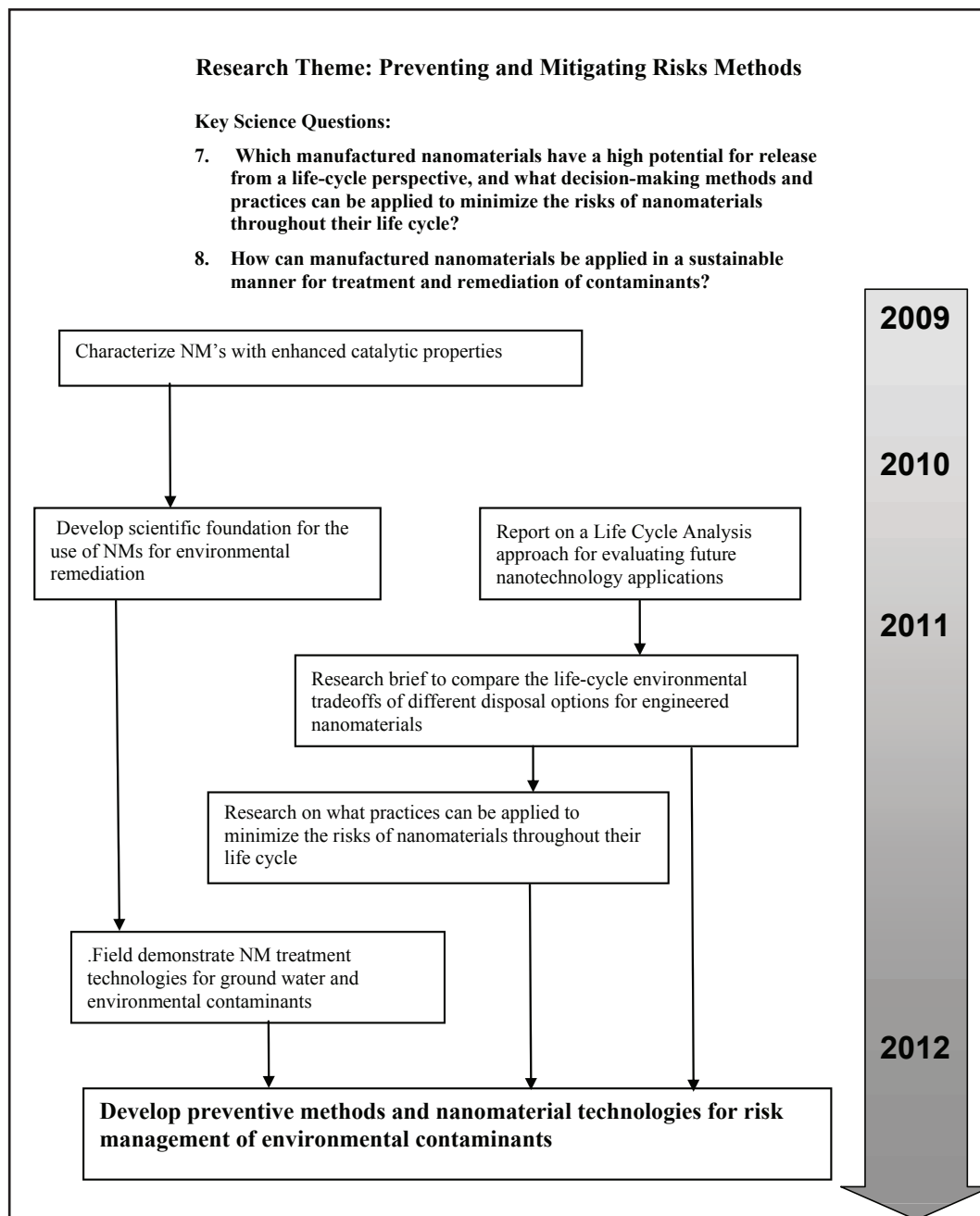atalysis. The objective is to identify and evaluate innovative, high performance or lower cost alternatives for treating critical contaminants. Improvements for many different treatment scenarios (e.g., matrices, contaminants, treatment technologies, and treatment goals) may become feasible. Examples of areas where such an approach could provide significant improvements in removal performance and cost savings is the use of nanotechnology to produce advanced sorbents for mercury control and water treatment. In the mercury area, the ability to directly link the physical and chemical nature of binding sites in the materials with the performance of those materials is the key to developing new or improved adsorbents with properties that exceed those that have conventionally been used. In the water area, nanomaterials may enable the manufacture of media that are more selective, efficient, and economical for removal or destruction of existing or emerging contaminants from drinking water, wastewater, and storm water. These improved media may arise from better design and uniformity of pore size, particle size, or composition made feasible by nano-scale design and control of the manufacturing process.

