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NOTICE

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Nanotechnology White Paper

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FOREWORD

Nanotechnology presents opportunities to create new and better products. It also has the potential to improve assessment, management, and prevention of environmental risks. However, there are unanswered questions about the impacts of nanomaterials and nanoproducts on human health and the environment.

In December 2004, EPA's Science Policy Council (SPC) formed a cross-Agency Nanotechnology Workgroup to develop a white paper examining potential environmental implications and applications of nanotechnology. This document describes the issues that EPA must address to ensure that society benefits from advances in environmental protection that nanotechnology may offer, and to understand any potential risks from environmental exposure to nanomaterials. Nanotechnology will have an impact across EPA. Agency managers and staff are working together to develop an approach to nanotechnology that is forward thinking and informs the risk assessment and risk management activities in our program and regional offices. This document is intended to support that cross-Agency effort.

We would like to acknowledge and thank the Nanotechnology Workgroup subgroup co-chairs and members and for their work in developing this document. We would especially like to acknowledge the Workgroup co-chairs Jim Willis and Jeff Morris for leading the workgroup and document development. We also thank SPC staff task lead Kathryn Gallagher, as well as Jim Alwood and Dennis Utterback, for their efforts in assembling and refining the document.

It is with pleasure that we present the EPA Nanotechnology White Paper.

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ACRONYMS

ADME	Absorption, Distribution, Metabolism, Elimination
ANSI	American National Standards Institute
ASTM	American Society for Testing and Materials
CAA	Clean Air Act
CAAA	Clean Air Act Amendments
CAS	Chemical Abstracts Service
CDC	Centers for Disease Control and Prevention
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act
CFCs	Chlorofluorocarbons
ChemSTEER	Chemical Screening Tool for Exposures and Environmental Releases
CNT	Carbon nanotubes
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DfE	Design for Environment
DHHS	Department of Health and Human Services
DHS	Department of Homeland Security
DNA	Deoxyribonucleic Acid
DOC	Department of Commerce
DOE	Department of Energy
DOI	Department of Interior
DOJ	Department of Justice
DOS	Department of State
DOT	Department of Transportation
DOTreas	Department of the Treasury
E-FAST	Exposure and Fate Assessment Screening Tool
EPA	Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-to-Know Act
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
GI	Gastrointestinal
GSH	Glutathione-S-Transferase
HAPEM	Hazardous Air Pollutant Exposure Model
HAPs	Hazardous Air Pollutants
HEPA	High Efficiency Particulate Air
HPV	High Production Volume
IAC	Innovation Action Council
ISO	International Organization for Standardization
ITIC	Intelligence Technology Information Center
Kow	Octanol-Water Partition Coefficient
LCA	Life Cycle Assessment
LEDs	Light Emitting Diodes

MCLGs	Maximum Contaminant Level Goals
MCLs	Maximum Contaminant Levels
MFA	Material Flow Analysis
MW	Molecular Weight
NAAQS	National Ambient Air Quality Standards
NASA	National Aeronautics and Space Administration
NCEI	National Center for Environmental Innovation
NCER	National Center for Environmental Research
NEHI	Nanotechnology Environmental and Health Implications (NNI work group)
NERL	National Exposure Research Laboratory
NHEERL	National Health and Environmental Effects Research Laboratory
NHEXAS	National Human Exposure Assessment Survey
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NNAP	National Nanotechnology Advisory Panel
NNCO	National Nanotechnology Coordinating Office
NNI	National Nanotechnology Initiative
NOx	Nitrogen oxides
NRC	National Research Council
NRML	National Risk Management laboratory
NSET	NSTC Committee on Technology, Subcommittee on Nanoscale Science, Engineering and Technology
NSF	National Science Foundation
NSTC	National Science and Technology Council
NTP	National Toxicology Program (DHHS)
OAR	Office of Air and Radiation
OCFO	Office of the Chief Financial Officer
OECD	Organization for Economic Cooperation and Development
OEM	Original Equipment Manufacturers
OEI	Office of Environmental Information
OLEDs	Organic Light Emitting Diodes
OPEI	Office of Policy, Economics and Innovation
OPPT	Office of Pollution Prevention and Toxics
OPPTS	Office of Prevention, Pesticides and Toxic Substances
ORD	Office of Research and Development
OSA	Office of the Science Advisor
OSHA	Occupational Safety and Health Administration
OSTP	Office of Science and Technology Policy (Executive Office of the President)
OSWER	Office of Solid Waste and Emergency Response
OW	Office of Water
PCAST	President's Council of Advisors on Science and Technology
PCBs	Polychlorinated Biphenyls
PM	Particulate Matter
PMN	Premanufacture Notice
PPE	Personal Protective Equipment

QSAR	Quantitative Structure Activity Relationship
RCRA	Resource Conservation and Recovery Act
SAMMS	Self-Assembled Monolayers on Mesoporous Supports
SAR	Structure Activity Relationship
SDWA	Safe Drinking Water Act
SDWIS	Safe Drinking Water Information System
SEM	Scanning electron microscopy
SFA	Substance Flow Analysis
SPC	Science Policy Council
STAR	Science To Achieve Results
STM	Scanning Tunneling Microscope
SWCNT	Single-Walled Carbon Nanotubes
TOC	Total Organic Carbon
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
USDA	US Department of Agriculture
USPTO	US Patent and Trade Office
ZVI	Zero Valent Iron

EXECUTIVE SUMMARY

Nanotechnology has the potential to change and improve many sectors of American industry, from consumer products to health care to transportation, energy and agriculture. In addition to these societal benefits, nanotechnology presents new opportunities to improve how we measure, monitor, manage, and minimize contaminants in the environment, and the U.S. Environmental Protection Agency (EPA, or "the Agency") will continue to support and advance these opportunities. However, as the applications of nanotechnology continue to expand, EPA also has the obligation and mandate to protect human health and safeguard the environment by better understanding and addressing potential risks from exposure to materials containing nano-scale particles (commonly known as "nanomaterials").

For the past five years, EPA has played a leading role in funding research and setting research directions to develop environmental applications for, and understand the potential human health and environmental implications of, nanotechnology. That research has already borne fruit, particularly in the use of nanomaterials for environmental clean-up and in understanding the disposition of nanomaterials in biological systems. Some environmental technologies using nanotechnology have progressed beyond the research stage. Also, a number of specific nanomaterials have come to the Agency's attention, whether as novel products intended to promote the reduction or remediation of pollution or because they have entered one of EPA's regulatory review processes. For EPA, nanotechnology has evolved from a futuristic idea to watch, to a current issue to address.

In December 2004, EPA's Science Policy Council created a cross-Agency workgroup charged with describing the issues EPA must address to ensure that society accrues the important benefits to environmental protection that nanotechnology may offer, as well as to better understand any potential risks from exposure to nanomaterials in the environment. This paper is the product of that workgroup.

The paper begins with an introduction that describes what nanotechnology is, why EPA is interested in it, and what opportunities and challenges exist regarding nanotechnology and the environment. It then moves to a discussion of the potential environmental benefits of nanotechnology, describing environmental technologies as well as other applications that can foster sustainable use of resources. Following is a brief section on risk management and the Agency's statutory mandates, which sets the stage for a discussion of risk assessment issues specific to nanotechnology. The paper then provides an extensive review of research needs for both environmental applications and implications of nanotechnology. To help EPA focus on priorities for the near term, the paper concludes with recommendations on next steps for addressing science policy issues and research needs.. Supplemental information is provided in a number of appendices.

Key recommendations include:

- **Pollution Prevention, Stewardship, and Sustainability.** The Agency should engage resources and expertise to encourage, support, and develop approaches that promote pollution prevention, sustainable resource use, and good product stewardship in the production and use of nanomaterials. Additionally, the Agency should draw on new, "next generation" nanotechnologies to identify ways to support environmentally beneficial approaches such as green energy and green manufacturing.

- **Research.** The Agency should undertake, collaborate on, and catalyze research to better understand and apply information regarding nanomaterials':
    - chemical identification and characterization,
    - environmental fate,
    - environmental detection and analysis,
    - potential releases and human exposures,
    - human health effects assessment,
    - ecological effects assessment, and
    - environmental technology applications.

- **Risk Assessment.** The Agency should conduct case studies on several engineered or manufactured nanomaterials. Such case studies would be useful in identifying unique considerations for conducting risk assessments on nanomaterials. The case studies would also aid in identifying information gaps, which would help map areas of research to inform the risk assessment process.

- **Collaboration and Leadership.** The Agency should continue and expand its collaborations regarding nanomaterial applications and potential human health and environmental implications.

- **Cross-Agency Workgroup.** The Agency should convene a standing cross-Agency group to foster information sharing on nanotechnology science and policy issues.

- **Training.** The Agency should continue and expand its nanotechnology training activities for scientists and managers.

Nanotechnology has emerged as a growing and rapidly changing field. New generations of nanomaterials will evolve, and with them new and possibly unforeseen environmental issues. It will be crucial that the Agency's approaches to leveraging the benefits and assessing the impacts of nanomaterials continue to evolve in parallel with the expansion of and advances in these new technologies.

1.0 Introduction

1.1 Purpose

Nanotechnology presents new opportunities to create better materials and products. Already, nanomaterial containing products are available in U.S. markets including coatings, computers, clothing, cosmetics, sports equipment and medical devices. A survey by EmTech Research of companies working in the field of nanotechnology has identified approximately 80 consumer products, and over 600 raw materials, intermediate components and industrial equipment items that are used by manufacturers. Our economy will be increasingly affected by nanotechnology as more products containing nanomaterials move from research and development into production and commerce.

Nanotechnology also has the potential to improve the environment, both through direct applications of nanomaterials to detect, prevent, and remove pollutants, as well as indirectly by using nanotechnology to design cleaner industrial processes and create environmentally friendly products. However, there are unanswered questions about the impacts of nanomaterials and nanoproducts on human health and the environment, and the US Environmental Protection Agency (EPA or "the Agency") has the obligation to ensure that potential risks are adequately understood to protect human health and the environment. As products made from nanomaterials become more numerous and therefore more prevalent in the environment, EPA is thus considering how to best leverage advances in nanotechnology to enhance environmental protection, as well as how the introduction of nanomaterials into the environment will impact the Agency's environmental programs, policies, research needs, and approaches to decision making.

In December 2004, the Agency's Science Policy Council convened a cross-Agency Nanotechnology Workgroup and charged the group with developing a white paper to examine the implications and applications of nanotechnology. This document describes the issues EPA must.address to ensure that society accrues the important benefits to environmental protection that nanotechnology may offer, and to make sure that we understand any potential risks from environmental exposure to nanomaterials.

The paper begins with an introduction that describes what nanotechnology is, why EPA is interested in it, and what opportunities and challenges exist regarding nanotechnology and the environment. It then moves to a discussion of the potential environmental benefits of nanotechnology, describing environmental technologies as well as other applications that can foster sustainable use of resources. Following is a brief section on risk management and the Agency's statutory mandates, which sets the stage for a discussion of risk assessment issues specific to nanotechnology. The paper then provides an extensive review of research needs for both environmental applications and implications of nanotechnology. To help EPA focus on priorities for the near term, the paper concludes with recommendations on next steps for addressing science policy issues and research needs. Supplemental information is provided in a number of appendices.

A discussion of an entire technological process or series of processes, as is nanotechnology, could be wide ranging. However, because EPA operates through specific programmatic activities and mandates, this document confines its discussion of nanotechnology science policy issues within the bounds of EPA's statutory responsibilities and authorities. In particular, the paper discusses what scientific information EPA will need, and how it will use that information, to address nanotechnology in environmental decision making.

1.2 Nanotechnology Defined

A nanometer is one billionth of a meter (10^{-9} m)—about one ten-thousandth the diameter of a human hair, a thousand times smaller than a red blood cell, or about half the size of the diameter of DNA. Figure 1 illustrates the scale of objects in the nanometer range. For the purpose of this document, nanotechnology is defined as: research and technology development at the atomic, molecular, or macromolecular levels using a length scale of approximately one to one hundred nanometers in any dimension; the creation and use of structures, devices and systems that have novel properties and functions because of their small size; and the ability to control or manipulate matter on an atomic scale.

Nanotechnology manipulates matter for particular applications, and includes the deliberate engineering of particles by certain chemical and/or physical processes (referred to as "bottom-up" production) to create materials with specific properties not displayed in their macro-scale counterparts, as well as the use of such manufacturing processes as milling or grinding ("top-down" production) to produce nano-sized particles that may or may not have properties different from those of the bulk material from which they are developed. For the remainder of this document such engineered or manufactured nanomaterials will be referred to as "intentionally produced nanomaterials," or simply "nanomaterials." The definition of nanotechnology does not include unintentionally produced nanomaterials, nano-sized particles or materials that occur naturally in the environment, such as viruses or volcanic ash, and nanoparticle byproducts of human activity, such as diesel exhaust particulates or other friction or airborne combustion byproducts. Where information from natural or incidentally formed nano-sized materials (such as ultrafine particulate matter or combustion products) may aid in the understanding of intentionally produced nanomaterials, this information will be discussed, but the focus of this document is not on these other materials.

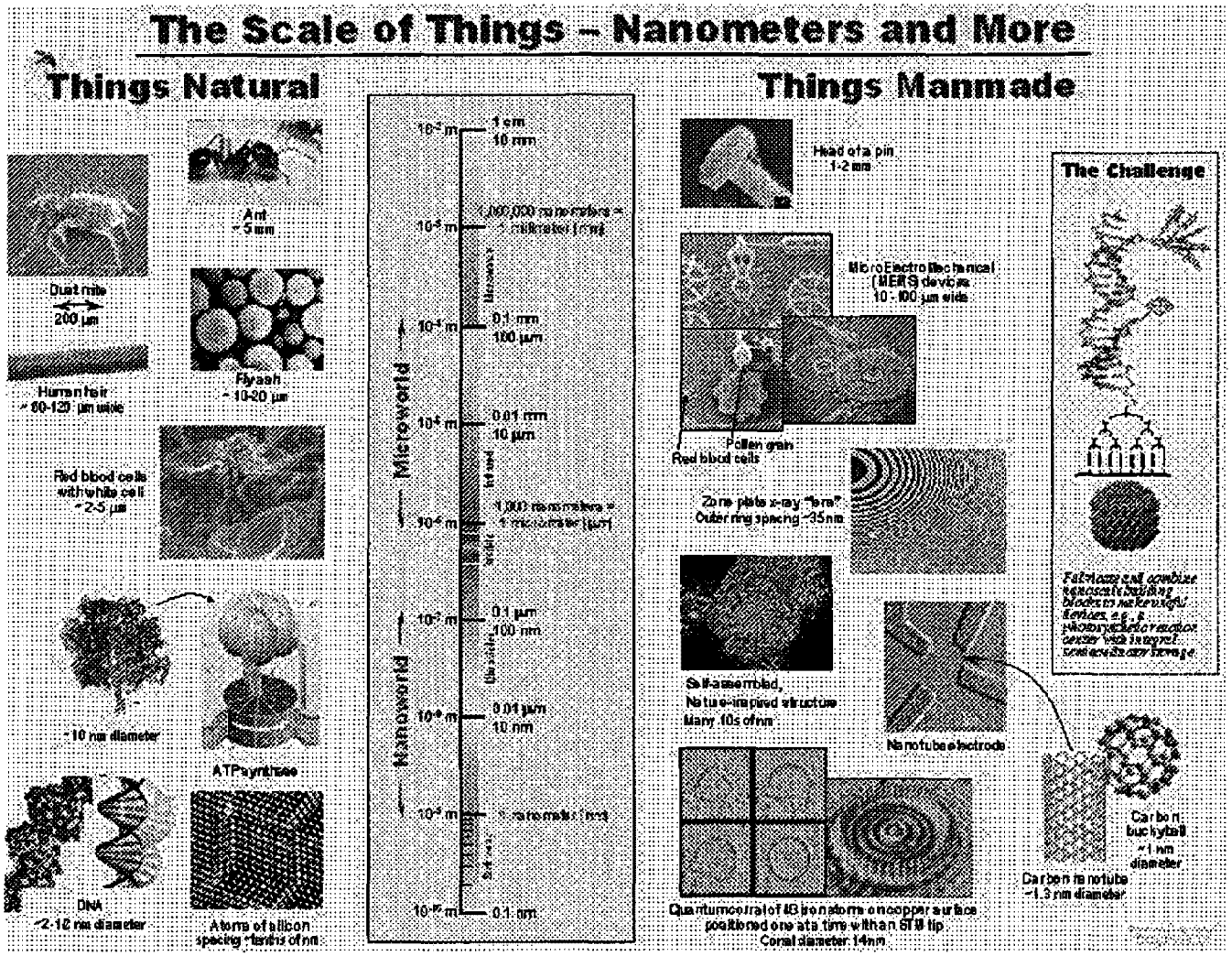


Figure 1. Diagram indicating relative scale of nano-sized objects. From NNI website, courtesy Office of Basic Energy Sciences, Office of Science, U.S. Department of Energy

There are many types of intentionally produced nanomaterials. For the purpose of this document, nanomaterials are organized into four types:

(1) **Carbon-based materials**. These nanoparticles are composed entirely of carbon taking the form of a hollow sphere, ellipsoid, or tube. Spherical fullerenes are sometimes called buckyballs, while cylindrical fullerenes are called nanotubes. These particles have many potential applications, including improved films and coatings, and stronger and lighter materials.

(2) **Metal-based materials** such as quantum dots, nanogold, nanosilver and reactive metal oxides like titanium dioxide. A quantum dot is a closely packed semiconductor crystal comprised of hundreds or thousands of atoms, and whose size is on the order of a few nanometers to a few hundred nanometers. Quantum dots can be manipulated to change their physical properties, particularly their optical properties. The small size also means that, typically, over 70 percent of the atoms are at surface sites, so that chemical changes at these sites allow tuning of the light-emitting properties of the dots, permitting the emission of multiple colors from a single dot.

3) **Dendrimers**, which are nano-sized polymers built from branched units. The surface of a dendrimer as numerous chain ends, which can be tailored to perform specific chemical functions. This property could also be useful for catalysis. Also, because three-dimensional dendrimers contain interior cavities into which other molecules could be placed, they may be useful for drug delivery.

(4) **Composites**, which combine nanoparticles with other nanoparticles or with larger, bulk-type materials. Already, nanoparticles, such as nano-sized clays, are being added to products ranging from auto parts to packaging materials, to enhance mechanical, thermal, barrier, and flame-retardant properties.

The unique properties of these various types of intentionally produced nanomaterials give them novel electrical, catalytic, magnetic, mechanical, thermal, or imaging features that are highly desirable for applications in commercial, medical, military, and environmental sectors. As we identify new uses for materials with these special properties, the number of products containing such nanomaterials and their possible applications continues to grow. Table 1 lists some examples of nanotechnology products. There are estimates that global sales of nanomaterials could exceed $1 trillion by 2015 (M.C. Roco, presentation to the NRC, 23 March 2005).

Table 1. Examples of nanotechnology products.

End User Applications	Therapeutic Systems	Components	Software	Capital Equipment	Imaging
Tennis balls and rackets Clothing, Cameras, Respirators, Razor blades, Cosmetics, Sunscreens, Beer bottles	Drugs, Sprays, Burn dressings, Medical equipment components	Transistors, Fillers, Catalytic converters, Fenders, Mirror housings, Fuel Cells, Step assists, Polarizers/ Wave plates, Displays-OLEDs	Modeling, Controllers for microscopes, Computer Aid Design navigation	Positioners, Cantilevers, Coaters, Probers/Manipulators, Lithography masks, Resists	Microscopes, Electron Beams, X-ray

1.2.1 Converging Technologies

In the long-term, nanotechnology increasingly will likely be discussed within the context of the convergence, integration, and synergy of nanotechnology, biotechnology, information technology, and cognitive technology. Convergence involves the development of novel products with enhanced capabilities that incorporate bottom-up assembly of miniature components with accompanying biological, computational and cognitive capabilities. The convergence of nanotechnology and biotechnology, already rapidly progressing, will result in the production of novel nanoscale materials. The convergence of nanotechnology and biotechnology with information technology and cognitive science is expected to rapidly accelerate in the coming decades. The increased understanding of biological systems will provide valuable information towards the development of efficient and versatile biomimetic tools, systems, and architecture.

Generally, biotechnology involves the use of microorganisms, or bacterial factories, which contain inherent "blueprints" encoded in the DNA, and a manufacturing process to produce molecules such as amino acids. Within these bacterial factories, the organization and self-assembly of complex molecules occurs routinely. Many "finished" complex cellular products are < 100 nanometers. For this reason, bacterial factories may serve as models for the organization, assembly and transformation for other nanoscale materials production.

Bacterial factory blueprints are also flexible. They can be modified to produce novel nanobiotechnology products that have specific desired physical-chemical (performance) characteristics. Using this production method could be a more material and energy efficient way to make new and existing products, in addition to using more benign starting materials. In this way, the convergence of nano- and biotechnologies could improve environmental protection. As an example, researchers have extracted photosynthetic proteins from spinach

chloroplasts and coated them with nanofilms that convert sunlight to electrical current, which one day may lead to energy generating films and coatings (Das et al., 2004). The addition of information and cognitive capabilities will provide additional features including programmability, miniaturization, increased power capacities, adaptability, and reactive, self-correcting capacities

Another example of converging technologies is the development of nanometer-sized biological sensor devices that can detect specific compounds within the natural environment; store, tabulate, and process the accumulated data; and determine the import of the data; providing a specific response for the resolved conditions would enable rapid and effective human health and environmental protection. Responses could range from the release of a certain amount of biological or chemical compound, to the removal or transformation of a compound.

The convergence of nanotechnology with biotechnology and with information and cognitive technologies may provide such dramatically different technology products that the manufacture, use and recycling/disposal of these novel products, as well as the development of policies and regulations to protect human health and the environment, may prove to be a daunting task.

The Agency is committed to keeping abreast of emerging issues within the environmental arena, and continues to support critical research, formulate new policies, and adapt existing policies as needed to achieve its mission. However, the convergence of these technologies will demand a flexible, rapid and highly adaptable approach within EPA. As these technologies progress and as novel products emerge, increasingly the Agency will find that meeting constantly changing demands will require proactive actions and planning.

We are currently nearing the end of basic research and development on the first generation of materials resulting from nanotechnologies that include coatings, polymers, more reactive catalysts, etc. (Figure 2). The second generation, which we are beginning to enter, involves targeted drug delivery systems, adaptive structures and actuators, and has already provided some interesting examples. The third generation, anticipated within the next 10-15 years, will bring novel robotic devices, three-dimensional networks and guided assemblies. The fourth stage will result in molecule-by-molecule design and self-assembly capabilities. Although it is not likely to happen for some time, this integration of these fourth-generation nanotechnologies with information, biological, and cognitive technologies will lead to products we can only now vaguely imagine. The Agency need not develop the ability to predict the future, it only needs to prepare for it. Towards that aim, understanding the unique challenges and opportunities afforded by converging technologies before they occur will provide the Agency with the essential tools required for the effective and appropriate handling of emerging technology and science.

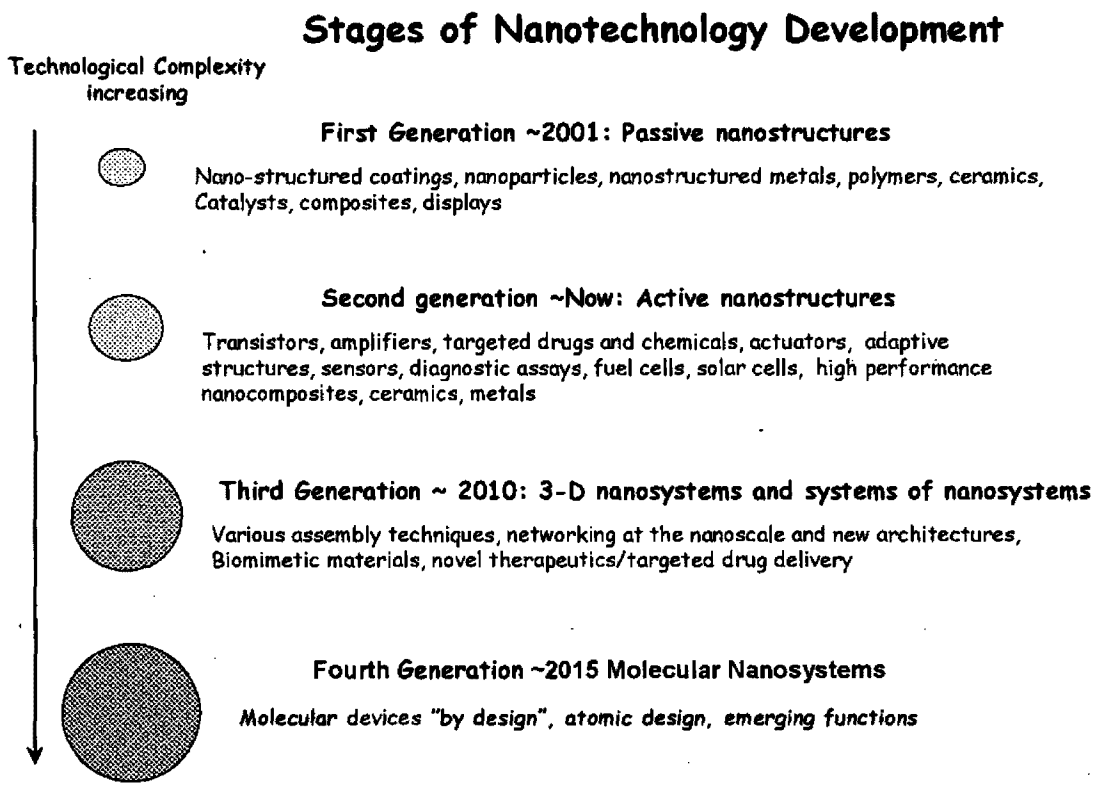


Figure 2. The stages of nanotechnology development

1.3 Why Nanotechnology Is Important to EPA

Nanotechnology holds great promise for creating new materials with enhanced properties and attributes. These properties, such as greater catalytic efficiency, increased electrical conductivity, and improved hardness and strength, are a result of nanomaterials' larger surface area per unit of volume and quantum effects that occur at the nanometer scale ("nanoscale"). Nanomaterials are already being used or tested in a wide range of products such as sunscreens, composites, medical and electronic devices, and chemical catalysts. Similar to nanotechnology's success in consumer products and other sectors, nanomaterials have promising environmental applications. For example, nano-sized cerium oxide has been developed to decrease diesel emissions, and iron nanoparticles can remove contaminants from soil and ground water. Nano-sized sensors hold promise for improved detection and tracking of contaminants. In these and other ways, nanotechnology presents an opportunity to improve how we measure, monitor, manage, and reduce contaminants in the environment.

Some of the same special properties that make nanomaterials useful are also properties that may cause some nanomaterials to pose hazards to humans and the environment, under specific conditions. Some nanomaterials that enter animal tissues may be able to pass through cell membranes or cross the blood-brain barrier. This may be a beneficial characteristic for

such uses as targeted drug delivery and other disease treatments, but could result in unintended impacts in other uses or applications. Inhaled nanoparticles may become lodged in the lung, and the high durability and reactivity of some nanomaterials raises issues of their fate in the environment. It may be that in most cases nanomaterials will not be of human health or ecological concern. However, at this point not enough information exists to assess environmental exposure for most engineered nanomaterials. This information is important, because EPA needs a sound scientific basis for assessing and managing any unforeseen future impacts resulting from the introduction of nanoparticles and nanomaterials into the environment.

A challenge for environmental protection is to allow full realization of the societal benefits of nanotechnology, while identifying and minimizing any adverse impacts to humans or ecosystems from exposure to nanomaterials. In addition, we need to understand how to best apply nanotechnology for pollution prevention in current manufacturing processes and in the manufacture of new nanomaterials and nanoproducts, as well as in environmental detection, monitoring, and clean-up. This understanding will come from scientific information generated by environmental research and development activities within government agencies, academia, and the private sector. How we prioritize, develop, and use this scientific information will determine how well we succeed at ensuring safe and sustainable development of nanotechnology.

1.4 What EPA is Doing with Respect to Nanotechnology

EPA is actively participating in nanotechnology development and evaluation. Some of the activities EPA has undertaken include: 1) actively participating in the National Nanotechnology Initiative, which coordinates nanotechnology research and development across the federal government, 2) funding nanotechnology research through EPA's Science To Achieve Results (STAR) grant program and Small Business Innovative Research (SBIR) program, 3) collaborating with scientists internationally in order to share the growing body of information on nanotechnology, 4) initiating the development of a voluntary pilot program for the evaluation of nanomaterials and reviewing of nanomaterial new chemical submissions in the Office of Pollution Prevention and Toxics ; and 5) reviewing nanomaterial registration applications in the Office of Air and Radiation/Office of Transportation and Air Quality.

1.5 Context for EPA's Environmental Science Roles

EPA's role in nanotechnology exists within a larger framework of activities that have been ongoing for several years. Many sectors—including US federal and state agencies, academia, the private sector, other national governments, and international bodies—are considering potential environmental applications and implications of nanotechnology. This section describes some of the major players in this arena, for two principal reasons: to describe EPA's role regarding nanotechnology and the environment, and to identify opportunities for collaborative and complementary efforts.

1.5.1 Federal Agencies – The National Nanotechnology Initiative

The National Nanotechnology Initiative (NNI) was launched in 2001 to coordinate nanotechnology research and development across the federal government. Investments into federally funded nanotechnology-related activities, coordinated through the NNI, have grown from $464 million in 2001 to approximately $1 billion in 2005.

The NNI supports a broad range of research and development including fundamental research on the unique phenomena and processes that occur at the nano scale, the design and discovery of new nanoscale materials, and the development of nanotechnology-based devices and systems. The NNI also supports research on instrumentation, metrology, standards, and nanoscale manufacturing. Most important to EPA, the NNI has made responsible development of this new technology a priority by supporting research on environmental health and safety implications.

Twenty-four federal agencies currently participate in the NNI, eleven of which have budgets dedicated to nanotechnology research and development. The other thirteen agencies have made nanotechnology relevant to their missions or regulatory roles. Only a small part of this federal investment aims at researching the social and environmental implications of nanotechnology including its effects on human health, the environment, and society. Nine federal agencies are investing in implications research including the National Science Foundation, the National Institutes of Health, the National Institute of Occupational Health and Safety, and the Environmental Protection Agency. These agencies coordinate their efforts through the NNI's Nanoscale Science, Engineering, and Technology Subcommittee (NSET) and its Nanotechnology Environmental Health Implications workgroup (NEHI) (Figure 3). The President's Council of Advisors on Science and Technology (PCAST) serves as an advisory body to the NNI.

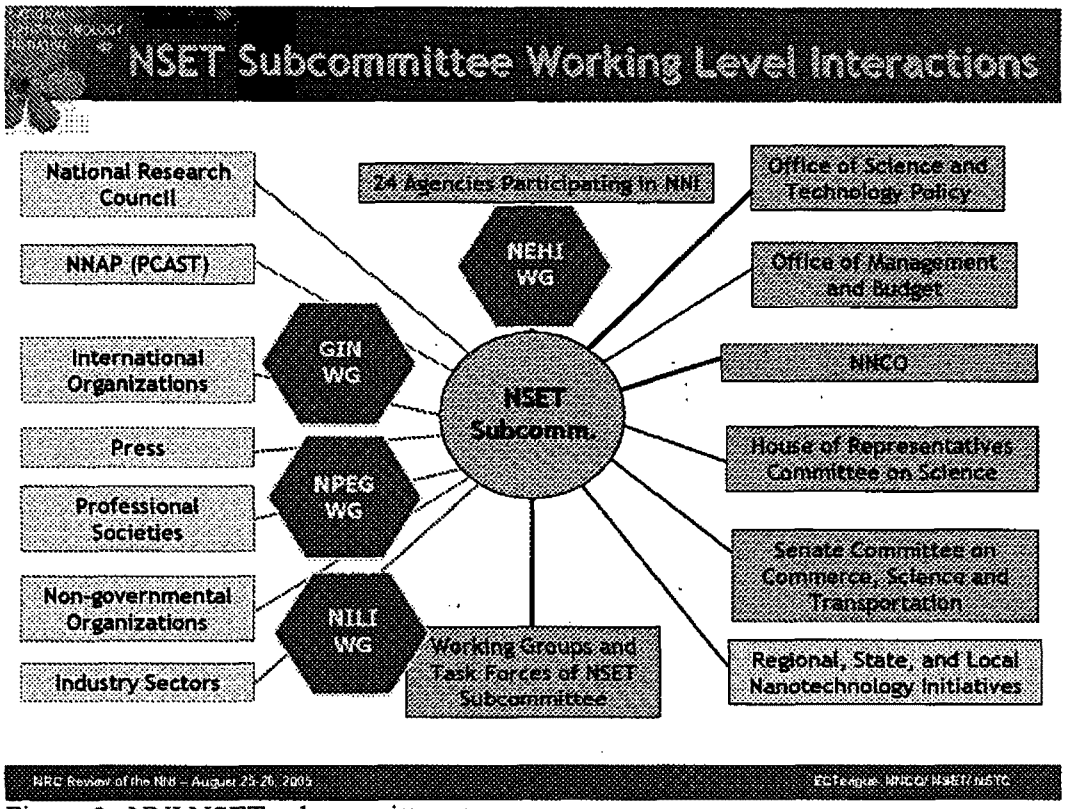


Figure 3. NNI NSET subcommittee structure

1.5.2 Efforts of Other Stakeholders

About $2 billion in annual research and development investment are being spent by non-federal US sectors such as states, academia, and private industry. State governments collectively spend an estimated $400 million on facilities and research aimed at the development of local nanotechnology industries.

Although the industry is relatively new, US nanotechnology trade associations have emerged. A directory of nanotechnology industry-related organizations can be found at http://www.nanovip.com. The American Chemistry Council also has a committee devoted to nanotechnology and is encouraging research into the environmental health and safety of nanomaterials.

Environmental nongovernmental organizations (NGOs) such as Environmental Defense, Greenpeace UK, and the Natural Resources Defense Council are engaged in nanotechnology issues. Also, scientific organizations such as the National Academy of Sciences, the Royal Society of the United Kingdom, and the International Life Sciences Institute are providing important advice on issues related to nanotechnology and the environment.

1.5.3 International Activities

Fully understanding the environmental applications and implications of nanotechnology will require the concerted efforts of scientists and policy makers across the globe. Europe and Asia match or exceed the US federal nanotechnology research budget. Globally, nanotechnology research and development spending is estimated at around $9 billion (Lux Research, 2005). Thus, a great opportunity exists for internationally coordinated and integrated efforts toward environmental research. International organizations such as the Asian-Pacific Economic Cooperation, the British Standards Institute, the National Institute of Standards and Technology, the American National Standards Institute, and the American Society of Testing Materials are involved in nanotechnology issues. The Organization for Economic Cooperation and Development (OECD) is currently engaging the topic of the implications of engineered nanomaterials among its members under the auspices of the Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology (Chemicals Committee). The OECD Chemicals Committee has identified this international forum for ensuring global cooperation, coordination, and communication between member countries, nonmembers, industry, and NGOs on nanotechnology issues. As a member of the Chemicals Committee, EPA will participate in this effort.

Additionally, the United States and European Union Initiative (June 2005) addresses both regulatory and research areas in nanotechnology. Specifically, the document states that the United States and the European Union will work together to, among other things, "support an international dialogue and cooperative activities for the responsible development and use of the emerging field of nanotechnology." EPA is currently working with the US State Department, the NNI, and the EU to bring about research partnerships in nanotechnology. Furthermore, in the context of environmental science, the EPA has worked with foreign research institutes and agencies (e.g., UK and Taiwan) to help inform nanotechnology and related environmental research programs.

By continuing to actively participate in international scientific fora, EPA will be well positioned to inform both domestic and international environmental policy. This will provide essential support for US policy makers who work to negotiate international treaties and trade regimes. As products made from nanomaterials become more common in the domestic and international channels of trade, policy makers will then be able to rely on EPA for the high quality science necessary to make effective decisions that could have a significant impact, both domestically and internationally, on human and environmental health, and economic well-being.

1.5.4 EPA's Nanotechnology Research Activities

Since 2001, EPA's Office of Research and Development (ORD) STAR grants program has funded 39 research grants for more than $11 million in the applications of nanotechnology to protect the environment, including the development of: 1) low-cost, rapid, and simplified methods of removing toxic contaminants from surface water, 2) new sensors that are more sensitive for measuring pollutants, 3) green manufacturing of nanomaterials;

and 4) more efficient, selective catalysts. Additional applications projects have been funded through the Small Business Innovative Research (SBIR) program.

In addition, 14 recent STAR program projects focus on studying the possible harmful effects, or implications, of engineered nanomaterials. EPA has awarded or selected 32 grants to date in this area, totaling $10 million. The most-recent research solicitations include partnerships with the National Science Foundation, the National Institute for Occupational Safety and Health, and the National Institute for Environmental Health Sciences. Research areas of interest for this proposal include the toxicology, fate, transport and transformation, bioavailability, human exposure, and life cycle assessment of nanomaterials.

EPA's own scientists have done research in areas related to nanotechnology, such as on the toxicity of ultrafine particulate matter. In addition, EPA scientists have begun to gather information on various environmental applications currently under development. However, EPA has not yet initiated an in-house research program for nanotechnology.

1.5.5 Regional Nanotechnology Research Activities for Remediation

A pilot study is planned at an EPA Region 5 National Priorities List site in Ohio. The pilot study will inject zero valent iron nanoparticles into the groundwater to test its effectiveness in removing the pesticide Mirex. The study includes smaller pre-pilot studies and an investigation of the ecological effects of the treatment method. Information on the pilot can be found at http://www.epa.gov/region5/sites/index.htm#nease.

1.5.6 Office of Pollution Prevention and Toxics Voluntary Pilot Program for Nanoscale Materials

EPA's Office of Pollution Prevention and Toxics (OPPT) convened a public meeting in June 2005 regarding a potential voluntary pilot program for nanoscale materials and the information needed to adequately inform the conduct of the pilot program. ("Nanoscale Materials; Notice of Public Meeting," 70 Fed. Reg. 24574, May 10, 2005). At the meeting EPA received comment from a broad spectrum of stakeholders concerning all aspects of the voluntary pilot program. On September 29 and October 12, 2005, OPPT's National Pollution Prevention and Toxics Advisory Committee held public meetings of its Interim Ad Hoc Work Group on Nanoscale Materials. The purpose of the meetings was to further discuss and receive additional public input on issues pertaining to the voluntary pilot program for nanoscale materials. The Interim Ad Hoc Work Group on Nanoscale Materials developed overview documents proposing the general parameters of a voluntary pilot program, which EPA is considering in its development and implementation of the final pilot program. OPPT is also simultaneously considering development and implementation of regulatory approaches for nanomaterials. OPPT is already reviewing new chemical submissions for nanomaterials under the Toxics Substances Control Act (TSCA).

1.5.7 Office of Air and Radiation/Office of Transportation and Air Quality-Nanomaterials Registration Applications

EPA's Office of Air and Radiation/Office of Transportation and Air Quality has received and is reviewing an application for registration a diesel additive containing cerium oxide. Nano-cerium oxide particles are being employed in Europe as on- and off-road diesel fuel additives to decrease emissions and some manufacturers are claiming fuel economy benefits.

1.6 Communication and Outreach

Gaining and maintaining public trust and support is important to fully realize the societal benefits and clearly communicate the impacts of nanotechnology. Responsible development of nanotechnology should involve and encourage an open dialogue with all concerned parties about potential risks and benefits. EPA is committed to keeping the public informed of the potential environmental impacts associated with nanomaterial development and applications. As an initial step, EPA has developed a dedicated web site, www.epa.gov/nano, to provide comprehensive information and enable transparent dialogue concerning nanotechnology. In addition, EPA has been conducting outreach by organizing and sponsoring sessions at professional society meetings, speaking at industry, state, and international nanotechnology meetings.

EPA already has taken steps to obtain public feedback on issues, alternative approaches, and decisions. For example, the previously noted OPPT public meetings were designed to discuss and receive public input. EPA will continue to work collaboratively with all stakeholders, including industry, other governmental entities, public interest groups, and the general public, to identify and assess potential environmental hazards and exposures resulting from nanotechnology, and to discuss EPA's roles in addressing issues of concern. EPA's goal is to earn and retain the public's trust by providing information that is objective, balanced, accurate and timely in its presentation, and by using transparent public involvement processes.

1.7 Opportunities and Challenges

For EPA, the rapid development of nanotechnology and the increasing production of nanomaterials and nanoproducts present both opportunities and challenges. Using nanomaterials in applications that advance green chemistry and engineering, and lead to the development of new environmental sensors and remediation technologies, may provide us with new tools for preventing, identifying, and solving environmental problems. In addition, at this early juncture in nanotechnology's development, we have the opportunity to develop approaches that will allow us to produce, use, recycle, and eventually dispose of nanomaterials in ways that protect human health and safeguard the natural environment. The integration and synergy of nanotechnology, biotechnology, information technology, and cognitive technology will present opportunities as well as challenges to EPA and other regulatory agencies. To take advantage of these opportunities and to meet the challenge of

ensuring the environmentally safe and sustainable development of nanotechnology, EPA must understand both the potential benefits and the potential impacts of nanomaterials and nanoproducts. The following chapters of this document discuss the science issues surrounding how EPA will gain and apply such understanding.

2.0 Environmental Benefits of Nanotechnology

2.1 Introduction

As applications of nanotechnology develop over time, they have the potential to help shrink the human footprint on the environment. This is important, because over the next 50 years the world's population is expected to grow 50%, global economic activity is expected to grow 500%, and global energy and materials use is expected to grow 300% (World Resources Institute, 2000). So far, increased levels of production and consumption have offset our gains in cleaner and more-efficient technologies. This has been true for municipal waste generation, as well as for environmental impacts associated with vehicle travel, groundwater pollution, and agricultural runoff (OECD, 2001). This chapter will describe how nanotechnology can create materials and products that will not only directly advance our ability to detect, monitor, and clean-up environmental contaminants, but also help us avoid creating pollution in the first place. By more effectively using atoms and energy throughout a product lifecycle, nanotechnology may contribute to reducing pollution or energy intensity per unit of economic output, reducing the "volume effect" described by the OECD.

2.2 Benefits Through Environmental Technology Applications

2.2.1 Remediation/Treatment

Environmental remediation includes the degradation, sequestration, or other related approaches that result in reduced risks to human and environmental receptors posed by chemical and radiological contaminants such as those found at Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), Resource Conservation and Recovery Act (RCRA), or other state and local hazardous waste sites. The benefits from use of nanomaterials for remediation could include more rapid or cost-effective cleanup of wastes relative to current conventional approaches. Such benefits may derive from the enhanced reactivity, surface area, subsurface transport, and/or sequestration characteristics of nanomaterials.

Chloro-organics are a major class of contaminants at U.S. waste sites, and several nanomaterials have been applied to aid in their remediation. Zero-valent iron has been used successfully in the past to remediate groundwater by construction of a permeable reactive barrier (iron wall) of zero-valent iron to intercept and dechlorinate chlorinated hydrocarbons such as trichloroethylene in groundwater plumes. Laboratory studies indicate that a wider range of chlorinated hydrocarbons may be dechlorinated using various nanoscale iron particles (principally by abiotic means, with zero-valent iron serving as the bulk reducing agent), including chlorinated methanes, ethanes, benzenes, and polychlorinated biphenyls (Elliot and Zhang, 2001). Nanoscale zero-valent iron may not only treat aqueous dissolved chlorinated solvents in situ, but also may remediate the dense nonaqueous phase liquid (DNAPL) sources of these contaminants within aquifers (Quinn, et al, 2005).

In addition to zero-valent iron, other nano-sized materials such as methalloporphyrinogens have been tested for degradation of tetrachlorethylene, trichloroethylene, and carbon tetrachloride under anaerobic conditions (Dror, 2005). Titanium oxide based nanomaterials have also been developed for potential use in the photocatalytic degradation of various chlorinated compounds (Chen 2005).

Metal remediation has also been proposed, using zero-valent iron and other classes of nanomaterials. Nanoparticles such as poly(amidoamine) dendrimers can serve as chelating agents, and can be further enhanced for ultrafiltration of a variety of metal ions (Cu (II), Ag(I), Fe(III), etc.) by attaching functional groups such as primary amines, carboxylates, and hydroxymates (Diallo, 2005). Other materials such as silica-titania nanocomposites can be used for elemental mercury removal from vapors such as those coming from combustion sources, with silica serving in enhanced adsorption and titania used to photocatalytically oxidize elemental mercury to the less volatile mercuric oxide (Pitoniak, 2005). Other research indicates that arsenite and arsenate may be precipitated in the subsurface using zero-valent iron, making arsenic less mobile (Kanel, 2005). Finally, self-assembled monolayers on mesoporous supports (SAMMS) are nanoporous ceramic materials that have been developed to remove mercury or radionuclides from wastewater (Mattigod, 2003).

Enhanced retention, as noted above, or solubilization of a contaminant may be helpful in a remediation setting. Nanomaterials may be useful in decreasing sequestration of hydrophobic contaminants, such as polycyclic aromatic hydrocarbons (PAHs), bound to soils and sediments. The release of these contaminants from sediments and soils could make them more accessible to *in situ* biodegradation. For example, nanomaterials made from poly(ethylene) glycol modified urethane acrylate have been used to enhance the bioavailability of phenanthrene (Tungittiplakorn, 2005).

2.2.2 Sensors

Sensor development and application based on nanoscale science and technology is growing rapidly due in part to the advancements in the microelectronics industry and the increasing availability of nanoscale processing and manufacturing technologies. In general, nanosensors can be classified in two main categories: (1) sensors that are used to measure nanoscale properties (this category comprises most of the current market) and (2) sensors that are themselves nanoscale or have nanoscale components. The second category can eventually result in lower material cost as well as reduced weight and power consumption of sensors, leading to greater applicability.

One of the near-term research products of nanotechnology for environmental applications is the development of new and enhanced sensors to detect biological and chemical contaminants. Nanotechnology offers the potential to improve exposure assessment by facilitating collection of large numbers of measurements at a lower cost and improved specificity. It soon will be possible to develop micro- and nanoscale sensor arrays that can detect specific sets of harmful agents in the environment at very low concentrations. Provided

adequate informatics support, these sensors could be used to monitor agents in real time, and the resulting data can be accessed remotely. The potential also exists to extend these small-scale monitoring systems to the individual level to detect personal exposures and *in vivo* distributions of toxicants.

In the environmental applications field, nanosensor research and development is a relatively uncharted territory. Much of the new generation nanoscale sensor development is driven by defense and biomedical fields. These areas possess high-need applications and the resources required to support exploratory sensor research. On the other hand, the environmental measurement field is a cost sensitive arena with less available resources for leading-edge development. Therefore, environmental nanosensor technology likely will evolve by leveraging the investment in nanosensor research by related fields.

2.3 Benefits through Other Applications that Support Sustainability

Nanotechnology may be able to advance environmental protection by addressing the long-term sustainability of resources and resource systems Listed in Table 1 are examples describing actual and potential applications relating to water, energy, and materials. Some applications bridge between several resource outcomes. For example, green manufacturing using nanotechnology (both top down and bottom up) can improve the manufacturing process by increasing materials and energy efficiency, reducing the need for solvents, and drastically reducing waste products.

Table 1. Outcomes for Sustainable Use of Major Resources and Resource Systems*

Water	sustain water resources of quality and availability for desired uses
Energy	generate clean energy and use it efficiently
Materials	use material carefully and shift to environmentally preferable materials
Ecosystems	protect and restore ecosystem functions, goods, and services
Land	support ecologically sensitive land management and development
Air	sustain clean and healthy air

*EPA Innovation Action Council, 2005

Many of the following applications can and should be supported by other agencies. However, EPA has an interest in helping to guide the work in these areas.