Remediation of contaminated sites is another area where ORD will explore the use of nanomaterials. Examples of these research and development efforts include the development of nanoscale metallic solids or biopolymers for the destruction of organic contaminants or the extraction of inorganic contaminants from ground water and soil. Ultimately, EPA can play a significant role in advancing the development and implementation of these technologies through research and testing. Using past experience implementing waste minimization, treatment, and remediation technologies, EPA can fulfill the much-needed role of a technical mediator between the commercial entities actively pursuing development of synthetic nanomaterials and those who may be negatively affected by the large-scale utilization of these materials.

4.4.2.2 Anticipated Outcomes

Nanotechnology research will play a role in providing environmental benefits to society through the development of new materials or technologies for waste minimization and treatment of conventional pollutants. Through this research ORD will report on the viability, performance, and benefits of the use of nanotechnology for the abatement and remediation of conventional toxic pollution.

Research Theme: Preventing and Mitigating Risks Methods

Key Science Questions:

7. **Which manufactured nanomaterials have a high potential for release from a life-cycle perspective, and what decision-making methods and practices can be applied to minimize the risks of nanomaterials throughout their life cycle?**

8. **How can manufactured nanomaterials be applied in a sustainable manner for treatment and remediation of contaminants?**

2009

Characterize NM's with enhanced catalytic properties

2010

Develop scientific foundation for the use of NMs for environmental remediation

Report on a Life Cycle Analysis approach for evaluating future nanotechnology applications

2011

Research brief to compare the life-cycle environmental tradeoffs of different disposal options for engineered nanomaterials

Research on what practices can be applied to minimize the risks of nanomaterials throughout their life cycle

.Field demonstrate NM treatment technologies for ground water and environmental contaminants

2012

Develop preventive methods and nanomaterial technologies for risk management of environmental contaminants

5.0
Conclusion

The ORD Nanomaterial Research Program is designed to provide information to support nanomaterial environmental, health, and safety decisions. The eight key science questions described in the NRS are intended to help decision makers answer the following questions:

- What nanomaterials, in what forms, are most likely to result in environmental exposure?

- What particular nanomaterial properties may raise toxicity concerns?

- Are nanomaterials with these properties likely to enter environmental media or biological systems at concentrations of concern, and what does this mean for risk?

- If we think that the answer to the previous question is "yes," can we change properties or mitigate exposure?

Providing information to answer these questions will serve the public by enabling decisions that minimize potential averse environmental impacts, and thereby maximize the net societal benefit from the development and use of manufactured nanomaterials.
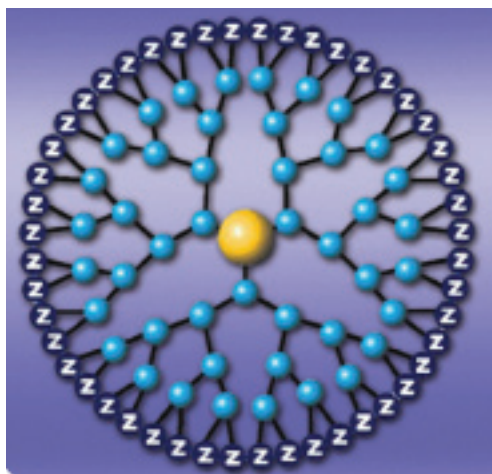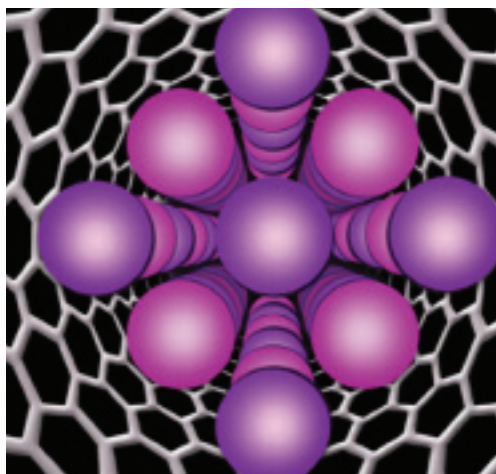
For more about EPA research on nanotechnology, please visit:
www.epa.gov/nanoscience

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