2.3.1 Water

Nanotechnology has the potential to contribute to long-term water quality, availability, and viability of water resources, such as through advanced filtration that enables more water re-use, recycling, and desalinization. For example, nanotechnology-based flow-through capacitors (FTC) have been designed that desalt seawater using one-tenth the energy of state-of-the art reverse osmosis and one-hundredth of the energy of distillation systems. The projected capital and operation costs of FTC-based systems are expected to be one-third less than conventional osmosis systems (NNI, 2000).

Applications potentially extend even more broadly to ecological health. One long-term challenge to water quality in the Gulf of Mexico, the Chesapeake Bay, and elsewhere is the build up of nutrients and toxic substances due to runoff from agriculture, lawns, and gardens. In general with current practices, about 150% of nitrogen required for plant uptake is applied as fertilizer (Frink et. al., 1996). More-targeted fertilizers and pesticides that result in less agricultural and lawn/garden runoff of nitrogen, phosphorous, and toxic substances is potentially an important emerging application for nanotechnology that can contribute to sustainability. These potential applications are still in the early research stage (USDA, 2003).

2.3.2 Energy

There is potential for nanotechnology to contribute to reductions in energy demand through lighter materials for vehicles, materials and geometries that contribute to more effective temperature control, technologies that improve manufacturing process efficiency, and materials that reduce electrical losses in electrical components. Table 2 illustrates some potential nanotechnology contributions to energy efficiency in transportation and electricity (adapted from Brown, 2005). Some estimates are that the eight technologies could result in national energy savings of about 14.6 quadrillion BTU's (British thermal units, a standard unit of energy) per year, which is about 14.6% of total US energy consumption per year.

Table 2: Potential US Energy Savings from 8 Nanotechnology Applications (Adapted from Brown, 2005)

Nanotechnology Application	**Estimated Percent Reduction in Total Annual US Energy Consumption****
Strong, lightweight materials in transportation	6.2 *
Solid state lighting (such as white light LED's)	3.5
Self-optimizing motor systems	2.0
Smart roofs (temperature-dependent reflectivity)	1.5
Novel energy-efficient separation membranes	0.8
Energy efficient distillation through supercomputing	0.3
Molecular-level control of industrial catalysis	0.2
Transmission line conductance	0.1
Total	**14.6**

*Assuming a 5.15 Million BTU/ Barrel conversion (corresponding to reformulated gasoline – from EIA monthly energy review, October 2005, Appendix A)
** Based on US annual energy consumption from 2004 (99.74 Quadrillion Btu/year) from the Energy Information Administration Annual Energy Review 2004

The items in Table 2 represent many different technology applications. For instance, one of many examples of molecular-level control of industrial catalysis is a nanostructured catalytic converter that is built from nanotubes and has been developed for the chemical process of styrol synthesis. This process revealed a potential of saving 50% of the energy at this process level. Estimated energy savings over the product life cycle for styrol were 8-9% (Steinfeldt et al., 2004).

Current average overall energy loss in transmission lines is 7%. Power transmission could be improved by using carbon nanotubes that provide better conduction of large quantities of high voltage electricity than copper wire, at one-sixth the weight.

There are additional emerging innovative approaches to energy management that could potentially reduce energy consumption. For example, nanomaterials arranged in superlattices could allow the generation of electricity from waste heat in consumer appliances, automobiles, and industrial processes. These thermoelectric materials could, for example, further extend the efficiencies of hybrid cars and power generation technologies (Ball, 2005).

In addition to increasing energy efficiency, nanotechnology also has the potential to contribute to alternative energy technologies that are environmentally cleaner. For example, nanotechnology is forming the basis of a new type of highly efficient photovoltaic cell that consists of quantum dots connected by carbon nanotubes (NREL, 2005). Also, gases flowing

over carbon nanotubes have been shown to convert to an electrical current, a discovery with implications for novel distributed wind power (Ball, 2004).

Nanotechnology may also contribute to a hydrogen economy. Multi-walled nanotubes may increase the performance of hydrogen fuel cells; nanomaterials might safely store hydrogen for hydrogen transportation infrastructure; and nanocatalysts may efficiently create hydrogen from water using solar energy, and achieve the DOE goal of 10% efficiency for commercial viability.

2.3.3 Materials

Nanotechnology may also lead to more efficient and effective use of materials. For example, nanotechnology may improve the functionality of catalytic converters and reduce by up to 95% the mass of platinum group metals required. Because platinum group metals occur in low concentration in ore, this reduction in use may reduce ecological impacts from mining (Lloyd et. al., 2005).

Nanostructured catalysts can also increase yield (and therefore reduce materials use) at the process level. For example, the petroleum industry now uses nanotechnology in zeolite catalysts to crack hydrocarbons at a significantly improved process yield (NNI, 2000).

With nanomaterials' increased material functionality, it may be possible in some cases to replace toxic materials and still achieve the desired functionality (in terms of electrical conductivity, material strength, heat transfer, etc.), often with other life-cycle benefits in terms of material and energy use. One example is lead-free conductive adhesives formed from self-assembled monolayers based on nanotechnology, which could eventually substitute for leaded solder. Leaded solder is used broadly in the electronics industry; about 3900 tons lead use/year in the United States alone. In addition to the benefits of reduced lead use, conductive adhesives could simplify electronics manufacture by eliminating several processing steps, including the need for acid flux and cleaning with detergent and water (Georgia Tech, 2005).

Nanotechnology is also used for Organic Light Emitting Diodes (OLEDs). OLEDs are a display technology substitute for Cathode Ray Tubes, which contain lead. OLEDs also do not require mercury, which is used in conventional Flat Panel Displays (Frazer, 2003). The OLED displays have additional benefits of reduced energy use and overall material use through the lifecycle (Masciangioli and Wang, 2003).

2.3.4 Fuel Additives

Nanomaterials also show potential as fuel additives and automotive catalysts. For example, nano-cerium oxide particles are being employed in the United Kingdom as on- and off-road diesel fuel additives to decrease emissions. These manufacturers also claim a more than 5% decrease in fuel consumption with an associated decrease in vehicle emissions. Such a reduction in fuel consumption and decrease in emissions would result in obvious environmental benefits. Limited published research and modeling have indicated that the addition of cerium oxide to fuels may increase levels of specific organic chemicals in exhaust,

and result in emission of cerium oxide (Health Effects Institute, 2001); the health impacts associated with such alterations in diesel exhaust were not examined. As noted above in section 1.5.7, a manufacturer of a diesel additive containing cerium oxide has applied to Office of Air and Radiation/Office of Transportation and Air Quality for registration of this fuel additive. Nanocatalysts can also be used to increase energy efficiency in utility boilers and other energy-producing facilities.

3.0 Risk Management and Statutes

3.1 Risk Management

EPA makes risk management decisions within the statutory framework laid out in this chapter. Risk management options and how risks are characterized vary based on the program area (air, water, toxic substances etc.) and also the specific statute involved (for example, Clean Air Act, Clean Water Act, Toxic Substances Control Act). Risk management decisions at EPA are informed by an understanding of the risk from exposure to potential hazard. Section 4 of this paper discusses the risk assessment process and the types of information that EPA will need to inform its decisions. An understanding the toxicity of nanomaterials, dose metrics, probable exposure pathways, and environmental fate is needed to provide sound scientific information that informs the risk management process.

3.1.1 Risk Management and Nanoscale Materials

Nanomaterials may present risk management issues that are not easily characterized because of the breadth of categories of such substances. Some nanoscale materials are produced under established industrial hygiene practices based on their history of manufacturing processes and use. Human and environmental exposure information for these particular substances likely would already be available to inform risk management decisions. For some other nanoscale materials, there is less certainty of expected exposure and potential hazard. The uncertainty may be greater where new industrial methods are employed.

EPA realizes the potential benefits of nanomaterials. To fully realize that potential, the responsible development of such products is in the interest of EPA, producers and users of nanotechnology, as well as society as a whole. EPA believes that a proactive approach is appropriate in risk management, and using the principles of pollution prevention is an important first step. To that end, EPA expects producers and users of nanotechnology to develop stewardship programs and workplace practices based on pollution prevention principles. Additionally, EPA believes that partnerships with industrial sectors will ensure that proactive risk management approaches are part of initial decision making. Working in partnership with producers and users of nanotechnology to develop best practices and standards in the workplace, as well as other environmental programs, would help ensure that the production and use of nanomaterials results in minimal risk to human and environmental health.

EPA will review nanotechnology products and processes as they are introduced. This would occur under EPA's product review authorities under TSCA, FIFRA, and the Clean Air Act. EPA will work with producers and users of nanotechnology to prescribe protocols and approaches that limit exposure and address any potential risks. As knowledge becomes incrementally available, a refinement of risk management approaches may be needed. In addition, EPA will use its other statutory authorities, where appropriate, as the technology

develops in the marketplace. This would allow EPA to address any risks not identified by pollution prevention principles or product review statutes.

3.1.2 Environmental Stewardship

Nanotechnology provides an opportunity for EPA to lead discussions with industry and other stakeholders on best practices for acting first to prevent pollution at its source, using less toxic and more environmentally benign materials, and conserving natural resources whenever possible. Environmental stewards incorporate this approach voluntarily, to any and all stakeholders that might be affected by their actions, as part of their overall strategy for producing and using goods and services. These are the fundamental characteristics of environmental stewardship; Appendix B contains a fuller discussion of stewardship principles. At EPA, there are a number of programs already in place that are based upon environmental stewardship principles.

EPA has a number of programs that address processes, including inputs; waste streams; and the design, use, disposal, and stewardship of products consistent with the goal of pollution prevention. Information on nanotechnologies and materials could be supplied through existing information networks, and EPA could pursue additional voluntary initiatives or integrate nanotechnology and nanomaterials into already existing voluntary programs. For example, the National Pollution Prevention Resource Exchange National Networks have topic hubs that provide overviews on common operations and typical waste streams, as well as what pollution prevention opportunities exist and where specialized expertise can be found. Also, the Green Engineering Program is working on a number of industrial sectors (e.g., pulp and paper) to apply green engineering concepts and tools in evaluating and improving environmental performance of processes and products. These efforts could be targeted at the facility level and their operations, sectors, as well as supply chains.

EPA also could continue to expand its own work within the areas of Life Cycle Analysis (LCA) to targeted nanomaterials and products. EPA's Design for Environment (DfE) program already uses LCAs to examine the environmental impact of products over their entire life cycle from materials acquisition, through use, to disposal. LCAs can evaluate impacts on human health, atmospheric deposition/air quality, soil, sediment, water quality, and natural resource consumption. LCA also focuses the assessment on the product life stage of greatest environmental impact so that preventive measures can be taken. Material flow analysis also gives information about the environmental impacts throughout the product life cycle.

Another role for EPA is to supply information so that others can act as environmental stewards. EPA can provision directly new information appropriate to nanotechnology and nanomaterial producers, users and consumers, and can also work with state technology assistance organizations and other tech transfer groups to integrate an environmental stewardship orientation into their ongoing assistance efforts. For example, at the state level, the Office of Technical Assistance (OTA) conducts site visits to manufacturers in

Massachusetts to help them assess their processes and identify opportunities to reduce or eliminate the use of toxic chemicals, and to conserve water.

3.2 Statutes

EPA administers a wide range of environmental statutes. Some of these statutes will apply to nanomaterials depending on their specific media of application or release. Other statutes will apply to certain nanomaterials depending on their specific uses, applications, and processes and will require EPA to evaluate the nanomaterials before they enter into commerce. Some risk management activities carried out under these statutes could also utilize nanomaterials or products for environmental remediation or pollution prevention technologies.

The framework of environmental statutes outlined below is a starting point for evaluating and managing risks and benefits from products of nanotechnology. Some current EPA policies and regulations may require modifications to address this new technology. For example, some nanomaterials are not currently well characterized by existing nomenclature conventions. Until adequate nomenclature conventions are developed, it will be difficult to determine in some instances if reporting to EPA is required because the nanomaterials are not contained on the TSCA Inventory, or if use of a nanoscale material results in a change to a pesticide product already registered under FIFRA.

Nanoscale materials will present other novel risk assessment/management challenges. Standards that will need to be developed include not only terminology/nomenclature, but also physical standards such as dimensions and behaviors, testing procedures, and instrumentation. There is also a need to review conventional hazard, exposure, and risk assessment tools for their applicability to nanomaterials, as well as development of risk mitigation options that are tailored to nanoscale materials (e.g., use of personal protective equipment). These issues are discussed in detail throughout the paper.

3.2.1 Toxic Substances

Under the Toxic Substances Control Act (TSCA) section 5(a), Premanufacture Notices (PMNs) must be submitted to EPA by a person intending to manufacture or import chemical substances not on the TSCA Inventory of Chemical Substances. Nanoscale materials that are chemical substances under TSCA and which are not on the TSCA Inventory must be reported to EPA. The premanufacture review process serves as a gatekeeper to identify concerns and exercise appropriate regulatory oversight. For example, use restrictions, occupational exposure limits/controls, limits on releases to the environment and limits on manufacture may be required until toxicity and fate data are developed to better inform a risk assessment of the chemical. Section 5(a)(2) of TSCA authorizes EPA to determine that a use of a chemical substance is a "significant new use." EPA must make this determination by rule after considering all relevant factors, including a series of risk-related factors that are listed in section 5(a)(2) of TSCA. Once EPA promulgates a rule specifying that a use of a chemical substance is a significant new use, section 5(a)(1)(B) of TSCA

requires persons to submit a notice to EPA at least 90 days before they manufacture, import, or process the substance for that use (40 CFR 721.5).

Under TSCA section 6, EPA has the authority to, by rule, prohibit or limit the manufacture, import, processing, distribution in commerce, use, or disposal of a chemical substance if there is a reasonable basis to conclude that the chemical "presents or will present an unreasonable risk" of injury to health or the environment. Section 8(e) of TSCA requires that chemical manufacturers, processors, and distributors notify EPA of information that "reasonably supports the conclusion that a chemical substance or mixture presents a substantial risk of injury to human health or the environment." Under section 8(a) of TSCA EPA may collect information associated with chemical substances. Some of the types of information that can be required include categories of use, production volume, byproducts, an estimate of the number of individuals exposed, and duration of such exposures. EPA may require manufacturers of chemical substances to submit unpublished health and safety studies under section 8(d) of TSCA. EPA also engages in voluntary programs such as the High Production Volume Challenge program to gather information on chemical substances. Nanomaterials that are chemical substances under TSCA could be subject to all these provisions and programs.

Voluntary and regulatory measures for evaluating nanomaterials are being developed and implemented by OPPT under TSCA, as noted in the introduction. OPPT is already reviewing new chemical submissions for nanomaterials under TSCA.

3.2.2 Pesticides

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), EPA is responsible for registering pesticide products for use in the United States. An application for registration under FIFRA must disclose the specific chemicals in the pesticide formulation. Pesticide registration decisions are based on a detailed assessment of the potential effects of a product on human health and the environment, when used according to label directions. These approved labels have the force of law, and any use that is not in accordance with the label directions and precautions may be subject to civil and/or criminal penalties. FIFRA also requires that EPA reevaluate older pesticides to ensure that they meet more recent safety standards. FIFRA requires EPA and states to establish programs to protect workers, and provide training and certification for applicators. It is expected that pesticide products containing nanomaterials will come under FIFRA review and registration.

3.2.2.1 Registration

Under FIFRA sections 3 and 12, EPA must approve all new pesticide products, as well as new uses and changes in the composition of existing pesticide products, before the products may be sold or distributed in commerce. EPA issues its approvals in the form of registrations or amended registrations. In order to evaluate an application for registration, EPA requires the applicant to provide a complete characterization of the composition of the product, proposed labeling which describes the intended use of the product, and the results of extensive health

and safety testing. Using this information, EPA determines whether the product may "cause unreasonable adverse effects on the environment." FIFRA defines "unreasonable adverse effects on the environment" as any "unreasonable risk to man or the environment taking into account the economic, social, and environmental costs and benefits of the use of any pesticide..." EPA may refuse to approve an application unless the applicant agrees to modify the composition or labeling of the product to reduce its risks to acceptable levels.

3.2.3 Clean Air Act

The Clean Air Act (most recently amended in 1990) has provided the primary legal framework for protecting public health and welfare from the harmful effects of air pollution. The Act has a number of provisions that need to be considered in determining its applicability to nanotechnology. These provisions are summarized below.

3.2.3.1 Criteria Air Pollutants

Two sections of the Clean Air Act (CAA) govern the establishment, review and revision of national ambient air quality standards (NAAQS). Section 108 of the Act (42 U.S.C. 7408) directs the Administrator to identify certain pollutants which "may reasonably be anticipated to endanger public health and welfare" and to issue air quality criteria for them. These criteria air pollutants could result from use or manufacture of nanomaterials. These air quality criteria are to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of [a] pollutant in the ambient air . . . ". Section 109 of the Act (42 U.S.C. 7409) directs the Administrator to propose and promulgate "primary" and "secondary" NAAQS for pollutants identified under section 108 of the Act. Section 109(b)(1) of the Act defines a primary standard as one "the attainment and maintenance of which in the judgment of the Administrator, based on [the] criteria and allowing an adequate margin of safety, are requisite to protect the public health."

3.2.3.2 Air Toxics (Hazardous Air Pollutants (HAPs)

Title III if the 1990 CAA Amendments (CAAA) significantly changed the pre-existing system for control of hazardous air pollutants (HAPs) which required the Agency to both identify and develop health-based emission standards for each pollutant. The HAPs could result from use or manufacture of nanomaterials. Under the CAA Amendments, 189 Air Toxics (hazardous air pollutants) are identified for regulation. The law directs EPA to identify the sources of the 189 pollutants and establishes a ten year time period for EPA to issue technology-based emissions standards for each source category. Section 112(r) of the CAA also contains requirements that address accidental releases of hazardous substances from stationary sources that potentially can have serious adverse effects to human health or the environment.

3.2.3.3 Registration of Fuels and Fuel Additives

Section 211 of the Clean Air Act (CAA) provides EPA with the authority to designate any mobile source fuel or additive for registration. Section 211(b) requires, for the purpose of registration, that the manufacturer provide certain compositional and related information, and available health-effects data. Section 211(b) also provides EPA with the authority to require health-effects testing. EPA promulgated health effects testing requirements for fuels and fuel additives on June 27, 1994 in Part II 40 CFR Part 79. Gasoline and diesel fuels and their additives (regardless of claims categorizing an additive as nanotechnology) are subject to the regulations promulgated by EPA in 1994. These fuels and additives for use in on-road applications may not be introduced into commerce until it has been registered by EPA.

EPA's Office of Air and Radiation/Office of Transportation and Air Quality has received and is reviewing an application for registration of a diesel additive containing cerium oxide. Nano-cerium oxide particles are being employed in Europe as on and off-road diesel fuel additives to decrease emissions and some manufacturers are claiming fuel economy benefits.

3.2.4 Pollution Prevention

3.2.4.1 Legislation

The Pollution Prevention Act of 1990 (Public Law 101-508) was enacted in November 1990 and amended through Public Law 107-377 in December 2002. The Act was considered a turning point in how the nation looks at the control of pollution. Instead of focusing on waste management and pollution control, Congress declared a national policy for the United States to address pollution based on "source reduction." The policy established a hierarchy of measures to protect human health and the environment, where multi-media approaches would be anticipated: (1) pollution should be prevented or reduced at the source, (2) pollution that cannot be prevented should be recycled in an environmentally safe manner, (3) pollution that cannot be prevented or recycled should be treated in an environmentally safe manner; and (4) disposal or other release into the environment should be employed only as a last resort and should be conducted in an environmentally safe manner.

The first tier of the hierarchy is the preferred strategy for addressing potential environmental issues, and is referred to as "source reduction." Source reduction is defined in the Act as: "Any practice which: (1) reduces the amount of any hazardous substance, pollutant, or contaminant entering any waste stream or otherwise released into the environment (including fugitive emissions) prior to recycling, treatment, or disposal; and (2) reduces the hazards to public health and the environment associated with the release of such substances, pollutants, or contaminants."

3.2.4.2 Implementation of the Pollution Prevention Act.

The Act required EPA to establish an office to carry out the functions of the Act. In 1990, EPA formally established the Office of Pollution Prevention and Toxics (OPPT). Within this office were initiated two programs, with two different approaches, to meet the spirit of the new national policy: the Design for the Environment (DfE) Program and the Green Chemistry Program. Under DfE, EPA works in partnership with industry sectors to improve performance of commercial processes while reducing risks to human health and the environment. The Green Chemistry Program promotes research to design chemical products and processes that reduce or eliminate the use and generation of toxic chemical substances. In 1998, EPA complimented these two programs with the Green Engineering Program, which applies approaches and tools for evaluating and reducing the environmental impacts of processes and products (see http://www.epa.gov/oppt/greenengineering/textbook.html). As described in the environmental stewardship discussion above, nanotechnology offers an opportunity to implement pollution prevention principles into the design of a new technology.

3.2.5 Clean Water Act

If a wastewater stream of nanomaterials is produced, it will be subject to effluent guidelines of the Clean Water Act. Depending on the nature of the wastewater stream other water quality guidelines or standards could apply. Nanomaterials have been proposed for use as bactericides.

3.2.6 Safe Drinking Water Act

The Safe Drinking Water Act (SDWA), as amended in 1996, is the main federal law that protects public health by regulating hazardous contaminants in drinking water. SDWA authorizes the Agency to establish non-enforceable health-based Maximum Contaminant Level Goals (MCLGs) and enforceable Maximum Contaminant Levels (MCLs) or required treatment techniques, as close as feasible to the MCLGs, taking into consideration costs and available analytical and treatment technology. Nanotechnology has the potential to influence the setting of MCLs through improvements in analytical methodology or treatment techniques, or by nanomaterials themselves potentially qualifying for regulation as drinking water contaminants based on health risks and occurrence in drinking water.

Nanotechnology has the potential to contribute to better and cost-effective removal of drinking water contaminants, such metals (e.g. arsenic or chromium), toxic halogenated organic chemicals, suspended particulate matter and pathogenic microorganisms. Nanotechnology-based sensors are being developed that result in vastly improved sensitivity for measuring contaminants in drinking water. Improved, cost-effective treatment technology and analytical techniques have the potential to lead to maximum contaminant levels (MCL) closer to the public health-based MCL Goals and therefore, to better public health protection.

If nanoparticles enter drinking water, such as through their use in water treatment, then exposure to nanomaterials may occur through drinking water ingestion or inhalation (e.g.

from showering). The magnitudes of exposure and toxicity of nanomaterials in drinking water are unknown at present. However, the possibility exists that, based on their toxicity and occurrence in drinking water supplies, nanomaterials would need to be regulated under the SDWA.

3.2.7 CERCLA

The Comprehensive Environmental Response Compensation and Liability Act (CERCLA) addresses problems associated with closed and abandoned waste sites. CERCLA gives EPA the authority to respond to actual or threatened releases of hazardous substances to the environment or to actual or threatened releases to the environment of pollutants or contaminants that may present an imminent and substantial danger to the public health or welfare. Nanomaterials that meet these criteria would be subject to this authority.

If a compound is comprised of a chemical or chemicals that are listed as hazardous substances under the Clean Water Act, the Clean Air Act, RCRA, or TSCA, or under section 102 of CERCLA, then the compound is considered a hazardous substance under CERCLA. If a compound is not listed as a hazardous substance under CERCLA, then EPA may still address an actual or threatened release to the environment of that substance under CERCLA if the substance is a pollutant or contaminant that may present an imminent and substantial danger to the public health or welfare.

3.2.8 RCRA

The Resource Conservation and Recovery Act (RCRA), which amended the Solid Waste Disposal Act, regulates the transportation, treatment, disposal (other than to surface water), and cleanup of hazardous wastes being generated by businesses, industries, and government agencies. RCRA transportation, treatment, and disposal requirements apply to RCRA hazardous wastes; RCRA groundwater monitoring and corrective action requirements apply to releases of RCRA hazardous wastes and RCRA hazardous constituents. Nanomaterials that meet the definition of RCRA hazardous wastes would be subject to these regulations.

3.2.8.1 RCRA Hazardous Wastes

A waste is a RCRA hazardous waste only if it is a solid waste and is either listed or exhibits a hazardous characteristic. A solid waste may be solid, liquid, or gas, must be discarded (abandoned, released to the environment); and, excludes domestic sewage, industrial wastewater to publicly owned treatment works, nuclear wastes, and certain mining materials. A solid waste is a RCRA hazardous waste if it is listed in the Code of Federal Regulations (CFR), or if it exhibits a hazardous characteristic. RCRA hazardous constituents are listed in 40 CFR Part 261 Appendix VIII. Appendix VIII has no independent regulatory status, but this list is referenced by groundwater monitoring, corrective action, and delisting regulations.

3.2.9 Toxics Release Inventory Program

Some producers of nanomaterials containing materials listed on the Toxic Release Inventory (TRI) may be subject to reporting under the TRI Program (www.epa.gov/tri/). In 1986 when Congress passed the Emergency Planning and Community Right to Know Act (EPCRA) the TRI was established. The TRI is a publicly available database containing information on toxic chemical releases and other waste management activities that are reported annually by manufacturing facilities and facilities in certain other sectors, as well as federal facilities. Facilities required to report TRI chemical releases and other waste management quantities are those that met or exceeded the minimum criteria of number of employees and total mass of chemical manufactured, processed, or otherwise used in a calendar year. Of the nearly 650 toxic chemicals and chemical compounds on the TRI, several are metallic elements and the compounds composed of these metals. The TRI includes compounds containing cadmium, chromium, copper, cobalt and antimony. Some of these metals are a part of the composition of nanomaterials like quantum dots.

4.0 Risk Assessment of Nanomaterials

4.1 Introduction

EPA's mission and mandates require an understanding of the health and environmental implications of intentionally produced nanomaterials. A challenge in evaluating risk associated with the manufacture and use of nanomaterials is the diversity and complexity of the types of materials available and under development as well as the seemingly limitless potential uses of these materials. A risk assessment is the evaluation of scientific information on the hazardous properties of environmental agents, the dose-response relationship, and the extent of exposure of humans or environmental receptors to those agents. The product of the risk assessment is a statement regarding the probability that humans (populations or individuals) or other environmental receptors so exposed will be harmed and to what degree (risk characterization). EPA generally follows the risk assessment paradigm described by the National Academy of Sciences (NAS) (NAS/NRC, 1983 1994).

The overall risk assessment approach used by EPA for conventional chemicals is thought to be generally applicable to nanomaterials. It is important to note that nanomaterials have large surface areas per unit of volume, and novel electrical and magnetic properties relative to conventional chemicals. Some of the special properties that make nanomaterials useful are also properties that may cause some nanomaterials to pose hazards to humans and the environment, under specific conditions, as noted below. It will be necessary to consider these unique properties and their potential impacts on fate, exposure, and toxicity in developing risk assessments for nanomaterials. At this point in time, we assume that the NAS paradigm is appropriate for the assessment of nanomaterials. However, we note that modifications of the NAS risk assessment approach for other stressors such as biotechnology products and particulate matter research have been proposed (Committee on Environment and Natural Resources, 2002).

Occupational and environmental exposures to engineered nanomaterials have been reported (Baron et al., 2004). Uncertainties in health, ecology, and the environment effects associated with exposure to engineered nanomaterials raise questions about potential risks from such exposures (Dreher, 2004; Swiss Report Reinsurance Company, 2004; UK Royal Society Report, 2004; European Commission Report, 2004; European NanoSafe Report 2004; Health and Safety Executive, 2004).

The purpose of this chapter is to briefly review the state of knowledge regarding the components needed to conduct a risk assessment on nanomaterials. The following key aspects of risk assessment are addressed as they relate to nanomaterials: chemical identification and characterization, environmental fate, environmental detection and analysis, human exposure, human health effects, and ecological effects. Each of these aspects is discussed by providing a synopsis of key existing information on each topic. Additional technical discussion and details on specific studies for several topics are provided in Appendix C.

4.2 Chemical Identification and Characterization of Nanomaterials

The identification and characterization of chemical substances and materials is an important first step in assessing their risk. Understanding the physical and chemical properties in particular is necessary in the evaluation of hazard (both toxicological and ecological) and exposure (all routes). Chemical properties that are important in the characterization of discrete chemical substances include, but are not limited to, molecular weight, melting point, boiling point, vapor pressure, octanol-water partition coefficient, water solubility, reactivity, and stability. In addition, information on a substance's manufacture and formulation is important in understanding purity, product variability, performance, and use.

The diversity and complexity of nanomaterials makes chemical identification and characterization not only more important but also more difficult. A broader spectrum of properties will be needed to sufficiently characterize a given nanomaterial for the purposes of evaluating hazard and assessing risk. Chemical properties such as those listed above may be important for some nanomaterials, but other properties such as particle size and distribution, surface/volume ratio, magnetic properties, coatings, and conductivity are expected to be more important for the majority of nanoparticles.

A given nanomaterial can be produced in many cases by several different processes yielding several derivatives of the same material. For example, single-walled carbon nanotubes can be produced by four different processes that can generate products with different physical-chemical properties (e.g., size, shape, composition) and potentially different ecological and toxicological properties. It is not clear whether existing physical-chemical property test methods are adequate for sufficiently characterizing various nanomaterials in order to evaluate their hazard and exposure and assess their risk. It is clear that chemical properties such as boiling point and vapor pressure are insufficient. Alternative methods for measuring properties of nanomaterials may need to be developed both quickly and cost effectively.

Because of the current state of development of chemical identification and characterization, current chemical representation and nomenclature conventions may not be adequate for some nanomaterials. Nomenclature conventions are important to eliminate ambiguity when communicating differences between nanomaterials and bulk materials and in reporting for regulatory purposes. EPA's OPPT is participating in new and ongoing workgroup/panel deliberations with the American National Standards Institute (ANSI), the American Society for Testing and Materials (ASTM), and the International Organization for Standards (ISO) concerning the development of terminology and chemical nomenclature for nano-sized substances, and will also continue with its own nomenclature discussions with the Chemical Abstracts Service (CAS).

4.3 Environmental Fate of Nanomaterials

4.3.1 Introduction

Potential nanomaterials release sources include direct and/or indirect releases to the environment from the manufacture and processing of nanomaterials, releases from oil refining processes, chemical and material manufacturing processes, chemical clean up activities including the remediation of soil-contaminated sites, releases of nanomaterials incorporated into materials used to fabricate products for consumer use including pharmaceutical products, and releases resulting from disposal of consumer products containing nanoscale materials (e.g., disposal of screen monitors, computer boards, automobile tires, clothing and cosmetics). The fundamental properties concerning the environmental fate of nanomaterials are not well understood (European Commission, 2004), as there are few available studies on the environmental fate of nanomaterials. The following sections summarize what is known or can be inferred about the fate of nanomaterials in the atmosphere, in soils, and in water. These summaries are followed by sections discussing: 1) biodegradation, bioavailability, and bioaccumulation of nanomaterials; 2) the potential for transformation of nanomaterials to more toxic metabolites; 3) possible interactions between nanomaterials and other environmental contaminants; and 4) the applicability of current environmental fate and transport models to nanomaterials. Appendix C contains additional details on the environmental fate of nanomaterials.

4.3.2 Fate of Nanomaterials in Air

Several processes influence the fate of airborne nanomaterials in addition to their initial dimensional and chemical characteristics: the length of time the particles remain airborne, the nature of their interaction with other airborne particles or molecules, and the distance that they may travel prior to deposition. The processes important to understanding the potential atmospheric transport of nano-sized particles are diffusion, agglomeration, wet and dry deposition, and gravitational settling.

With respect to the length of time particles remain airborne, particles with aerodynamic diameters in the nanoscale range (<100 nm) follow the laws of gaseous diffusion when released to air. The rate of diffusion is inversely proportional to particle diameter, while the rate of gravitational settling is proportional to particle diameter (Aitken et al., 2004). Airborne particles can be classified by size and behavior into three general groups: Small particles (diameters <80 nm) are described as being in the agglomeration mode; they are short-lived because they rapidly agglomerate to form larger particles. Large particles (>2000 nm) are described as being in the coarse mode and are subject to gravitational settling. Intermediate-sized particles (>80 nm and < 2000 nm) are described as being in the accumulation mode and can remain suspended in air for the longest time, days to weeks, and can be removed from air via dry or wet deposition (Bidleman, 1988; Preining, 1998; Spurny, 1998; Atkinson, 2000; Royal Society, 2004; Dennenkamp et al., 2002). Note that these generalizations apply to environmental conditions and do not preclude the possibility that humans and other organisms may be exposed to large as well as smaller particles by

inhalation. Additionally, intentionally produced nanomaterials may or may not behave in similar fashion to the ultrafine particles described in the above citations.

Deposited nanoparticles are typically not easily resuspended in the air or re-aerosolized (Colvin 2003; Aitken et al. 2004). Because physical particle size is a critical property of nanomaterials, maintaining particle size during the handing and use of nanomaterials is a priority. Current research is underway to produce carbon nanotubes that do not form clumps either by functionalizing the tubes themselves, or by treatment with a coating or dispersing agent (Royal Society, 2004; Colvin, 2003), so future materials may be more easily dispersed.

Many nano-sized particles are reported to be photoactive (Colvin, 2003), but their susceptibility to photodegradation in the atmosphere has not been studied. Nanomaterials are also known to readily adsorb a variety of materials, and many act as catalysts. However, no studies are currently available that examine the interaction of nano-sized adsorbants and chemicals sorbed to them, and how this interaction might influence their respective atmospheric chemistries.

4.3.3 Fate of Nanomaterials in Soil

The fate of nanomaterials released to soil is likely to vary depending upon the physical and chemical characteristics of the nanomaterial. Nanomaterials released to soil can be strongly sorbed to soil due to their high surface areas and therefore be immobile. On the other hand, nanomaterials are small enough to fit into smaller spaces between soil particles, and might therefore travel farther than larger particles before becoming trapped in the soil matrix. The strength of the sorption of any intentionally produced nanoparticle to soil will be dependent on its size, chemistry, applied particle surface treatment, and the conditions under which it is applied. Studies have demonstrated the differences in mobility of a variety of insoluble nano-sized materials in a porous medium. (Zhang, 2003; Lecoanet and Wiesner, 2004; Lecoanet et al., 2004).

Additionally, the properties of the soil and environment can affect nanomaterial mobility. For example, the mobility of mineral colloids in soils and sediments is strongly affected by charge. Surface photoreactions provide a pathway for nanomaterial transformation on soil surfaces. Humic substances, common constituents of natural particles, are known to photosensitize a variety of organic photoreactions on soil and other natural surfaces that are exposed to sunlight. Studies of nanomaterial transformations in field situations are further complicated by the presence of naturally occurring nanomaterials of similar molecular structures and size ranges. Iron oxides are one example.

4.3.4 Fate of Nanomaterials in Water

Fate of nanomaterials in aqueous environments is controlled by aqueous solubility or dispersability, interactions between the nanomaterial and natural and anthropogenic chemicals in the system, and biological and abiotic processes. There are limited data on the fate and transport of nanoparticles, but existing data show that their behavior can be very different

from much larger particles of the same materials. Nanoparticles generally will be retained in the water column due to diffusion and dispersion. Waterborne nanoparticles generally settle more slowly than larger particles of the same material but can be removed from water by agglomeration or sorption and sedimentation. Dispersed insoluble nanoparticles can be stabilized in water by interactions with naturally-occurring humic substances or other species. Biodegradation or association with biological materials may remove nanomaterials. Photocatalyzed reactions may alter the physical and chemical properties of nanomaterials and so alter their behavior in water. Processes that control transport and removal of nanoparticles in water and wastewater are being studied to understand nanoparticle fate. Nanoparticle photochemistry is being studied with respect to its possible application in water treatment.

Dispersed insoluble nanoparticles can be stabilized by naturally-occurring colloids made up of humic acids and other organics, which would also delay settling from the water column. Insoluble materials may also form stable colloidal suspensions in water. For example, researchers at Rice University have reported that although C_{60} fullerene is initially insoluble in water, it spontaneously forms aqueous colloids containing nanocrystalline aggregates. The concentration of nanomaterials in the suspensions can be as high as 100 parts per million (ppm), but is more typically in the range of 10-50 ppm. The stability of the particles and suspensions is sensitive to pH and ionic strength.

Due to their high surface-area-to-mass ratios, nano-sized particles have the potential to sorb to suspended soil and sediment particles (Oberdorster et al., 2005). However, there are not yet any published studies on sorption of nanomaterials to particles in the water column. In the case of abiotic processes, both chemical and photoactivated reactions in particle/water systems are likely involved in nanomaterial transformations.

Certain organic and metallic nanomaterials may possibly be transformed under anaerobic conditions, such as in aquatic (benthic) sediments. From past studies, it is known that several types of organic compounds are generally susceptible to reduction under such conditions. Complexation by natural organic materials such as humic colloids can facilitate reactions that transform metals in anaerobic sediments (see Nurmi et al., 2005 and references therein).

Particles in the upper layers of aquatic environments, on soil surfaces, and in water droplets in the atmosphere are exposed to sunlight. Light-induced photoreactions often are important in determining environmental fate of chemical substances. Heterogeneous photoreactions on metal oxide surfaces are increasingly being used as a method for drinking water, wastewater and groundwater treatment. Semiconductors such as titanium dioxide and zinc oxide as nanomaterials have been shown to effectively catalyze both the reduction of halogenated chemicals and oxidation of various other pollutants, and heterogeneous photocatalysis has been used for water purification in treatment systems.

The fate of nano-sized particles in wastewater treatment plants is not well characterized. Wastewater may be subjected to many different types of treatment, including physical, chemical and biological processes, depending on the characteristics of the

wastewater, whether the plant is a publicly owned treatment work (POTW) or onsite industrial facility, etc. Broadly speaking, nano-sized particles are most likely to be affected by sorption processes (for example in primary clarifiers) and chemical reaction. The ability of either of these processes to immobilize or destroy the particles will depend on the chemical and physical nature of the particle and the residence times in relevant compartments of the treatment plant. As noted above, sorption, agglomeration and mobility of mineral colloids are strongly affected by pH; thus pH is another variable that may affect sorption and settling of nanomaterials. Current research in this area includes the production of microbial granules that are claimed to remove nanoparticles from simulated wastewater (Ivanov et al., 2004). Nanomaterials that escape sorption in primary treatment may be removed from wastewater after biological treatment via settling in the secondary clarifier. Normally the rate of gravitational settling of particles such as nanomaterials in water is dependent on particle diameter, and smaller particles settle more slowly. However, settling of nanomaterials could be enhanced by entrapment in the much larger sludge flocs, removal of which is the objective of secondary clarifiers.

4.3.5 Biodegradation of Nanomaterials

Biodegradation of nanoparticles may result in their breakdown as typically seen in biodegradation of organic molecules, or may result in changes in the physical structure or surface characteristics of the material. The potential for and possible mechanisms of biodegradation of nano-sized particles have just begun to be investigated. As is the case for other fate processes, the potential for biodegradation will depend strongly on the chemical and physical nature of the particle. Many of the nanomaterials in current use are composed of inherently nonbiodegradable inorganic chemicals, such as ceramics, metals and metal oxides, and are not expected to biodegrade. However, a recent preliminary study found that C_{60} and C_{70} fullerenes were taken up by wood decay fungi after 12 weeks, suggesting that the fullerene carbon had been metabolized (Filley et al., 2005). For other nanomaterials biodegradability may be integral to the material's design and function. This is the case for some biodegradable polymers being investigated for use in drug transport (Madan et al., 1997; Brzoska et al., 2004), for which biodegradability is mostly a function of chemical structure and not particle size.

Biodegradability in waste treatment and the environment may be influenced by a variety of factors. Recent laboratory studies on C_{60} fullerenes have indicated the development of stable colloid structures in water that demonstrate toxicity to bacteria under aerobic and anaerobic conditions (CBEN, 2005; Fortner et al., 2005). Further studies are needed to determine whether fullerenes may be toxic to microorganisms under environmental conditions. One must also consider the potential of photoreactions and other abiotic processes to alter the bioavailability and thus biodegradation rates of nanomaterials. In summary, not enough is known to enable meaningful predictions on the biodegradation of nanomaterials in the environment and much further testing and research are needed.

4.3.6 Bioavailability and Bioaccumulation of Nanomaterials

Bacteria and living cells can take up nano-sized particles, providing the basis for potential bioaccumulation in the food chain (Biswass and Wu, 2005). Aquatic and marine filter feeders near the base of the food chain feed on nano-sized and larger particles. The bioavailability of specific nanomaterials in the environment will depend in part on the particle. Environmental fate processes may be too slow for effective removal of persistent nanomaterials before they can be taken up by an organism. In the previous section, it was noted that some physical removal processes, such as gravitational settling, are slower for nano-sized particles than for microparticles. This would lead to an increased potential for inhalation exposure to terrestrial organisms and for increased exposure of aquatic organisms to aqueous colloids. Not enough information has been generated on rates of deposition of nanomaterials from the atmosphere and surface water, or of sorption to suspended soils and sediments in the water column, to determine whether these processes could effectively sequester specific nanoparticles before they are taken up by organisms.

Complexation of metallic nanomaterials may have important interactive effects on biological availability and photochemical reactivity. For example, the biological availability of iron depends on its free ion concentrations in water and the free ion concentrations are affected by complexation. Complexation reduces biological availability by reducing free metal ion concentrations and dissolved iron is quantitatively complexed by organic ligands. Solar UV radiation can interact with these processes through photoreactions of the complexes. Further, iron and iron oxides can participate in enzymatic redox reactions that change the oxidation state, physical chemical properties and bioavailability of the metal (Reguera et al. 2005).

4.3.7 Potential for Toxic Transformation Products from Nanomaterials

Certain nanomaterials are being designed for release as reactants in the environment, and therefore are expected to undergo chemical transformation. One example of this is iron (Fe^0) nanoparticles employed as reactants for the dechlorination of organic pollutants (Zhang, 2003). As the reaction progresses, the iron is oxidized to iron oxide. Other metal particles are also converted to oxides in the presence of air and water. Whether the oxides are more or less toxic than the free metals depends on the metal. Under the right conditions, certain metal compounds could be converted to more mobile compounds. In these cases, small particle size would most likely enhance this inherent reactivity. Degradation products from carbon nanomaterials (fullerenes and nanotubes) have not yet been reported.

4.3.8 Interactions Between Nanomaterials and Organic or Inorganic Contaminants: Effects and the Potential for Practical Applications

The examples cited in this section illustrate how nanomaterials have been demonstrated to alter the partitioning behavior of chemicals between environmental compartments and between the environment and living organisms. Furthermore, several nanomaterials are reactive toward chemicals in the environment, generate reactive species, or catalyze reactions of other chemicals. These properties are currently under study for use in

waste remediation operations. It should be noted that the potential also exists for nanomaterials to effect unforseen changes if released to the environment in large quantities.

Two types of effects under study for possible exploitation are sorption and reaction. The high surface area of nano-sized particles provides enhanced ability to sorb both organic and inorganic chemicals from environmental matrices compared to conventional forms of the same materials. This property potentially can be utilized to bind pollutants to enhance environmental remediation. Many examples of immobilized nanomaterials for use in pollution control or environmental remediation have been described in the literature. These include nanosponges or nanoporous ceramics, large particulate or bead materials with nano-sized pores or crevasses (Christen, 2004), and solid support materials with coatings of nanoparticles (for example, see Comparelli et al., 2004). This section will instead focus on releases of free nanoparticles and the effects they have had on chemicals in the environment. The remainder of this section will be organized into known changes in the mobility of chemicals caused by their sorption to nanoparticles, and known instances of reactivity and catalytic activity toward chemicals mediated by nanoparticles.

No single overall effect can be described for the sorption of chemicals to nanomaterials based on their size or chemical makeup alone. In air, aerosolized nanoparticles can adsorb gaseous or particulate pollutants. In soil or sediments, nanomaterials might increase the bioavailability of pollutants, thereby increasing the pollutant's availability for biodegradation (U.K. Royal Society, 2004). Depending on the conditions, nano-sized carbon such as C_{60} or nanotubes could either enhance or inhibit the mobility of organic pollutants. (Cheng et al., 2004). Stable colloids of hydrophobic nanomaterials in an aqueous environment could provide a hydrophobic microenvironment that suspends hydrophobic contaminants and retards their rate of deposition onto soils and sediments. Similar effects are known to happen with naturally occurring colloids made up of humic acids and suspended sediment particles (Schwarzenbach et al., 1993). Nanoparticles can be altered to optimize their affinities for particular pollutants by modifying the chemical identity of the polymer.

Several studies investigating the sorption of organic pollutants and metals in air, soil, and water to nano-sized materials have recently been reported in the literature. The sorption of naphthalene to C_{60} from aqueous solution was compared to sorption to activated carbon (Cheng et al., 2004). The investigators observed a correlation between the surface area of the particles and the amount of naphthalene adsorbed from solution. In other studies, nanoparticles made of an amphiphilic polymer have been shown to mobilize phenanthrolene from contaminated sandy soil and increase its bioavailability (Tungittiplakorn et al., 2004,2005). .It has been reported that magnetite crystals adsorb arsenic and chromium (CrVI) from water (CBEN 2005; Hu et al. 2004), suggesting potential purification techniques for metal-laden drinking water (CBEN, 2005). The adsorption and desorption of volatile organic compounds from ambient air by fullerenes has been investigated (Chen et al., 2000). Inhalation exposures of benzo(a)pyrene sorbed to ultrafine aerosols of Ga_2O_3 (Sun et al, 1982) and diesel exhaust (140 nm) (Sun et al., 1984) were studied in rats. The studies showed that when compared to inhalation of pure benzo(a)pyrene aerosols, material sorbed to the gallium

oxide had increased retention in the respiratory tract, and increased exposure to the stomach, liver, and kidney.

Nanoscale materials are typically more reactive than larger particles of the same material. This is true especially for metals and certain metal oxides. In the environment, nanomaterials have the potential to react with a variety of chemicals; their increased or novel reactivity coupled with their sorptive properties allows for accelerated removal of chemicals from the environment. Many groups are currently investigating the use of nanomaterials for the destruction of persistent pollutants in the environment.

Nanoscale iron particles have been demonstrated to be effective in the *in situ* remediation of soil contaminated with tetrachloroethylene. A wide variety of additional pollutants are claimed to be transformed by iron nanoparticles in laboratory experiments, including halogenated (Cl, Br) methanes, chlorinated benzenes, certain pesticides, chlorinated ethanes, polychlorinated hydrocarbons, TNT, dyes, and inorganic anions such as nitrate, perchlorate, dichromate, and arsenate. Further investigations are underway with bimetallic nanoparticles (iron nanoparticles with Pt, Pd, Ag, Ni, Co, or Cu deposits) and metals deposited on nanoscale support materials such as nanoscale carbon platelets and nanoscale polyacrylic acid (Zhang, 2003). Nanosized clusters of C_{60} have been shown to generate reactive oxygen species in water under UV and polychromatic light. Similar colloids have been reported to degrade organic contaminants and act as bacteriocides (Boyd et al., 2005). Fullerol ($C_{60}(OH)_{24}$) has also been demonstrated to produce reactive oxygen species under similar conditions (Pickering and Wiesner, 2005).

4.3.9 Applicability of Current Environmental Fate and Transport Models to Nanomaterials

When performing exposure assessments on materials for which there are no experimental data, models are often used to generate estimated data, which can provide a basis for making regulatory decisions. It would be advantageous if such models could be applied to provide estimated properties for nanomaterials, since there is very little experimental data available for these materials. The models used by EPA's Office of Pollution Prevention and Toxics (OPPT) to assess environmental fate and exposure, are, for the most part, designed to provide estimates for organic molecules with defined and discrete structures. These models are not designed for use on inorganic materials; therefore, they cannot be applied to inorganic nanomaterials. Many models derive their estimates from structural information and require that a precise structure of the material of interest be provided. Since many of the nanomaterials in current use, such as quantum dots, ceramics and metals, are solids without discrete molecular structures, it is not possible to provide the precise chemical structures that these models need. While it is usually possible to determine distinct structures for fullerenes, the models cannot accept the complex fused-ring structures of the fullerenes. Also, the training sets of chemicals with which the quantitative structure-activity relationships (QSAR) in the models were developed do not include fullerene-type materials. Fullerenes are unique materials with unusual properties, and they

cannot be reliably modeled by QSARs developed for other substantially different types of materials.

In general, models used to assess the environmental fate and exposure to chemicals are not applicable to intentionally produced nanomaterials. Depending on the relevance of the chemical property or transformation process, new models may have to be developed to provide estimations for these materials; however, models cannot be developed without the experimental data needed to design and validate them. Before the environmental fate, transport and multimedia partitioning of nanomaterials can be effectively modeled, reliable experimental data must be acquired for a variety of intentionally produced nanomaterials.

However, models are also used which focus on the fate and distribution of particulate matter (air models) and/or colloidal materials (soil; water; landfill leachates; ground water), rather than discrete organics. For example, fate of atmospheric particulate matter (e.g. PM_{10}) has been the subject of substantial research interest and is a principal regulatory focus of EPA's Office of Air and Radiation. Since intentionally produced nanomaterials are expected to be released to and exist in the environment as particles in most cases, it is wise to investigate applicability of these other models. In fact it can be reasoned that the most useful modeling tools for exposure assessment of nanomaterials are likely to be found not in the area of environmental fate of specific organic compounds (more precisely, prediction of their transport and transformation), rather in fields in which the focus is on media-oriented pollution issues: air pollution, water quality, ground water contamination, etc. A survey of such tools should be made and their potential utility for nanomaterials assessed.

4.4 Environmental Detection and Analysis of Nanomaterials

The challenge in detecting nanomaterials in the environment is compounded not only by the extremely small size of particles of 100 nanometers or less, but also by their unique physical structure and chemical characteristics. The varying of physical and chemical properties can significantly impact the extraction and analytical techniques that can be used for the analysis of a specific nanomaterial. As noted above, the chemical properties of particles at the nanometer size can significantly differ from the chemical properties of larger particles consisting of the same chemical composition. Independent of the challenges brought on by the intrinsic chemical and physical characteristics of nanomaterials, the interactions of nanomaterials with the environment also provide significant analytical challenges. Some nanomaterials are being developed with chemical surface treatments that maintain nanoparticle properties in various environments. These surface treatments can also complicate the detection and analysis of nanomaterials.

In characterizing an environmental sample for intentionally produced nanomaterials, one must be able to distinguish between the nanoparticles of interest and other ultra-fine particles, such as nanoscale particles in the atmosphere generated from coal combustion or forest fires, or nanoscale particles in aquatic environments derived from soil runoff, sewage treatment, or sediment resuspension. Information used to help characterize nanomaterials includes particle size, morphology, surface area and chemical composition. Other

information taken into consideration in identifying the source of nanomaterials includes observed particle concentrations mapped over an area along with transport conditions (e.g. meteorology, currents) at the time of sampling. For nanomaterials with unique chemical composition as found in some quantum dots containing heavy metals, chemical characterization can play an important role in their detection and source identification.

The level of effort (and in turn costs) needed to perform analysis for nanomaterials will depend on which environmental compartment samples are being taken from, as well as the type of desired analytical information. The analysis of nanomaterials from an air matrix requires significantly less (if any) "sample" preparation than samples taken from a soil matrix where it is necessary to employ greater efforts for sample extraction and/or particle isolation. Analytical costs also depend on the degree of information being acquired. Analyzing samples for number concentration—*i.e.* the number and size distribution of nanoparticles per unit volume—requires significantly less effort than broadening such analyses to include characterization of particle types (fullerenes, quantum dots, nanowires, etc.). The level of effort also increases for elemental composition analyses.

Although significant advancements in particle measurement technology have been made over the past two decades in response to National Ambient Air Quality Standards (USEPA, 2004), many of these technologies were designed to effectively function on micron sized particles, particles hundreds to a thousand times larger than nanoparticles. Many of these technologies are not effective in the separation or analysis of particles at the nanometer scale. However, some of these technologies can be applied for the separation and collection of fine particulates that may be composed of an agglomeration of nanoparticles or contain nanoparticles that have attached to larger particulates by way of weak molecular forces. The fine particulates collected using these methodologies would need to undergo test methods capable of analyzing for the nanoparticles of interest.

The information available from the bulk analysis of nanomaterials from environmental samples has limitations when one is trying to identify a specific nanomaterial. As stated previously, nanoscale particles generated by natural and other anthropogenic sources cannot be separated from nanomaterials of interest using sampling methodologies based upon particle size. During analysis, detected signals generated by nanoscale particles that are not of interest can mask or augment the signals of nanomaterials of interest, resulting in inadequate or erroneous data. Where procedures are available for the selective extraction of nanomaterials of interest, one can avoid interfering signals from other nanoscale particles obtained during sampling. In the case of inseparable mixtures of natural and engineered/manufactured nanomaterials, the use of single particle analysis methodologies such as scanning electron microscopy may be necessary to provide definitive analysis for the engineered/manufactured nanomaterials.

Even given all the challenges presented in analyzing for specific nanomaterials of interest, methods and technologies are available that have demonstrated success. Scanning Mobility Particle Sizers can isolate aerosol nanoparticle fractions down to a few nanometers and provide the concentration of that fraction in the sample taken. Commercial samplers are

available that use electrostatic precipitation to collect aerosol nanoparticle fractions for future analysis using technologies like Transmission Electron Microscopy (TEM). TEM can provide both morphological and chemical composition information. Atomic Force Microscopy, a relatively new technology, can also provide morphological and compositional information on single nanoparticles in both liquid and gas media. Appendix C provides more information on these and other methods and technologies available for the detection and analysis of nanomaterials in the environment.

4.5 Human Exposures and Their Measurement and Control

4.5.1 Introduction

As the use of nanomaterials in society increases, it is reasonable to assume that their presence in environmental media will increase proportionately, with consequences for human and environmental exposure. Potential human exposures to nanomaterials, or mixtures of nanomaterials, include workers exposed during the production and use of nanomaterials, general population exposure from releases to the environment during the production or use in the workplace, and direct general population exposure during the use of commercially available products containing nanomaterials. This section identifies potential sources, pathways, and routes of exposure, discusses potential means for mitigating or minimizing worker exposure, describes potential tools and models that may be used to estimate exposures, and identifies potential data sources for these models.

4.5.2 Exposure to Nanomaterials

The exposure paradigm accounts for a series of events beginning from when external mechanisms (e.g., releases or handling of chemicals) make a chemical available for absorption or other mode of entry at the outer body boundary to when the chemical or its metabolite is delivered to the target organ. Between outer body contact with the chemical and delivery to the target organ, a chemical is absorbed and distributed. Depending on the nature of the chemical and the route of exposure, the chemical may be metabolized. For the purposes of this section, we will limit the discussion to the types of resources that are needed (and available) to assess exposure up to the point where it is distributed to the target organ.

4.5.3 Sources and Pathways of Exposure

The potential for intentionally produced nanomaterials to be released into the environment or used in quantities that raise human exposure concerns are numerous given their predicted widespread applications in products. This section discusses some of the potential sources and pathways by which humans may be exposed to nanomaterials.

4.5.3.1 Occupational Exposure

Table 3 presents the potential sources of occupational exposure during the common methods for nanoscale material synthesis: gas phase synthesis, vapor deposition, colloidal, and attrition methods.

Table 3. Potential Sources of Occupational Exposure for Various Synthesis Methods (adapted from Aitken, 2004)

Synthesis Process	Particle Formation	Exposure Source or Worker Activity	Primary Exposure Route
Gas Phase	in air	Direct leakage from reactor, especially if the reactor is operated at positive pressure.	Inhalation
		Product recovery from bag filters in reactors.	Inhalation / Dermal
		Processing and packaging of dry powder.	Inhalation / Dermal
		Equipment cleaning/maintenance (including reactor evacuation and spent filters).	Dermal (and Inhalation during reactor evacuation)
Vapor Deposition	on substrate	Product recovery from reactor / dry contamination of workplace.	Inhalation
		Processing and packaging of dry powder.	Inhalation / Dermal
		Equipment cleaning/maintenance (including reactor evacuation).	Dermal (and Inhalation during reactor evacuation)
Colloidal	liquid suspension	If liquid suspension is processed into a powder, potential exposure during spray drying to create a powder, and the processing and packaging of the dry powder.	Inhalation / Dermal
		Equipment cleaning/maintenance.	Dermal
Attrition	liquid suspension	If liquid suspension is processed into a powder, potential exposure during spray drying to create a powder, and the processing and packaging of the dry powder.	Inhalation / Dermal
		Equipment cleaning/maintenance.	Dermal

Note: Ingestion would be a secondary route of exposure from all sources/activities from deposition of nanomaterials on food or mucous that is subsequently swallowed (primary exposure route inhalation) and from hand-to-mouth contact (primary exposure route dermal).

While there are several potential exposure routes for each manufacturing process, packaging and transfer operations may provide the greatest potential for occupational exposure. "The risk of particle release during production seems to be low, because most

production processes take place in closed systems with appropriate filtering systems. Contamination and exposure to workers is more likely to happen during handling and bagging of the material and also during cleaning operations." (Luther, 2004).

During the formulation of the nanomaterials into products (e.g., coatings and composite materials), releases and exposures may occur during transfer/unloading operations; however, once the nanomaterial is incorporated into the formulation, the nanoparticles are typically linked into the matrix. For some of these products, release and exposures of nano-sized material after incorporation into the product are expected to be low (Luther, 2004). The most notable exceptions would include consumer exposures to nanomaterials incorporated into cosmetics, sunscreens, and other lotions.

4.5.3.2 Release and General Population Exposure

General population exposure may occur from environmental releases from the production and use of nanomaterials and direct use of products containing nanomaterials. During the production of nanomaterials, there are several potential sources for environmental releases including the evacuation of production chambers, filter residues, losses during spray drying, and wastes from equipment cleaning and product handling. No data have been identified quantifying the releases of nanomaterials from industrial processes or of the fate of nanomaterials after release into the environment. However, due to the small size of nanomaterials, they will likely stay airborne for a substantially longer time than other types of particulate. The most likely pathway for general population exposure from releases from industrial processes is direct inhalation of materials released into the air during manufacturing (U.K. Royal Society, 2004). Releases from industrial accidents, natural disasters, or malevolent activity such as a terrorist attack may also lead to exposure of workers or the general public.

Nanoscale materials have potential applications in many consumer products resulting in potential general population exposure. Electronics, medicine, cosmetics, chemistry, and catalysis are potential beneficiaries of nanotechnology. Widespread exposure via direct contact with these products is expected. Table 4 presents several examples of potential sources of general population and consumer exposure associates with the use of such products.

Table 4. Examples of Potential Sources of General Population and / or Consumer Exposure for Several Product Types

Product Type	Release and/ or Exposure Source	Exposed Population	Potential Exposure Route
Sunscreen containing nanoscale material	Product application by consumer to skin	Consumer	Dermal
	Release by consumer (e.g., washing with soap and water) to water supply	General Population	Ingestion
	Disposal of sunscreen container (with residual sunscreen) after use (to landfill or incineration)	General Population	Ingestion or Inhalation

Product Type	Release and/ or Exposure Source	Exposed Population	Potential Exposure Route
Metal catalysts in gasoline for reducing vehicle exhaust*	Release from vehicle exhaust to air (then deposition to surface water)	General Population	Inhalation or Ingestion

Note: Ingestion would be a secondary route of exposure from some sources from deposition of nanomaterials on food or mucous that is subsequently swallowed (primary exposure route inhalation) and from hand-to-mouth contact (primary exposure route dermal).
* Metal catalysts are not currently being used in gasoline in the U.S. Nano-cerium oxide particles are being employed in Europe as on and off-road diesel fuel additives.

4.5.4 Exposure Routes

Much remains to be scientifically demonstrated about the mechanisms by which human exposure to nanomaterials can occur. Intentionally produced nanomaterials share a number of characteristics, such as size and dimensions, with other substances (e.g., ultrafine particles) for which significant information exists on how they access the human body to cause toxicity. The data from these other substances focus primarily on inhalation as the route of exposure. However, as the range of applications of nanomaterials expands, other routes of exposure, such as dermal and oral, may also be found to be significant in humans.

4.5.4.1 Inhalation Exposure

A UK Health and Safety Executive reference suggests that aerosol science would be applicable to airborne nanoparticle behavior. Aerosol behavior is primarily affected by particle size and the forces of inertia, gravity, and diffusion. Other factors affecting nanoparticle airborne concentrations are agglomeration, deposition, and re-suspension. (Health and Safety Executive, 2004) All of these issues, which are discussed in more detail in the reference, are relevant for understanding, predicting, and controlling airborne concentrations of nanomaterials.

One reference study was found to have investigated issues involved with aerosol release of a single-walled carbon nanotube (SWCNT) material. This study noted that while laboratory studies indicate that sufficient agitation can release fine particles into the air, aerosol concentrations of SWCNT generated while handling unrefined material in the field at the work loads and rates observed were very low (Maynard et al, 2004). The study suggests that more research will be needed in this area.

4.5.4.2 Ingestion Exposure

Information on exposure to nanoscale environmental particles via oral exposure is lacking. In addition to traditional ingestion of food, food additives, dust and soil (particularly in the case of children), ingestion of inhaled particles can also occur (such as through the activities of the mucocilliary escalator). However, the quantity ingested is anticipated to be

relatively small in terms of mass, though not much can be concluded at this time about toxicity based on the mass ingested.

4.5.4.3 Dermal Exposure

Dermal exposure to nanomaterials has received much attention, perhaps due to concerns with occupational exposure and the introduction of nanomaterials such as nano-sized titanium dioxide into cosmetic and drug products. One reference study was found to have investigated issues involved with potential dermal exposure to a single-walled carbon nanotube (SWCNT) material. The study suggests that more research will be needed in this area. This study noted that larger-than-respirable airborne particles of SWCNT may contribute to potential dermal exposure along with surface deposits due to material handling. Surface deposits on gloves were estimated to be between 0.2 mg and 6 mg per hand. (Maynard et al, 2004)

Hart (2004) highlights physiological characteristics of the skin that may permit the absorption of nano-sized materials. In particular the review highlights a conceivable route for the absorption of nanoparticles as being through interstices formed by stacking and layering of the calloused cells of the top layer of skin (Hart, 2004). Movement through these interstices will subsequently lead to the skin beneath, from which substances can be absorbed into the blood stream. Nanomaterials also have a greater risk of being absorbed through the skin than macro-sized particles. Reports of toxicity to human epidermal keratinocytes in culture following exposure to carbon nanotubes have been made (Shvedova et al., 2003; Monteiro-Riviere et al, 2005)

4.5.5 Personal Protective Equipment (PPE)

Properly fitted respirators with a high efficiency particulate air (HEPA) filter may be effective at removing nanomaterials. Contrary to intuition, fibrous filters trap smaller and larger particles more effectively than mid-sized particles. Small particles (<100 nm) tend to make random Brownian motions due to their interaction with gas molecules. The increased motion causes the particle to "zig-zag around" and have a greater chance of hitting and sticking to the fiber filter (Luther, 2004). As noted in the fate section above, small particles (diameters <80 nm) are short-lived because they rapidly coagulate to form larger particles. Large particles (>2000 nm) are subject to gravitational settling. Intermediate-sized particles (>80 nm and < 2000 nm) can remain suspended in air for the longest time. (Bidleman, 1988; Preining, 1998; Spurny, 1998; Atkinson, 2000; Royal Society, 2004; Dennenkamp et al., 2002)

Particle filter efficiencies are typically measured at 300 nm because they are the most likely to penetrate the filters and represent a worst case. However, as with all respirators, the greatest factor in determining their effectiveness is not penetration through the filter, but rather the face-seal leakage bypassing the device. Due to size and mobility of nanomaterials in the air, leakage may be more prevalent although no more than expected for a gas (Aitken, 2004). No available data on face-seal leakage has been identified.

PPE may not be as effective at mitigating occupational dermal exposure. PPE is likely to be less effective against dermal exposure to nanomaterials than macro-sized particles from both human causes (e.g., touching face with contaminated fingers) and PPE penetration (Aitken, 2004). However, no studies were identified that discuss the efficiency of PPE at preventing direct penetration of nanomaterials through PPE or from failure due to human causes.

4.5.6 Quantifying Exposure to Nanomaterials

A potential issue when quantifying exposure is that mass dose (most commonly used by the Agency) may not be an appropriate metric to characterize exposure to nanomaterials. Many studies have indicated that toxicity increases with decreased particle size and that particle surface area is a better metric for measuring exposures (Aitken, 2004). This is of particular concern for nanomaterials, which typically have very high surface-area-to-mass ratios. Additionally, there currently are no convenient methods for monitoring the surface area of particles in a worker's breathing zone or ambient air. While there could be a correlation between mass and surface area (i.e., mass / weight of each particle x surface area of each particle), there are typically large variations between particle weight and surface area within a given batch. The average particle weight and average particle surface area of the nanomaterials being assessed would also be required for any assessments based on surface area.

4.5.7 Tools for Exposure Assessment

Several tools exist for performing exposure assessments including monitoring data, exposure models, and the use of analogous data from existing chemicals. The following sections discuss these tools and their potential usefulness in assessing exposure to nanoscale materials.

4.5.7.1 Monitoring Data

Types of monitoring data that can be used in exposure assessment include biological monitoring, personal sampling, and ambient air monitoring. Although monitoring and measurement are discussed earlier in section 4.4, the discussion below includes coverage of some issues directly pertinent to exposure.

Biological Monitoring

Biomonitoring data, when permitted and applied correctly, provides the best information on the dose and levels of a chemical in the human body. Examples of bio-monitoring include the Centers for Disease Control and Prevention (CDC) national monitoring program and smaller surveys such as the EPA's National Human Exposure Assessment Survey (NHEXAS). Biomonitoring can be the best tool for understanding the degree and spread of exposure, information that cannot be captured through monitoring concentrations in ambient media. Biomonitoring, however, is potentially limited in its application to nanotechnology because it is a science that is much dependent on knowledge of

biomarkers, and its benefits are highest when there is background knowledge on what nanomaterials should be monitored. Given the current limited knowledge on nanoscale materials in commerce, their uses, and their fate in the environment and in the human body, it is difficult to identify or prioritize nanomaterials for biomonitoring. Should biomonitoring become more feasible in the future, it presents an opportunity to assess the spatial and temporal distribution of nanomaterials in the population.

Personal Sampling

Personal sampling data provide an estimate of the exposure experienced by an individual. It is limited in that it does not account for changes to the dose administered to the target organ after the biological processes of absorption, distribution, metabolism and excretion. Generally, for cost and feasibility reasons, personal and biomonitoring data are not available for all chemicals on a scale that is meaningful to policymakers. Also, the applicability of personal sampling to nanomaterials is dependent on the development of tools for accurately detecting and measuring such materials in ambient media.

Ambient Monitoring

Ambient media monitoring measures concentrations in larger spaces such as in homes or in the general environment. Ambient data are used as assumed exposure concentrations of chemicals in populations when it is not feasible or practical to conduct personal sampling for individuals in the populations. Typically, these data are used in models in addition to other assumptions regarding exposure parameters, including population activities and demographics such as age.

4.5.7.2 Exposure Modeling

A recent use of ambient monitoring data to estimate the exposure of a population is the cumulative exposure project for air toxics recently completed for hazardous air toxics using the Hazardous Air Pollutant Exposure Model (HAPEM). This model predicts inhalation exposure concentrations of air toxics from all outdoor sources, based on ambient concentrations from modeling or monitor data for specific air toxics at the census tract level. As with personal sampling, the immediate applicability of ambient media monitoring to nanomaterials is unclear.

Other EPA screening level models include the Chemical Screening Tool for Exposures and Environmental Releases (ChemSTEER) and the Exposure and Fate Assessment Screening Tool (E-FAST). ChemSTEER estimates potential dose rates for workers and environmental releases from workplaces. E-FAST uses the workplace releases to estimate potential dose rates for the general population. E-FAST also estimates potential dose rates for consumers in the general public. However, whether ChemSTEER and E-FAST will be useful for assessments of nanoscale materials is not clear because of the significantly different chemical and physical properties of nanomaterials.

Challenges of Using Models with Nanoscale Materials

There are several models that span multiple levels of complexity and are designed to estimate exposure at several points in the exposure paradigm. The effectiveness of these models at predicting human exposure will depend on the parameters and assumptions of each model. For models that are based on assumptions specific to the chemical such as the physical and chemical properties, and interactions in humans and the environment based on these properties, much substance-specific data may be required.

Data Sets for Modeling

Clearly, critical to modeling exposure using ambient data is the availability of such data. There are a number of resources within EPA for this type of data. In some cases such as for pesticides, the exposure can be anticipated based on the quantity of the substance that is proposed to be applied and the anticipated residue on a food item as an example. Sometimes there are data collected under statutory obligations, such as data collected for the Toxics Release Inventory (TRI) under the Environmental Community Right to Know Act (EPCRA). For contaminants in drinking water, the data may be reported to the Safe Drinking Water Information System (SDWIS). Generating data for nanomaterials necessitates the identification of nanomaterials as separate and different from other chemicals of identical nomenclature, and their classification as toxic substances, or in a manner that adds nanomaterials to the list of reportable releases/contaminants. For reporting that is dependent on quantity thresholds (e.g., TRI), there is also the need for understanding whether these thresholds apply to nanoscale materials. For intentionally produced nanomaterials, quantity thresholds might prove to be cumbersome given that their toxicity and reactivity do not seem to be directly proportional to quantity and size. It is also worthwhile to note that reporting systems dependent on a quantity threshold may not be directly applicable to intentionally produced nanomaterials because of the smaller quantities of nanomaterials that are required to achieve the same or better functions as their identical larger-size chemical analogues. Should this prove correct, the Agency will have to adapt in ways that permit the collection of meaningful data on nano-sized materials.

Though not fully representative of population exposure, workplace data have frequently provided the foundation for understanding exposure and toxicity for many chemicals in industrial production. A recent study in the United States, in which ambient air concentrations and glove deposit levels were measured, identified a concern for exposure during handling of nanotubes (Maynard et al., 2004). In the work environment, data on workplace exposure is frequently collected under the purview of Occupational Safety and Health Administration (OSHA)-mandated programs to assess worker exposure and assure compliance with workplace regulations and worker protection. Employers, however, are not required to report these data. In addition, OSHA standards are typically airborne exposure levels that are based on health or economic criteria or both, and typically only defined exceedences of these standards are documented. To understand nanotechnology risks in the workplace, the National Institute of Occupational Safety and Health (NIOSH) is advancing initiatives to investigate amongst other issues, nanoparticle exposure and ways of controlling exposure in the workplace (NIOSH, 2004).

4.6 Human Health Effects of Nanomaterials

4.6.1 Introduction

There is a significant gap in our knowledge of the environmental, health, and ecological implications associated with nanotechnology (Dreher, 2004; Swiss Report 2004; UK Royal Society, 2004; European NanoSafe, 2004; Health and Safety Executive, 2004). This section provides an overview of currently available information on the toxicity of nanoparticles; much of the information is for natural or incidentally formed nano-sized materials, and is presented to aid in the understanding of intentionally produced nanomaterials.

4.6.2 Adequacy of Current Toxicological Database

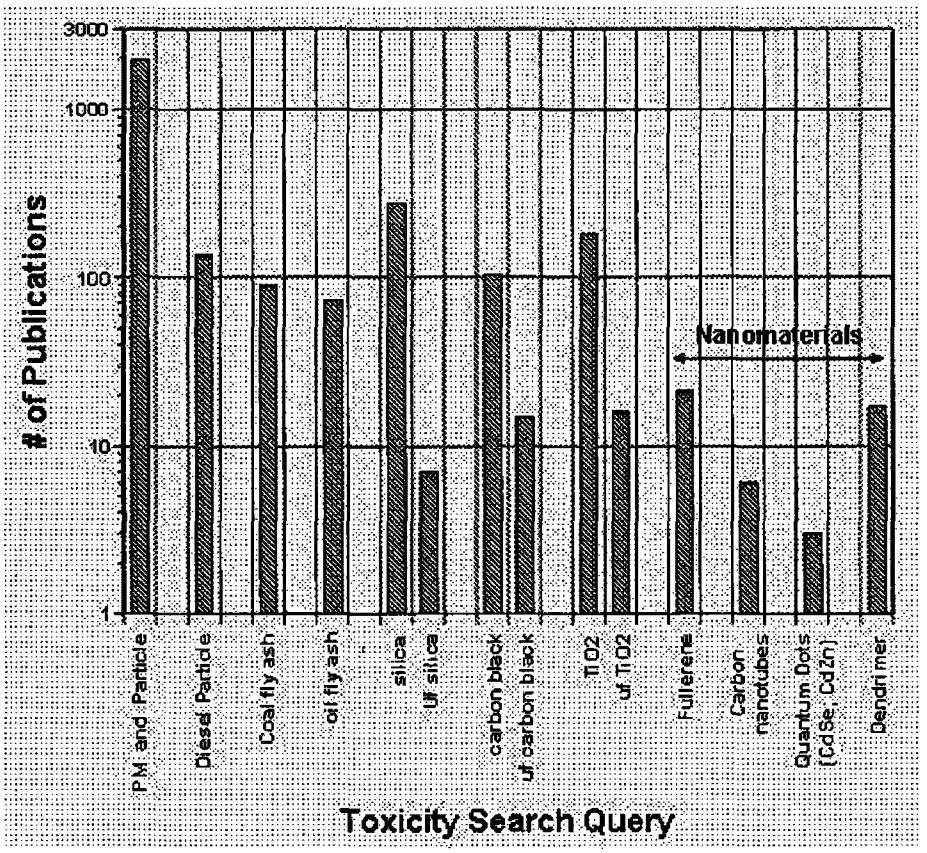
The Agency's databases on the health effects of particulate matter (PM), asbestos, silica, or other toxicological databases of similar or larger sized particles of identical chemical composition (US EPA, 2004; US EPA, 1986; US EPA 1996) should be evaluated for their potential use in conducting toxicological assessments of intentionally produced nanomaterials. The toxicology chapter of the recent *Air Quality Criteria for Particulate Matter* document cites hundreds of references describing the health effects of ambient air particulate matter including ultrafine ambient air ($PM_{0.1}$), silica, carbon, and titanium dioxide particles (US EPA 2004). However, it is important to note that ambient air ultrafine particles are distinct from intentionally produced nanomaterials since they are not purposely engineered and represent a physicochemical and dynamic complex mixture of particles derived from a variety of natural and combustion sources. In addition, only approximately five percent of the references cited in the current *Air Quality Criteria for Particulate Matter* document describe the toxicity of chemically defined ultrafine particles, recently reviewed by Oberdorster et al. (2005).

A search of the literature on particle toxicity studies published up to 2005 confirms the paucity of data describing the toxicity of chemically defined ultrafine particles and to an even greater extent that of intentionally produced nanomaterials (Figure 3). The ability to assess the toxicity of intentionally produced nanomaterials by extrapolating from the current particle toxicological database was examined by Lam et al. (2004) and Warheit et al. (2004). Their findings demonstrate that graphite is not an appropriate safety reference standard for carbon nanotubes, since carbon nanotubes displayed very different mass-based dose-response relationships and lung histopathology when directly compared with graphite.

These initial findings indicate a high degree of uncertainty in the ability of current particle toxicological databases to assess or predict the toxicity of intentionally produced carbon-based nanomaterials displaying novel physicochemical properties. Additional comparative toxicological studies are required to assess the utility of the current particle toxicological databases in assessing the toxicity of other classes or types of intentionally

produced nanomaterials, as well as to relate their health effects to natural or anthropogenic ultrafine particles.

Figure 3. **Particle Toxicology Citations.** Results depict the number of toxicological publications for each type of particle obtained from a PubMed search of the literature up to 2005 using the indicated descriptors. Uf denotes ultrafine size (<0.1nm) particles.



4.6.3 Toxicity and Hazard Identification of Engineered/Manufactured Nanomaterials

Studies assessing the role of particle size on toxicity have generally found that ultrafine or nanosize range (<100nm) particles are more toxic on a mass-based exposure metric when compared to larger particles of identical chemical composition (Oberdorster et al., 1994; Li et al., 1999; Hohr et al., 2002). Studies conducted by Lam et al. (2004) and Warheit et al. (2004) examining the pulmonary toxicity of carbon nanotubes, have provided evidence that intentionally produced nanomaterials can display unique toxicity that cannot be explained by differences in particle size alone. For example, Lam reported single walled

carbon nanotubes displayed greater pulmonary toxicity than carbon black nanoparticles. Similar results have been obtained from comparative *in vitro* cytotoxicity studies (Jia et al., 2005). Muller et al. (2005) reported multi-walled carbon nanotubes to be more proinflammatory and profibrogenic when compared to ultrafine carbon black particles on an equivalent mass dose metric. Shvedova et al. (2005) reported unusual inflammatory and fibrogenic pulmonary responses to specific nanomaterials, suggesting that they may injure the lung by new mechanisms. Exposure of human epidermal keratinocyte cells in culture to single-walled carbon nanotubes was reported to cause dermal toxicity, including oxidative stress and loss of cell viability (Shvedova et al., 2003). Several studies have demonstrated that nanoparticle toxicity is extremely complex and multi-factorial, potentially being regulated by a variety of physicochemical properties such as size and shape, as well as surface properties such as charge, area, and reactivity (Sayes et al., 2004; Cai et al., 1992; Sclafani and Herrmann 1996, Nemmar et al., 2003; Derfus et al., 2005).

Toxicological assessment of intentionally produced nanomaterials will require information on the route (inhalation, oral, dermal) that carries the greatest risk for exposure to these materials, as well as comprehensive physicochemical characterization of them in order to provide information on size, shape, as well as surface properties such as charge, area, and reactivity. Establishment of dose-response relationships linking physicochemical properties of intentionally produced nanomaterials to their toxicities will identify the appropriate exposure metrics that best correlates with adverse health effects.

One of the most striking findings regarding particle health effects is the ability of particles to generate local toxic effects at the site of initial deposition as well as very significant systemic toxic responses (US EPA, 2004). Pulmonary deposition of polystyrene nanoparticles was found to not only elicit pulmonary inflammation but also to induce vascular thrombosis (Nemmar et al., 2003). Pulmonary deposition of carbon black nanoparticles was found to decrease heart rate variability in rats and prolonged cardiac repolarization in young healthy individuals in recent toxicological and clinical studies (Holker et al., 2005; Frampton et al., 2004). Submicron particles have been shown to penetrate the stratum corneum of human skin following dermal application, suggesting a potential route by which the immune system may be affected by dermal exposure to nanoparticles (Tinkle et al., 2003). It is clear that toxicological assessment of intentionally produced nanomaterials will require consideration of both local and systemic toxic responses (e.g., immune, cardiovascular, neurological toxicities) in order to ensure that that we identify the health effects of concern from these materials.

4.6.4 Capabilities of Current Test Methodologies

A challenge facing the toxicological assessment of intentionally produced nanomaterials is the wide diversity and complexity of the types of materials that are available commercially or are under development. In many cases, the same type of nanomaterial can be produced by several different processes, giving rise to a number of versions of the same type of nanomaterial. For example, single-walled carbon nanotubes can be mass produced by four different processes, each of which generates products of different size, shape, composition,

and potentially different toxicological properties (Bekyarova, 2005). It is not known whether the toxicological assessment of one type and source of nanomaterial will be sufficient to assess the toxicity of the same class/type of nanomaterial produced by a different process. Manufactured materials may also be treated with coatings, or other surface modifications, in order to generate mono-dispersed suspensions that extend and enhance their unique properties. The extent to which surface modifications of intentionally produced nanomaterials affect their toxicity is not known. Test methods that determine the toxicity and hazardous physiochemical properties of intentionally produced nanomaterials in an accepted, timely and cost effective manner are needed in order provide health risk assessment information for the diversity of such nanomaterials that are currently available (ILSI 2005).

4.6.5 Dosimetry and Fate of Intentionally Produced Nanomaterials

Much of what is known regarding particle dosimetry and fate has been derived from pulmonary exposure studies using ultrafine metal oxide and carbon black studies (US EPA 2004; Oberdorster,1996; Oberdorster et al., 2005; Oberdorster et al., 2004; Kreyling et al. 2003). Ultrafine carbon black and metal oxide particles display differential deposition patterns within the lung when compared to larger sized particles of identical chemical composition. For example, 1 nm particles are preferentially deposited in the nasopharyngeal region while 5nm particles are deposited throughout the lung and 20 nm particles are preferentially deposited in the distal lung within the alveolar gas exchange region (Oberdorster et al., 2005). Host susceptibility factors such as pre-existing lung disease significantly affect the amount and location of particles deposited within the lung. For example, individuals with chronic obstructive pulmonary disease have 4-fold higher levels of particles deposited in their upper bronchioles when compared to health individuals exposed to the same concentration of particles (US EPA, 2004). Also, pulmonary deposited ultrafine particles can evade the normal pulmonary clearance mechanisms and translocate by a variety of pathways to distal organs (Oberdorster et al., 2005; Oberdorster et al., 2004; Kreyling et al. 2003; Renwick et al., 2001).

The deposition and fate of the class of nanomaterials called dendrimers have been examined to some degree due to their potential drug delivery applications (Malik et al 2000; Nigavekar et al. 2004.). Both studies demonstrated the critical role which surface charge and chemistry play in regulating the deposition and clearance of dendrimers in rodents.

A significant amount of intradermally injected nanoscale quantum dots were found to disperse into the surrounding viable subcutis and to draining lymph nodes via subcutaneous lymphatics (Roberts et al., 2005). Other studies (Tinkle et al., 2003) have shown enhanced penetration of submicron fluorospheres into the stratum corneum of human skin following dermal application and mechanical stimulation. Drug delivery studies using model wax nanoparticles have provided evidence that nanoparticle surface charge alters blood-brain barrier integrity and permeability (Lockman et al., 2004). Toxicological studies have demonstrated the direct cellular uptake of multi-walled carbon nanotubes by human epidermal keratinocytes (Monteiro-Riviere et al., 2005).

Very little is known regarding the deposition and fate (metabolism, dissolution, clearance, translocation) of other types or classes of intentionally produced nanomaterials following either inhalation, ingestion, or dermal exposures. Knowledge of tissue and cell specific deposition, fate and persistence of engineered or manufactured nanomaterials, as well as factors such as host susceptibility and nanoparticle physicochemical properties regulating their deposition and fate, is needed to determine exposure-dose-response relationships associated with various routes of exposures. Information on the fate of nanomaterials is needed to assess their persistence in biological systems, a property that regulates accumulation of these particles to levels that may produce adverse health effects following long-term exposures to low concentrations of these particles.

At a 2004 nanotoxicology workshop at the University of Florida, concerns were expressed about the ability of existing technologies to detect and quantify intentionally produced nanomaterials in biological systems. New detection methods or approaches, such as the use of labeled or tagged nanomaterials, may have to be developed in order to analyze and quantify nanomaterials within biological systems.

4.6.6 Susceptible Subpopulations

Particle toxicology research has shown that not all individuals in the population respond to particle exposures in the same way or to the same degree (US EPA, 2004). Host susceptibility factors that influence the toxicity, deposition, fate and persistence of intentionally produced nanomaterials are unknown. This information is critically needed to understand the exposure-dose-response relationships of intentionally produced nanomaterials in order to recommend safe exposure levels that protect the most susceptible subpopulations.

4.6.7 Health Effects of Environmental Technologies That Use Nanomaterials

The potential for adverse health effects may arise from direct exposure to intentionally-produced nanomaterials and/or byproducts associated with their applications. Nanotechnology is being employed to develop pollution control and remediation applications. Reactive zero-valent iron nanoparticles are being used to treat soil and aquifers contaminated with halogenated hydrocarbons, such as TCE (trichloroethylene) or DCE (dichloroethylene), and heavy metals (www.bioxtech.com). However, the production of biphenyl and benzene associated with nanoscale zero-valent iron degradation of more complex polychlorinated hydrocarbons has been recently reported (Elliott et al., 2005).

Photocatalytic nano-titanium dioxide (nano-TiO_2) particles are being incorporated into building materials such as cement and surface coatings in order to reduce ambient air nitrogen oxides (NOx) levels. The European Union Photocatalytic Innovative Coverings Applications for Depollution Assessment has evaluated the effectiveness of photocatalytic nano-TiO_2 to decrease ambient air NOx levels and has concluded that this technology represents a viable approach to attain 21 ppb ambient air NOx levels in Europe by 2010 (www.picada-project.com). However, the extent to which nano-TiO_2 reacts with other ambient air co-pollutants and alters their corresponding health effects is not known.

Nano-cerium oxide particles are being employed in the United Kingdom as on- and off-road diesel fuel additives to decrease emissions and some manufacturers are claiming fuel economy benefits. However, one study employing a cerium additive with a particulate trap has shown cerium to significantly alter the physicochemistry of diesel exhaust emissions resulting in increased levels of air toxic chemicals such as benzene, 1,3-butadiene, and acetaldehyde. Modeling estimates have predicted that use of a cerium additive in diesel fuel would significantly increase the ambient air levels of cerium (Health Effects Institute, 2001). The health impacts associated with these alterations in diesel exhaust have not been examined and are currently not known.

Environmental technologies using nanotechnology lead to direct interactions of reactive, intentionally produced nanomaterials with chemically complex mixtures present within a variety environmental media such as soil, water, ambient air, and combustion emissions. The health effects associated with these interactions are unknown. Research will be needed to assess the health and environmental risks associated with environmental applications of nanotechnology.

4.7 Ecological Effects of Nanomaterials

4.7.1 Introduction

Nanomaterials may affect aquatic or terrestrial organisms differently than larger particles of the same materials. As noted above, assessing nanomaterial toxicity is extremely complex and multi-factorial, and is potentially influenced by a variety of physicochemical properties such as size and shape, and surface properties such as charge, area, and reactivity. Furthermore, use of nanomaterials in the environment may result in novel byproducts or degradates that also may pose risks. The following section summarizes available information and considerations regarding the potential ecological effects of nanomaterials; Appendix C contains additional detailed analyses of existing information.

4.7.2 Uptake and Accumulation of Nanomaterials

Based on analogy to physical-chemical properties of larger molecules of the same material, it may be possible to estimate the tendency of nanomaterials to cross cell membranes and bioaccumulate. However, current studies have been limited to a very small number of nanomaterials and target organisms. Similarly, existing knowledge could lead us to predict a mitigating effect of natural materials in the environment (e.g., organic carbon); however, this last concept would need to be tested for a wide range of intentionally produced nanomaterials.

Molecular weight (MW) and effective cross-sectional diameter are important factors in uptake of materials across the gill membranes of aquatic organisms or the GI tract of both aquatic and terrestrial organisms. Uptake via passive diffusion of neutral particles is low, but still measurable within a range of small molecular weights (600-900) (Zitko, 1981; Opperhuizen et al., 1985; Niimi and Oliver, 1988; McKim et al., 1985). The molecular weight of some nanomaterials falls within this range. For example, the MW of n-C_{60}

fullerene is about 720, although the MW of a C_{84} carbon nanotube is greater than 1000. Passive diffusion through gill membranes or the GI tract also depends on the cross sectional diameter of particles (Opperhuizen et al., 1985; Zitko, 1981; OPPT data). Existing evidence indicates that the absolute limit for passive diffusion through gills is in the nanometer range (between 0. 95 and 1.5 nm), which suggests that passive diffusion may be possible for nanomaterials within this range, but not for nanomaterials with larger effective cross-sectional diameters.

Charge is also an important characteristic to consider for nanomaterial uptake and distribution. For example, as noted above, drug delivery studies using model wax nanoparticles have provided evidence that nanoparticle surface charge alters blood-brain barrier integrity and permeability in mammals (Lockman et al., 2004).

Other chemical and biotic characteristics may need to be considered when predicting accumulation and toxicity of nanoparticles in aquatic systems. For example, the Office of Water uses several specific characteristics, including water chemistry (e.g., dissolved organic carbon and particulate organic carbon) and biotic (lipid content and trophic level) characteristics, when calculating national bioaccumulation factors for highly hydrophobic neutral organic compounds (U.S.EPA, 2003).

Because the properties of some nanomaterials are likely to result in uptake and distribution phenomena different from many conventional chemicals, it is critically important to conduct studies that will provide a solid understanding of these phenomena with a range of nanomaterials and species. Studies related to human health effects assessment will provide an important foundation for understanding mammalian exposures and some cross-species processes (e.g., ability to penetrate endothelium and move out of the gut and into the organism). However, other physiology differs among animal classes, most notably respiratory physiology (e.g., gills in aquatic organisms and air sacs and unidirectional air flow in birds), while plants and invertebrates (terrestrial and aquatic) have even greater physiological differences. Because of their size, the uptake and distribution of nanomaterials may follow pathways not normally considered in the context of conventional materials (e.g., pinocytosis, facilitated uptake, and phagocytosis).

4.7.3 Aquatic Ecosystem Effects

To date, very few ecotoxicity studies with nanomaterials have been conducted. Studies have been conducted on a limited number of nanoscale materials, and in a limited number of aquatic species. There have been no chronic or full life-cycle studies reported.

For example, Oberdorster (2004b) studied effects of fullerenes in the brain of juvenile largemouth bass and concluded that C_{60} fullerenes induce oxidative stress, based on their observations that (a) there was a trend for reduced lipid peroxidation in the liver and gill, (b) significant lipid peroxidation was found in brains, and (c) the metabolic enzyme glutathione-S-transferease (GST) was marginally depleted in the gill. However, no concentration-response relationship was evident as effects observed at a low dose were not observed at the

single higher dose and no changes in fish behavior were observed; effects could have been due to random variation in individual fish. Oberdorster et al. (2005) and Oberdorster (2004) tested un-coated, water soluble, colloidal fullerenes (nC_{60}) and estimated a daphnid 48-h LC_{50} at 800 ppb, using standard EPA protocols. Lovern et al. (in press) tested titanium dioxide (TiO_2) and uncoated C_{60} fullerenes in a standard forty-eight hour acute toxicity test. These authors found that both nanomaterials were somewhat toxic to the *Daphnia magna* with toxicities in the low ppm range and fullerenes exhibiting a slightly greater toxicity than TiO_2. However, the way the particles were prepared impacted toxicity, with filtering of the water to remove larger particles enhancing apparent toxicity. Large particles of titanium dioxide (the kind found in sunblock, paint, and toothpaste) did not cause toxicity. Additionally, in behavior tests with filtered fullerenes, *Daphnia* exhibited behavioral responses, with juveniles showing an apparent inability to swim down from the surface and adults demonstrating sporadic swimming and disorientation. Further research on ecological species is clearly needed.

Toxicity studies and structure-activity relationship predictions for carbon black and suspended clay particles suggest that some suspended natural nano-sized particles in the aquatic environment will have low toxicity to aquatic organisms, with effects thresholds ranging from tens to thousands of parts per million (see Appendix C). Limited preliminary work with engineered/manufactured nanomaterials seems to substantiate this conclusion. For example, Cheng and Cheng (2005) reported that aggregates of single-walled carbon nanotubes (SWNT) added to zebrafish embryos reduced hatching rate at 72 hrs, but by 77 hrs post fertilization all embryos in the treated group had hatched. However, when evaluating a limited data set of nanoscale materials (i.e., carbon black and clay only), available information on differences in toxicity observed between natural and engineered or manufactured nanomaterials should be considered. For example, as noted previously, SWNTs displayed greater pulmonary toxicity than carbon black nanoparticles (Lam et al 2004). Shvedova et al. (2005) reported unusual inflammatory responses to specific nanomaterials in mammals, suggesting that some nanomaterials may injure organs by novel mechanisms.

Recent reports suggest that nanomaterials may be effective bactericidal agents against both gram positive and negative bacteria in growth media. The ability of these "nano-C_{60}" aggregates to inhibit the growth and respiration of microbes needs to be demonstrated under more realistic conditions. For example, effects on microbes in sewage sludge effluent and natural communities of bacteria in natural waters should be examined.

4.7.4 Terrestrial Ecosystem Effects

To date, very few studies have successfully been conducted to assess potential toxicity of nanomaterials to ecological terrestrial test species (plants, wildlife, soil invertebrates, or soil microorganisms).

For terrestrial mammals, toxicity test data on rats and mice obtained for human health risk assessments should be considered. For example, studies described above indicate that ultrafine or nanosize range particles are more toxic on a mass-based exposure metric when compared to larger particles of identical chemical composition in studies of lung toxicity

(Oberdorster et al. 1994; Li et al. 1999; Hohr et al. 2002), and some nanomaterials can display unique toxicity that cannot be explained by differences in particle size alone (Lam et al. 2004; Warheit et al. 2004). Toxicity to mammalian epidermal cell in culture has also been reported (Shvedova et al. 2003).

The same properties of nanomaterials that regulate uptake in aquatic organisms may limit uptake of nanoparticles by plant roots (i.e., reducing passive transport at lower MW or size) or transport through plant leaves and stomata. Additionally, because many nanomaterials are designed to have strongly reactive surfaces, it is quite possible that significant pathways for toxicity may exist without uptake (e.g., disruption of respiratory epithelium structure/function or other surface cell structure/function). In a recent study of nanomaterial effects on plants, Yang and Watts (2005), reported that alumina nanoparticles (13 nm) slowed root growth in a soil-free exposure medium. Species tested included commercially important species used in ecological risk assessments of pesticides: corn (Zea mays), cucumber (Cucumis sativus), soybean (Glycine max), cabbage (Brassica oleracea), and carrot (Daucus corota). The authors reported that coating the alumina nanoparticles with an organic compound (phenanthrene), reduced the nanomaterial's effect of root elongation inhibition. Larger alumina particles (200-300 nm) did not slow root growth, indicating that the alumina itself was not causing the toxicity. The authors hypothesized that the surface charge on the alumina nanoparticles may have played a role in the decreased plant root growth. These studies were conducted in Petri dishes without soil, so environmental relevance is uncertain.

Fundamentally, our ability to extrapolate toxicity information from conventional substances to nanomaterials will require knowledge about uptake, distribution, and excretion rates as well as modes of toxic action, and may be based on existing structure-activity relationships (SARs), such as SARs for polycationic polymers, published in Boethling and Nabholz (1997). Synthesis of radio-labeled nanomaterials (e.g., carbon-14 labeled nanotubes) may be a useful tool, along with advanced microscopy (e.g., comparable to techniques used for asbestos quantification) for developing information on sites of toxic action and metabolic distribution.

4.7.5 Ecological Testing Requirements

Because nanomaterials are often engineered to have very specific properties, it seems reasonable to presume that they may end up having unusual toxicological effects. Experiences with conventional chemicals suggest that in these cases, chronic effects of exposure are often a more important component of understanding ecological risk than acute lethality (e.g., compare effects of pesticides with general narcotic chemicals). As such, initial studies should include longer-term exposures measuring multiple, sub-lethal endpoints. They should be conducted (using appropriate forms and routes of exposure) in a manner that will elucidate key taxonomic groups (i.e., highly sensitive organisms that may become indicator species) and endpoints that may be of greatest importance to determining ecological risk. These studies must also include careful tracking of uptake and disposition to understand toxicity as a function of dose at the site of action.

A number of existing test procedures that assess long-term survival, growth, development, and reproductive endpoints (both whole organism and physiological or biochemical) for invertebrates, fish, amphibians, birds, and plants (including algae, rooted macrophytes, and terrestrial plants) should be adaptable to nanomaterials. These tests are able to examine a wide range of species and endpoints to help pinpoint the types of effects most significant to the evaluation of nanomaterials, and have a strong foundation relative to projecting likely ecological effects. Both pilot toxicity testing protocols and definitive protocols should be evaluated with respect to their applicability to nanomaterials. In addition, field studies or mesocosm studies might be conducted in systems known to be exposed to nanomaterials to screen for food chain bioaccumulation and unanticipated effects or endpoints.

5.0 EPA's Research Needs for Nanomaterials

5.1 Introduction

Research is needed to inform EPA's actions related to the benefits and impacts of nanomaterials. However, there are significant challenges to addressing research needs for nanotechnology and the environment. The sheer variety of nanomaterials and nanoproducts adds to the difficulty of developing research needs. Since we don't have a complete understanding of how nanoparticles behave, each stage in their lifecycle, from extraction to manufacturing to use and then to ultimate disposal, will present separate research challenges. Nanomaterials also present a particular research challenge over their macro forms in that we lack a complete understanding of nanoparticles' scientific properties. Research should be designed from the beginning to identify beneficial applications and to inform risk assessment, pollution prevention, and potential risk management methods. Such research will come from many sources, including academia, industry, EPA, and other agencies and organizations.

An overarching, guiding principle for all testing, both human health and ecological, is to determine which nanomaterials are most used and/or have potential to be released to, and interact with, the environment. These nanomaterials should be selected from each of the broader classes of nanomaterials (carbon-based, metal-based, dendrimers, or composites) to serve as representative particles for testing/evaluation purposes.

5.2 Research Needs for Environmental Applications

5.2.1 Green Manufacturing Research Needs

Nanotechnology offers the possibility of changing manufacturing processes in at least two ways: (1) by using less materials and (2) using nanomaterials for catalysts and separations to increase efficiency in current manufacturing processes. Nanomaterial and nanoproduct manufacturing offers the opportunity to employ the principles of green chemistry and engineering to prevent pollution from currently known harmful chemicals. Research enabling this bottom-up manufacturing of chemicals and materials is one of the most important areas in pollution prevention in the long term. Research questions regarding green manufacturing include:

- How can nanotechnology be used to reduce waste products during manufacturing?
- How can nanomaterials be made using benign starting materials?
- How can nanotechnology be used to reduce the resources needed for manufacturing (both materials and energy)?
- What is the life cycle of various types of nanomaterials and nanoproducts under a variety of manufacturing and environmental conditions?

5.2.2 Green Energy Research Needs

Developing green energy approaches will involve research in many areas, including solar energy, hydrogen, power transmission, diesel, pollution control devices, and lighting. These areas have either direct or indirect impacts on environmental protection. In solar energy, nanomaterials may make solar cells more efficient and more affordable. In addition, nanocatalysts may efficiently create hydrogen from water using solar energy. Research questions for green energy include:

- What research is needed for incentives to encourage nanotechnology to enable green energy?

- How can nanotechnology assist "green" energy production, distribution, and use?

5.2.3 Environmental Remediation/Treatment Research Needs

The research questions in this area revolve around the effectiveness and risk parameters of nanomaterials to be used in site remediation. Materials such as zero-valent iron are expected to be useful in replacing current pump-and-treat or off site treatment methods. In addition, other nanoremediation approaches can involve the methods of coating biological particles, determining the effect on the particles (enzyme or bacteriophage) following coating, and application technologies. This is an area that has not been examined in any great detail. Therefore, research is needed to develop technologies using nanocoated biological particles for environmental decontamination or prophylactic treatment to prevent contamination. The products of this research would be technologies utilizing innocuous biological entities treated with nanoparticles to decontaminate or prevent bacterial growth. In an age of antibiotic resistance and aversion to chemical decontamination, enzyme and bacteriophage technologies offer an attractive option. Remediation and treatment research questions include:

- Which nanomaterials are most effective for remediation and treatment?

- What are the fate and effects of nanomaterials used in remediation applications?

- How can we improve methods for detecting and monitoring nanomaterials used in remediation and treatment?

- To what extent are these materials and their byproducts persistent, bioaccumulative, and toxic and what organisms are affected?

- If toxic byproducts are produced, how can they be reduced?

- What is needed to enhance the efficiency and cost-effectiveness of remediation and treatment technology?

5.3 Chemical Identification and Characterization

Research that can be replicated requires agreement on the identification and characterization of nanomaterials. In addition, understanding the physical and chemical properties in particular is necessary in the evaluation of hazard (both human and ecological) and exposure (all routes). It is not clear whether existing physical-chemical property test methods are adequate for sufficiently characterizing various nanomaterials. Alternative methods may be needed. Research questions include:

- What are the unique chemical and physical characteristics of nanomaterials? How do these characteristics vary among different types of particles (e.g., nanotubes, fullerenes)?
- How do these properties affect the material's reactivity, toxicity and other attributes?
- Should research be tailored to each type of particle and how they are used?
- Are there adequate measurement methods/technology available to distinguish between intentionally produced nanomaterials and ultrafine particles or naturally occurring nano-sized particles, and among different types of nanomaterials?
- Are current test methods adequate to evaluate hazard and exposure?
- Do nanomaterial characteristics vary from their pure form in the laboratory to their occurrence in the environment as components of products?
- What intentionally produced nanomaterials are now on the market and what new types of materials can be expected to be developed?
- How will manufacturing processes alter the characteristics of nanomaterials?

5.4 Environmental Fate Research Needs

EPA needs to ascertain the fate of nanomaterials in the environment to understand the availability of these materials for humans and other life forms. Research on the transport and potential transformation of nanomaterials in soil, subsurface, surface waters, wastewater, drinking water, and the atmosphere is essential as nanomaterials are used increasingly in products. To support these investigations, existing methods should be evaluated and if necessary, they should be modified or new methods should be developed. Research is needed to address the following high-priority questions.

5.4.1 Transport Research Questions

- What are the physicochemical factors that influence the transport and deposition of intentionally produced nanomaterials in the environment? How do nanomaterials

move through these media? Do novel materials, such as fullerenes without corresponding bulk materials, differ in their mobility from the bulk materials? Can existing information on soil colloidal fate and transport and atmospheric ultrafine particulate fate and transport inform our thinking?

- How are nanomaterials transported in the atmosphere? What nanomaterial properties and atmospheric conditions control the atmospheric fate of nanomaterials?

- To what extent are nanomaterials mobile in soils and in groundwater? What is the potential for these materials, if released to soil or landfills, to migrate to groundwater and within aquifers, with potential exposure to general populations via groundwater ingestion?

- What is the potential for these materials to be transported bound to particulate matter, sediments, or sludge in surface waters?

- How do the aggregation, sorption and agglomeration of nanoparticles affect their transport?

- How do nanomaterials bioaccumulate? Do their unique characteristics affect their bioavailability? Do nanomaterials bioaccumulate to a greater or lesser extent than macro-scale or bulk materials?

5.4.2 Transformation Research Questions

- How do nanoparticles react differently in the environment than their bulk counterparts?

- What are the physicochemical factors that affect the persistence of intentionally produced nanomaterials in the environment?

- Do particular nanomaterials persist in the environment, or undergo degradation via biotic or abiotic processes? If they degrade, what are the byproducts and their characteristics? Is the nanomaterial likely to be in the environment, and thus be available for bioaccumulation/biomagnification?

- How are the physicochemical and biological properties of nanomaterials altered in complex environmental media such as air, water, and soil? How do redox processes influence environmental transformation of nanomaterials? To what extent are nanomaterials photoreactive in the atmosphere, in water, or on environmental surfaces?

- How do the aggregation, sorption and agglomeration of nanoparticles affect transformation?

5.4.3. Chemical Interaction Research Questions

- How do nano-sized adsorbants and chemicals sorbed to them influence their respective environmental interactions? Can these materials alter the mobility of other substances in the environment? Can these materials alter the reactivity of other substances in the environment?

5.4.4. Treatment Research Questions

- What is the potential for these materials to bind to soil, subsurface materials, sediment or sludge in wastewater treatment plants?

- Are these materials effectively removed from wastewater using conventional wastewater treatment methods and, if so, by what mechanism?

- Do these materials have an impact on the treatability of other substances in wastewater, or on treatment plant performance?

- Are these materials effectively removed in drinking water treatment and, if so, by what mechanism?

- Do these materials have an impact on the removal of other substances during drinking water treatment, or on drinking water treatment plant performance?

- When nanomaterials are placed in groundwater treatment, how do they behave over time? Do they move in groundwater? What is their potential for migrating to drinking water wells?

- How effective are existing treatment methods such as carbon adsorption, filtration, and coagulation and settling for treating nanomaterials?

5.4.5. Assessment Approaches and Tools Questions

- Can existing information on soil colloidal fate and transport, as well as atmospheric ultrafine particulate fate and transport, inform our thinking? Do the current databases of ultrafines/fibers shed light on any of these questions?

- Do the different nanomaterials act similarly enough to be able to create classes of like compounds? Can these classes be used to predict structure-activity relationships for future materials?

- Should current fate and transport models need to be modified to incorporate the unique characteristics of nanomaterials?

5.5 Environmental Detection and Analysis Research Needs

A variety of methods currently exist to detect nanoparticles, including sampling methods, methods used to measure nanoparticle mass/mass concentrations, surface area, particle count concentration, size, physical structure (morphology), and chemical composition. Research is needed to address the following high-priority questions:

5.5.1 Existing Methods and Technologies Research Questions

- Are existing methods and technologies capable of detecting, characterizing, and quantifying intentionally produced nanomaterials by measuring particle number, size, shape, surface properties (e.g., reactivity, charge, and area), etc.? Can they distinguish between intentionally produced nanomaterials of interest and other ultrafine particles? Can they distinguish between individual particles of interest and particles that may have agglomerated or attached to larger particles?

- Are standard procedures available for both sample preparation and analysis?

- Are quality assurance and control reference materials and procedures available?

5.5.2. New Methods and Technologies Research Needs

- What low-cost, portable, and easy-to-use technologies can detect, characterize, and quantify nanomaterials of interest in environmental media and for personal exposure monitoring.

5.6 Releases and Human Exposures

Potential sources of human exposure to nanomaterials include workers exposed during the production and use of nanomaterials, general population exposure from releases to the environment during the production or use in the workplace, and direct general population exposure during the use of commercially available products containing nanoscale materials. Releases from industrial accidents, natural disasters, or malevolent activity such as a terrorist attack should also be considered. Research is needed to identify potential sources, pathways, and routes of exposure, potential tools and models that may be used to estimate exposures, and potential data sources for these models. Research is needed to address the following high-priority questions.

5.6.1. Risk and Exposure Assessment Research Questions

- Is the current exposure assessment process adequate for assessing exposures to nanomaterials? Is mass dose an effective metric for measuring exposure? What alternative metric (e.g., particle count, surface area) should be used to measure exposure? Are sensitive populations' (e.g., endangered species, children, asthmatics, etc.) exposure patterns included?

- How do physical and chemical properties of nanomaterials affect releases and exposures?

5.6.2. Release and Exposure Quantification Research Questions

- What information is available about unique release and exposure patterns of nanomaterials? What additional information is needed?

- What tools/resources currently exist for assessing releases and exposures within EPA (chemical release information/ monitoring systems (e.g., TRI), measurement tools, models, etc)? Are these tools/resources adequate to measure, estimate, and assess releases and exposures to nanomaterials? Is degradation of nanomaterials accounted for?

- What research is needed to develop sensors that can detect nanomaterials, including personal exposure monitoring?

5.6.3. Release and Exposure Reduction and Mitigation Research Questions

- What tools/resources exist for limiting release and/or exposure during manufacture, use or following release via waste streams? Are these tools/resources adequate for nanomaterials?

- Are current respirators, filters, gloves, and other PPE capable of reducing or eliminating exposure from nanomaterials?

- Are current engineering controls and pollution prevention devices capable of minimizing releases and exposures to nanomaterials?

- Are technologies and procedures for controlling spills during manufacture and use adequate for nanomaterials? Can current conventional technologies (i.e. for non-nanomaterials) be adapted to control nanomaterial spills?

- Do existing methods using vacuum cleaners with HEPA filters work to clean up a spill of solid nanomaterials? If not, would a wet vacuum system work?

- What PPEs would be suitable for use by operators during spill mitigation?

5.7 Human Health Effects Assessment Research Needs

Adverse health effects of intentionally produced nanomaterials may result from either direct exposure resulting from inadvertent release of these novel materials or unintentional byproducts produced by their intentional release into the environment. Very little data exist on the toxicity, hazardous properties, deposition and fate, as well as susceptibility associated

with exposure to intentionally produced nanomaterials, their application byproducts, or production waste streams. Finally, it is uncertain whether standard test methods will be capable of identifying toxicities associated with the unique physical chemical properties of intentionally produced nanomaterials.

It will be important for nanomaterial health effects risk assessment research to also establish whether current particle and fiber toxicological databases have the ability to predict or assess the toxicity of intentionally produced nanomaterials displaying unique physicochemical properties. The limited studies conducted to date indicate that the toxicological assessment of specific intentionally produced nanomaterials will be difficult to extrapolate from existing databases. The toxic effects of nanoscale materials have not been fully characterized, but it is generally believed that nanoparticles can have toxicological properties that differ from their bulk material. A number of studies have demonstrated that nanoparticle toxicity is complex and multifactorial, potentially being regulated by a variety of physiochemical properties such as size, chemical composition, and shape, as well as surface properties such as charge, area and reactivity. As the size of particles decreases, a resulting larger surface-to-volume ratio per unit weight for nanoparticles correlates with increased toxicity as compared with bulk material toxicity. Also as a result of their smaller size, nanoparticles may pass into cells directly through cell membranes or penetrate the skin and distribute throughout the body once translocated to the circulatory system. While the effects of shape on toxicity of nanoparticles appears unclear, the results of a recent *in vitro* cytotoxicity study appear to suggest that single-wall carbon nanotubes are more toxic than multi-wall carbon nanotubes. Therefore, with respect to nanoparticles, there is concern for systemic effects (e.g., target organs, cardiovascular, and neurological toxicities) in addition to portal-of-entry (e.g. lung, skin, intestine) toxicity.

Initially, it will be important to be specific with respect to the nature of the surface material/coating, the application for which the material is used, the likely route of exposure, the presence of other exposures which may affect toxicity (e.g., UV radiation) and not rely on information derived from a study conducted under one set of conditions to predict outcomes that may occur under another set of conditions. However, past experience with conventional chemicals suggests that toxicology research on nanomaterials should be designed from the beginning with an eye towards developing hypothesis-based predictive testing.

Research is also needed to examine health impacts of highly dispersive nanotechnologies that are employed for site remediation, monitoring, and pollution control strategies. It will be necessary to determine both the impacts these types of nanotechnologies have on regulated pollutants in air, soil, or water, as well as their corresponding potential health effects. Research should be conducted in the following areas:

A. Determining the adequacy of current testing schemes, hazard protocols, and dose metrics.
B. Identifying the properties of nanomaterials that are most predictive of toxicity to receptors and their sensitive subpopulations.

C. Identifying those nanomaterials with high commercial potential with dispersive applications, and their most probable exposure pathways.

These areas lead to the following research questions:

- What are the health effects (local and systemic; acute and chronic) from either direct exposure to nanomaterials, or to their byproducts, associated with dispersive nanotechnology applications? (Addresses area C, above)

- Are there specific toxicological endpoints that are of higher concern for nanomaterials, such as neurological, cardiovascular, respiratory, or immunological effects, etc.? (Addresses area C, above)

- Are current testing methods (organisms, exposure regimes, media, analytical methods, testing schemes) applicable to testing nanomaterials in standardized agency toxicity tests (http://www.epa.gov/opptsfrs/OPPTS_Harmonized/)? (Addresses area A, above)

- Are current test methods, for example OECD and EPA harmonized test guidelines, capable of determining the toxicity of the wide variety of intentionally produced nanomaterials and byproducts associated with their production and applications? (Addresses area A, above)

- Are current analytical methods capable of analyzing and quantifying intentionally produced nanomaterials to generate dose-response relationships? (Addresses area A, above)

- What physicochemical properties regulate nanomaterial adsorption, distribution, metabolism, and excretion (ADME)? (Addresses area A, above)

- What physicochemical properties and dose metrics best correlate with the toxicity (local and systemic; acute and chronic) of intentionally produced nanomaterials following various routes of exposure? (Addresses area A, above)

- Are there subpopulations that may be at increased risk of adverse health effects associated with exposure to intentionally produced nanomaterials? (Addresses area B, above).

- What are the best approaches to build effective predictive models of toxicity (SAR, PBPK, "omics", etc.)? (Addresses areas A and B, above)

5.8 Ecological Effects Research Needs

Ecosystems may be affected through inadvertent or intentional releases of intentionally produced nanomaterials. Drug and gene delivery systems, for example, are not likely to be used directly in the environment but may contaminate soils or surface waters

through waste water treatment plants (from human use) or more directly as runoff from concentrated animal feeding operations (CAFOs) or from aquaculture. Direct applications may include nanoscale monitoring systems, control or clean-up systems for conventional pollutants, and desalination or other chemical modifications of soil or water. Nanoscale particles may affect aquatic or terrestrial organisms differently than larger particles due to their extreme hydrophobicity, their ability to cross and/or damage cell membranes, and differences in electrostatic charge. Furthermore, use of nanomaterials in the environment may result in novel byproducts or degradates that also may pose significant risks.

Important considerations for prioritizing and defining the scope of the research needs include determining which nanomaterials are most used (volume), are likely to be used in the near future (imminence of use), and/or have most potential to be released into the environment (dispersive applications). Another consideration is the need to test representative materials from each of the four classes of nanomaterials (carbon-based, metal-based, dendrimers, composites).

The same general research areas used for prioritizing human health effects research needs were used to prioritize ecological research needs. Using these areas as a guide, the following research questions were identified:

- Are current testing schemes and methods (organisms, endpoints, exposure regimes, media, analytical methods) applicable to testing nanomaterials in standardized toxicity tests? Both pilot testing protocols and definitive protocols should be evaluated with respect to their applicability to nanomaterials.

- What is the distribution of nanomaterials in ecosystems? Research on model ecosystems studies (micro, mesocosms) is needed to assist in determining the distribution of nanomaterials in ecosystems and potentially affected compartments and species.

- What are the effects (local and systemic; acute and chronic) resulting from either direct exposure to nanomaterials, or to their byproducts, associated with dispersive nanotechnology applications and other uses?

- What are the absorption, distribution, metabolism, elimination (ADME) parameters for various nanomaterials for ecological receptors? This topic addresses the uptake, transport, bioaccumulation relevant to a range of species (fish, inverts, birds, amphibians, reptiles, plants, microbes).

- What research is needed to examine the interaction of nanomaterials with microbes in sewage treatment plants, in sewage effluent, and in natural communities of microbes in natural soil and natural water?

- What research is needed to develop structure activity relationships (SARs) for nanomaterials for aquatic organisms?

- What are the modes of action (MOA) for various nanomaterials for ecological species? Are the MOAs different or similar across ecological species?

5.9 Risk Assessment Research Needs

The overall risk assessment approach used by EPA for conventional chemicals is thought to be generally applicable to nanomaterials. It will be necessary to consider nanomaterials' special properties and their potential impacts on fate, exposure, and toxicity in developing risk assessments for nanomaterials. It may be useful to consider a tiered-testing scheme in the development of testing and risk assessment approaches to nanomaterials.

Case studies could be conducted based on publicly available information on several intentionally produced nanomaterials. Such case studies would be useful in further identifying unique considerations that should be focused in conducting risk assessments for various types of nanomaterials. From such case studies and other information, information gaps may be identified, which can then be used to map areas of research that are directly affiliated with the risk assessment process and the use of standard EPA tools such as tiered testing schemes. EPA frequently uses tiered testing schemes for specific risk assessment applications. A series of workshops involving a substantial number of experts from relevant disciplines could be held to use case studies and other information for the identification of any unique considerations for nanomaterials not previously identified, testing schemes, and associated research needs that will have to be met to carry out exposure, hazard and risk assessments.

6.0 Recommendations

This section provides recommendations for Agency actions related to nanotechnology. These recommendations are based on the discussion of nanotechnology environmental applications and implications discussed in this paper, and are presented to the Agency as proposals for EPA near- and long-term actions for science and regulatory policy, research and development, collaboration and communication, and other Agency initiatives.

6.1 Pollution Prevention and Environmental Stewardship Recommendations

Pollution prevention is a critical area to engage EPA resources and expertise as nanotechnology industries form and develop. It is critical that EPA apply the principles developed for green chemistry, green engineering, and environmentally benign manufacturing in EPA's approach to nanotechnology. EPA has the opportunity to work with stakeholders to apply approaches of pollution prevention and product stewardship to nanotechnology development, so that emissions and risks are reduced as productivity and the economy grow. The following is the primary recommendation for pollution prevention and environmental stewardship:

- OPPT should take Agency leadership to incorporate product stewardship, design for the environment, green engineering and green chemistry principles and approaches to nanomaterials and nanoproducts.

Other recommendations for pollution prevention and environmental stewardship:

- NCEI and OECA should take the lead to identify nanotechnology sectors, supply chains, analytical and design tools, and applications. OECA should take the lead to work with other Agency programs, such as OPPT's Green Supply Chain Network to identify nanotechnology sectors, supply chains, analytical and design tools, and applications.

- OCIR and OCFO should work with organizations such as the Ecological Council of the States (ECOS), state technology assistance organizations, and other tech transfer groups to integrate an environmental stewardship orientation for nanotechnology into their ongoing assistance efforts.

- OPEI and ORD should expand research on economic incentives for environmental stewardship behavior associated with nanomaterials and nanoproducts.

- EPA should create policy, program and research designs that encourage an environmental stewardship ethic and behaviors throughout the complete life cycle of nanomaterials and products.

6.2 Research Recommendations

The following are recommendations for research that EPA should conduct or otherwise fund to address the Agency's decision-making needs. Where possible, relative priorities have been given to these needs. Clearly, the ability of EPA to fund such research will depend on available resources and competing priorities. These recommendations should be seen as a point of departure for further Agency discussion and the possible development of an EPA research strategy for nanotechnology.

6.2.1 Research Recommendations for Environmental Applications

- ORD should take the lead in supporting studies to improve pollutant capture or destruction by exploiting novel nanoscale structure-property relations for nanomaterials used in environmental control and remediation applications.

- ORD should work with the other parts of the Agency to examine the implications (risks) of the applications of nanotechnology. For example, to determine the impact of certain airborne particles on the physicochemistry and health effects of diesel emissions and the health effects associated with interactions with complex ambient air aerosol mixtures. What is the nature of metal species being emitted including potentially hazardous complex nanoparticles, and the change in other emissions (including elemental carbon and organic species) as a result of the catalyst addition?

- ORD should take the lead in developing nanotechnology-enabled devices for measuring and monitoring conventional chemical and biological contaminants.

- ORD should take the lead in improving the methods for detecting and monitoring nanomaterials in the environment. ORD's laboratories should engage in collaborative research and development agreements to move fundamental research from the laboratory to the field. (e.g., sensors, treatment technologies).

- ORD should work with industrial partners to verify the performance of nanomaterials and nanoproducts used for environmental applications.

- ORD should continue to support research to develop non-polluting manufacture of nanomaterials and nanoproducts (e.g., using alternative solvents, lower energy processes, fewer processing steps, non-toxic starting materials. Further, the research should promote environmentally beneficial applications of nanomaterials (e.g., nanocatalysts, nanomembranes and reactors, efficient lighting, etc.).

- ORD should develop rapid screening methods that keep pace with rapid technological change for nanomaterials and nanoproducts building on existing Life Cycle Analysis methods. OPPTS, OW and OAR should collaborate with stakeholders developing rapid screening methods.

6.2.2 Research Recommendations for Environmental Implications

A multidisciplinary approach is needed that involves physics, biology, and chemistry to understand nanomaterials at basic level and how they interact with the environment. This requires a cross-media approach and one that involves collaboration with other federal agencies, and the private and non-profit sectors.

6.2.2.1 Research Recommendations for Fate, Treatment, Detection, Release, and Exposure

The following are recommendations, in numbered order of priority, in support of the fate, treatment, detection and release research needs identified as priorities in Chapter 5.

Fate and Treatment

1. OSWER and ORD should take the lead on research to assess the fate of nanomaterials such as zero valence iron used in the remediation of chemically contaminated soil sites. These offices should collaborate with state environmental programs and academia on this research. Based upon available field activities where nanomaterials are being used for site remediation, this research could be conducted within the next one to two years.

2. ORD and OAR should take the lead on research on the stability of various types of nanoparticles in the atmosphere. This effort should involve both theoretically derived information as well as some laboratory testing.

3. ORD, OSWER and OW should lead research on the biotic and abiotic degradation of nanomaterials in soils and aqueous solutions that are relevant to environmental conditions.

4. ORD should develop a report on how the physical and chemical properties of nanomaterials impact their environmental fate.

5. ORD, OSW and OW should collaboratively lead research wastewater treatment process, including the specific types of nanomaterials that would end up in large quantities in sewage treatment plants, the efficiency of removing nanoparticles from the effluent, as well as the impact nanomaterials may have on the removal or degradation of substances in sewage during the treatment process. EPA should collaborate with municipal sewage treatment facilities and academia on this research.

6. ORD, OPPT and OW should share the lead on research on the fate of nanomaterials used in the purification of drinking water. Research would be based on actual field and/or laboratory findings and recommendations would be provided on how to improve the nanomaterial removal process where human health issues are a concern. This research should also evaluate individual processes; i.e., whether methods such as

carbon adsorption, filtration, and coagulation and settling are effective for treating nanomaterials.

Environmental Detection and Analysis

Where applicable, the initial focus of environmental detection and analysis related research should be on nanomaterials or types of nanomaterials that have demonstrated potential human or ecological toxicity. The following is a prioritized list of research needs for environmental detection and analysis.

1. ORD should lead the development of a report on the assessment of available environmental detection methods and technologies for nanomaterials in environmental media and for personal exposure monitoring. ORD could collaborate with NIOSH, DOD, industry and academia in developing this report.

2. ORD should collaborate with NIST, NIOSH, DOD, nanomaterial manufacturers and government and private sector organizations in the development of quality control reference materials for analytical methods for nanomaterials.

3. ORD should lead development of a set of standard methods for the sampling and analysis for nanomaterials of interest in various environmental media. ORD should collaborate with NIOSH, DOD, industry, academia, the American Society for Testing Materials (ASTM) and the American National Standards Institute (ANSI) in developing these methods.

Release and Exposure

1. OPPT should conduct a literature search to evaluate the effects of nanomaterial physical/chemical properties on releases and exposures.

2. OPPT should conduct an evaluation of sources of information for assessing chemical releases and exposures for their applicability to nanomaterials. These sources, including release and exposure tools and models, would be evaluated for whether they would be applicable to assessing releases and exposures to nanomaterials. If found applicable, the sources would be evaluated to determine whether additional data or methods would be needed for assessing nanomaterials. Issues such as degradation would be considered also.

3. OPPT should lead the development of guidance to define risk assessment needs for various types of nanomaterials. This guidance should be developed by OPPT in consultation with other stakeholders.

4. OPPT should lead development of guidance for performing exposure assessments for nanomaterials for human and environmental species, including sensitive populations (e.g., endangered species, children, asthmatics, etc.). This guidance should be developed by OPPT in consultation with other stakeholders. A prerequisite for this

guidance development is the completion of above noted guidance for performing risk assessments for nanomaterials.

Some parts of the remaining exposure and release research initiatives below are contingent upon completion of the risk and exposure assessment guidance documents noted in the two paragraphs above. Until this contingency is met, many of the remaining research needs cannot be fully completed.

5. OPPT should lead the development of exposure and release scenarios for nanomaterials in manufacturing and use operations. This effort should be conducted by OPPT with possible consultation with industry, NIOSH, and ORD

6. OPPT and ORD should collaborate to evaluate and test of equipment for controlling and reducing chemical releases and exposures for their applicability to nanomaterials.

7. OPPT should lead the evaluation and testing of personal protective equipment for controlling and reducing chemical exposures for their applicability to nanomaterials, in collaboration with NIOSH and other external groups.

8. ORD should lead the development of sensors for monitoring personal exposures to nanoparticles

6.2.2.2 Human Health Effects Assessment Research Recommendations

The following is a prioritized list of health effects research needs:

Test Methods

1. ORD should collaborate with OPPTS on research to determine whether current testing methods (organisms, exposure regimes, media, analytical methods, testing schemes) (http://www.epa.gov/opptsfrs/home/testmeth.htm) are applicable to testing nanoparticles in standardized agency toxicity tests. These offices should consider whether OECD and EPA harmonized test guidelines are capable of determining the toxicity of the wide variety of intentionally produced nanomaterials and waste byproducts associated with their production. In this effort ORD should lead research evaluating whether current analytical methods are capable of analyzing and quantifying intentionally produced nanomaterials to generate dose-response relationships. This is an immediate research need.

Nanotoxicology

2. ORD should collaborate with other EPA offices on research to determine the health effects (local and systemic; acute and chronic) resulting from either direct exposure to nanomaterials, or to their byproducts, associated with dispersive nanotechnology applications such as remediation, pesticides, and air pollution control technologies. Research should determine whether there are specific toxicological endpoints that are of

high concern for nanoparticles, such as neurological, cardiovascular, respiratory, or immunological effects, etc. Research in this area should also provide information as to the adequacy of existing toxicological databases to predict or extrapolate the toxicity of intentionally produced nanomaterials. This is an immediate research need. The Agency should also collaborate with stakeholders in catalyzing this research.

Hazard Identification and Dosimetry & Fate

3. ORD should lead research to determine what physicochemical properties and dose metrics best correlate with the toxicity (local and systemic; acute and chronic) of intentionally produced nanomaterials. This is an immediate research need.

4. ORD should lead research on the adsorption, distribution, metabolism, and excretion (ADME) of intentionally produced nanomaterials following various routes of exposure. This research must also include determining what physicochemical properties regulate intentionally produced nanomaterial ADME. This is an immediate research need. ORD should collaborate with OPPTS on this research.

Susceptibility

5. ORD should take the lead on research to identify subpopulations that may be at increased risk for adverse health effects associated with exposure to intentionally produced nanomaterials. This is an intermediate need that cannot be established until information from earlier research needs have been collected.

Computational Nanotoxicology

6. ORD should take the lead on research to determine what approaches are most effective to build predictive toxicity assessment models (SAR, PBPK, "omics", etc.). While extremely useful, this is a long-term research need.

Research into the human health effects assessment of intentionally produced nanomaterials will be extremely challenging and the ability to interact with other federal, international, academic, and private activities in this area would be most beneficial. A number of organizations are engaged in health effects research. Collaboration with NASA, NIOSH, FDA, NCI, NTP, DOD/MURI, NIST, NEHI, DOE, the European Union, EPA grantees, academic institutions, and others will leverage resources in gaining knowledge on the potential health effects of nanomaterials.

6.2.2.3 Ecological Exposure and Effects

It is critical that research be focused specifically upon the fate, and subsequent exposure and effects, of nanomaterials on invertebrates, fish, and wildlife associated with ecosystems. What is the behavior of nano materials in aquatic and terrestrial environments?

How can environmental exposures be simulated in the laboratory? What are the acute and chronic toxic effects? There is a need for development and validation of analytical methodologies for measuring nanoscale substances (both parent materials and metabolites/complexes) in environmental matrices, including tissues of organisms. In terms of toxicity, a critical challenge in the area of ecosystem effects lies in determining the impacts of materials whose cumulative toxicity is likely to be a manifestation of both physical and chemical interactions with biological systems. The following is a prioritized list of ecological research needs:

Test Methods

1. ORD should collaborate with other EPA offices in research on the applicability of current testing schemes and methods (organisms, endpoints, exposure regimes, media, analytical methods) for testing nanomaterials in standardized toxicity tests. Both pilot testing protocols and definitive protocols should be evaluated with respect to their applicability to nanomaterials. This is a near-term research need.

Environmental Fate/Distribution of Nanomaterials in Ecosystems

2. ORD should take the lead on research on the distribution of nanomaterials in ecosystems. This is a near-term research need.

Nanotoxicology and Dosimetry

3. ORD should collaborate with program offices to determine the effects of direct exposure to nanomaterials or their byproducts, associated with dispersive nanotechnology uses, on a range of ecological species (fish, inverts, birds, amphibians, reptiles, plants, microbes). This research should be focused on organisms residing in ecological compartments that the nanomaterials in question preferentially distribute to, if any, as identified in 2 above. This research should include evaluation of the uptake, transport, and bioaccumulation of these materials. This was also identified as a near-term need.

4. ORD should collaborate with OW and OPPT on research regarding the interaction of nanomaterials with microbes in sewage treatment plants in sewage effluent and natural communities of microbes in natural soil and natural water. This is a mid-term need.

5. ORD should take the lead on research aimed at developing structure-activity relationships (SARs) for nanomaterials for aquatic organisms. This is a mid- to longer-term need.

6. ORD should take the lead on research on the modes of action for various nanomaterials for a range of ecological species. This is a long-term research need.

6.3 Recommendations to Address Overarching Risk Assessment Needs

One way to examine how a nanomaterial assessment would fit within EPA's overall risk assessment paradigm is to conduct a case study based on publicly available information on one or several intentionally produced nanomaterials. In the past, such case studies have proven useful to the Agency in adjusting the chemical risk assessment process for stressors such as bacteria. For example, assessments of recombinant bacteria need to account for reproduction, and other factors not considered with chemical risk assessments. From such case studies and other information, information gaps may be identified, which can then be used to map areas of research that are directly affiliated with the risk assessment process. This has been done in the past with research on airborne particulate matter.

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

6.4 Recommendations for Collaborations

In addition to the Agency's current collaborations on nanotechnology issues and our ongoing communication activities (see www.epa.gov/nano), we recommend the following additional actions.

- EPA should collaborate with other countries (e.g., through the OECD) on burden-sharing and harmonized approaches for generating data and assessing nanomaterials.

- OIA should consider potential human health and environmental impacts of nanotechnology, as appropriate within the context of environmental review of trade agreements, as EPA develops its research capacity and regulatory authority in this area.

- ORD's laboratories should put a special emphasis on establishing Cooperative Research and Development Agreements (CRADAs) to leverage non-federal resources to develop environmental applications of nanotechnology (CRADAs are established between the EPA and research partners to leverage personnel, equipment, services, and expertise for a specific research project.)

- OCIR should lead efforts to investigate the possibilities for collaboration with and through state and local government economic development, environmental and public health officials and organizations.

- OPA and program offices, as appropriate, should lead an Agency effort to implement the communication strategy for nanotechnology described at www.epa.gov/nano.

- OPEI (SBO) should lead efforts to engage in information exchange with small businesses, which comprise a large percentage of U.S. nanomaterial producers.

6.5 Recommendation to Convene a Cross-Agency Workgroup

The Agency should convene a standing cross-Agency group to foster information sharing regarding risk assessment or regulatory activities regarding nanomaterials across program offices and regions.

6.6 Recommendation for Training

EPA has begun educating itself about nanotechnology through seminars in the program and regional offices, an internal cross-Agency workgroup (NanoMeeters) with an extensive database, and a Millenium lecture series covering both the administrative and technical aspects of nanotechnology. The SPC Nanotechnology Workgroup also held a "primer" session on nanotechnology to help inform its members during the early stages of development of this paper. While this white paper also provides information for Agency managers and scientists, there should be ongoing education and training for EPA managers and staff to assist in the understanding of nanotechnology, its potential applications, regulatory and environmental implications, as well as unique considerations when conducting risk assessments on nanomaterials relative to macro-sized materials.

6.7 Summary of Recommendations

EPA should begin taking steps to help ensure both that society accrues the important benefits to environmental protection that nanotechnology may offer and that the Agency understands potential risks from environmental exposure to nanomaterials. The Table 7 summarizes the recommendations identified above.

Table 7. Summary of Workgroup Recommendations Regarding Nanomaterials
6.1 Pollution Prevention, Stewardship and Sustainability. EPA should engage resources and expertise as nanotechnology industries form and develop to encourage, develop and support nanomaterial pollution prevention at its source and an approach of stewardship. Detailed pollution prevention recommendations are identified in the text. Additionally, the Agency should draw on the "next generation" nanotechnologies for applications that support environmental stewardship and sustainability, such as green energy and green manufacturing.
6.2 Research. EPA should undertake, collaborate on, and catalyze research on the various types of nanomaterials to better understand and apply information regarding their: i) chemical identification and characterization, ii) environmental fate, iii) environmental detection and analysis, iv) potential releases and human exposures, v) human health effects assessment, and vi) ecological effects assessment, and vii) environmental technology applications. Specific research recommendations for each area are identified in the text.
6.3 Risk Assessment. EPA should conduct case studies based on publicly available information on several intentionally produced nanomaterials. Such case studies would be useful in further identifying unique considerations that should be focused in conducting risk assessments for the various types of nanomaterials. The case studies would also aid in further identifying information gaps which can then be used to map areas of research which are directly affiliated with the risk assessment process.
6.4 Collaboration. EPA should continue and expand its collaborations regarding nanomaterial applications and potential human and environmental health implications.
6.5 Cross-Agency Workgroup. EPA should convene a standing cross-Agency group to foster information sharing regarding risk assessment or regulatory activities for nanomaterials across program offices and regions.
6.6 Training. EPA should continue and expand its activities aimed at training Agency scientists and managers regarding potential environmental applications and environmental implications of nanotechnology.

7.0 References

Aitken, R.J., Creely, K.S., Tran, C.L. 2004. Nanoparticles: An Occupational Hygiene Review. Research Report 274. Prepared by the Institute of Occupational Medicine for the Health and Safety Executive, North Riccarton, Edinburgh, England.

Atkinson, R. 2000. Atmospheric Oxidation (Chapter 14), in Boethling, R.S.; Mackay, D. (eds.), Handbook of Property Estimation Methods for Chemicals, Environmental and Health Sciences, Lewis Publishers, CRC Press, Boca Raton, FL.

Australia Department of Defence. 2004. The Risk Management Process – Application of AS/NZS 4360:1999. http://www.defence.gov.au/cfo/privfin/manual/07.htm

Ball, P. 2005. Nanomaterials Draw Electricity from Heat. Nature Materials Update. 24 March 2005.

Ball, P. 2004. Nanotubes Show the Way to Wind Power. Nature Materials Update. 2 September 2004.

Baron et al., 2004. Exposure to Carbon Nanotube Material: Aerosol Release During Handling of Unrefined Single Walled Carbon Nanotube Material. J. Toxicol. Environ. Health, Part A, 67:87-107.

Baron, P.A., Maynard, A.D., Foley, M. 2003. Evaluation of Aerosol Release During the Handling of Unrefined Single Walled Carbon Nanotube Material. NIOSH-DART-02-191 Rev. 1.1, April 2003.

Bekyarova E. et al., 2005. Applications of Carbon Nanotubes in Biotechnology and Biomedicine. J. Biomedical Nanotechnology 1:3-17.

Bidleman, T.F. 1988. Atmospheric Processes, Wet and Dry Deposition of Organic Compounds are Controlled by their Vapor-Particle Partitioning. Environ. Sci. Technol. 22(4), 361-367.

Biswas P, Chang-Yu W. 2005 Nanoparticles and the Environment. J. Air & Waste Manage. Assoc. 55:708-746.

Boethling, R.S., Nabholz, J.V. 1997. Environmental Assessment of Polymers Under the U.S. Toxic Substances Control Act, Chapter 10. pp. 187-234. in Hamilton, J. D. and R. Sutcliffe (eds.), Ecological Assessment of Polymers: Strategies for Product Stewardship and Regulatory Programs. Van Nostrand Reinhold, New York. 345 p.

Borm, P.J.A., Hreyling, W. 2004. A Need for Integrated Testing of Products in Nanotechnology, in Nanotechnologies: A Preliminary Risk Analysis on the Basis of a Workshop, Organized in Brussels on 1-2 March 2004 by the Health and Consumer Protection Directorate General of the European Commission. http://europa.eu.int/comm/health/ph_risk/events_risk_en.htm

Boyd, A.M., Lyon, D., Velasquez, V., Sayes, D.Y., Fortner, J., Colvin, V.L. 2005. Photocatalytic Degradation of Organic Contaminants by Water-Soluble Nanocrystalline C60. ACS Meeting Abstracts, 229th ACS National Meeting, San Diego, CA, March 13-17, 2005.

Broadleaf Capital International Pty Ltd. 1999. Tutorial Notes: The Australian and New Zealand Standard on Risk Management, AS/NZS 4360:1999. Pymble, Australia. http://www.rudnicki.com.pl/pub/RMStd_Austral_comment.pdf#search='AS/NZS%204360:1999'

Brown, M. 2005. Nano-Bio-Info Pathways to Extreme Efficiency. Presentation to the AAAS Annual Meeting, Washington, DC. http://www.ornl.gov/sci/eere/aaas/abstracts.htm

Brzoska, M., Langer, K., Coester, C. Loitsch, S., Wagner, T.O., Mallinckrodt, C. 2004. Incorporation of Biodegradable Nanoparticles into Human Airway Epithelium Cells-In vitro Study of the Suitability as a Vehicle for Drug or Gene Delivery in Pulmonary Diseases. Biochem. Biophys. Res. Commun. 318(2): 562-570.

Cabada, J., Rees, S., Takahama S. et. al. 2004. Mass Size Distributions and Size Resolved Chemical Composition of Fine Particulate Matter at the Pittsburgh Supersite. Atmospheric Environ. 38, pp. 3127-3141.

Cai R. et al. 1992. Increment of Photocatalytic Killing of Cancer Cells Using TiO2 with the Aid of Superoxide Dismutase. The Chemical Society of Japan, Chemistry Letters: 427-430.

Canada. Government of British Columbia. 2002. Risk Management Principles. http://srmwww.gov.bc.ca/imb/3star/sdlc/8manage/risks/risk_principles.html

Cash, G., Nabholz, J. 2002. Minimum Cross-sectional Diameter: Calculating When Molecules May Not Fit Through a Biological Membrane. Environmental Toxicology and Chemistry 21(10):2095-2098.

CBEN. 2005. Center for Biological and Environmental Nanotechnology, Rice University. Information about the center and current research summaries are available online: http://cohesion.rice.edu/centersandinst/cben/

Chen, C., Sheng, G., Wang, X., Fu, J., Chen, J., Liu, S. 2000. Adsorption Characteristics of Fullerenes and Their Application for Collecting VOCs in Ambient Air. Juanjing Juaxue, 19(2), 165-169. [The original report is published in Chinese. The abstract published in Chemical Abstracts does not specify if the fullerenes used are free particles or immobilized.]

Cheng, S.H., Cheng, J. 2005. Carbon Nanotubes Delay Slightly the Hatching Time of Zebrafish Embryos. 229th American Chemical Society Meeting, San Diego, CA March 2005.

Cheng, X., Kan, A.T., Tomson, M.B. 2004. Naphthalene Adsorption and Desorption from Aqueous C60 Fullerene. J. Chem. Eng. Data 49: 675-683.

Chow J.C., Johann P.E., Natalie C.G., et. al. 2002. Chapter One: Exposure Measurements. Chemosphere, Vol. 49(9): 873-901.

Christen, K. 2004. Novel Nanomaterial Strips Contaminants from Waste Streams. Environ. Sci. Technol. 38(23): 453A-454A.

Colfen, H., 2004. Analysis of Nanoparticles < 10 nm by Analytical Ultracentrifugation, Particle Sizing and Characterization. ACS Symposium Series, pp. 119-137.

Colvin, V. 2003. The Potential Environmental Impact of Engineered Nanoparticles. Nature Biotechnol. 21(10), 1166-1170.

Committee on Environment and Natural Resources. 2002. Strategic Plan for Particulate Matter. NOAA, 38 pp.

Comparelli, R., Cozzoli, P.D., Curri, M.L., Agostiano, A., Mascolo, G., Lovecchio, G. 2004. Photocatalytic Degradation of Methyl-red by Immobilized Nanoparticles of TiO2 and ZnO. Water Sci. Technol. 49(4): 183-188.

Corti, C.W., Holliday, R.J., Thompson, D.T. 2002. A Developing New Industrial Applications for Gold: Gold Nanotechnology. Gold Bulletin: 111.

Das R., Kiley, P.J., Segal, M., Norville, J., Yu, A.A., Wang, L., Trammell, S.A., Reddick, L.E., Kumar, R., Stellacci, F., Lebedev, N., Schnur, J., Bruce, B.D, Zhang, S., Baldo, M. 2004. Integration of Photosynthetic Protein Molecular Complexes in Solid-State Electronic Devices. Nano Letters: 4(6): 1079-1083.

Dennekamp, M., Mehenni, O.H., Cherrie, J., Seaton, A. 2002. Exposure to Ultrafine Particles and PM2.5 in Different Micro-Environments. Annals of Occupational Hygiene 46 (suppl. 1): 412–414.

Derfus, A.M. et al. 2004. Probing the Cytotoxicity of Semiconductor Quantum Dots. Nano Letters 4(1):11-18

Dreher, K.L 2004. Health and Environmental Impact of Nanotechnology: Toxicological Assessment of Manufactured Nanoparticles. Toxicological Sciences 77:3-5.

Elliott et al. 2005. Novel Products From the Degradation of Lindane by Nanoscale Zero Valent Iron. American Chemical Society Annual Meeting, San Diego, CA, Abstract.

European Commission. 2004. European Commission, Community Health and Consumer Protection. Nanotechnologies: A Preliminary Risk Analysis on the Basis of a Workshop Organized in Brussels on 1-2 March 2004 by the Health and Consumer Protection Directorate General of the European Commission. http://europa.eu.int/comm/health/ph_risk/events_risk_en.htm

European NanoSafe Report. 2004. Technical Analysis: Industrial Application of Nanomaterials Chances and Risks. www.nano.uts.edu.au/nanohouse/nanomaterials%20risks.pdf

Filley, T.R., Ahn, M., Held, B.W., Blanchette, R.A. 2005. Investigations of Fungal Mediated (C60-C70) Fullerene Decomposition. Preprints of Extended Abstracts Presented at the ACS National Meeting, American Chemical Society, Division of Environmental Chemistry 45(1), 446-450.

Florence, A.T., and Hussain, N. 2001 Transcytosis of Nanoparticle and Dendrimer Delivery Systems: Evolving Vistas. Adv. Dru Deliv. Rev. 50 Suppl 1: S69-89.

Fortner, J.D., Lyon, D.Y., Sayes, C.M., Boyd, A.M, Falkner, J.C., Hotze, E.M., Alemany, L.B, Tao, Y.J., Guo, W., Ausman, K.D., Colvin, V.L. and J.B. Hughes. 2005. C60 in water: Nanocrystal Formation and Microbial Response. Environ. Sci. Technol. 39:4307-4316.

Fortner, J.D., Falkner, J.C., Hotze, E.M., Lyon, D.Y., Sayes, C.M., Ausman, K.D., Colvin, V.L., Hughes, J.B. 2005. C60 Aggregates in Water: Formation Dynamics and Further Characterization. ACS Meeting Abstracts, 229th ACS National Meeting, San Diego, CA, March 13-17, 2005.

Forzani E., Zhang H., Chen W., Tao N. 2005. Detection of Heavy Metal Ions in Drinking Water Using a High-Resolution Differential Surface Plasmon Resonance Sensor. Environ. Sci. Technol. 39:1257.

Frampton, M.W. et al. 2004. Research Report. Health Effects Institute 126:1-47

Fraser, L. 2003. Organic Electronics: A Cleaner Substitute for Silicon. Environ. Health Perspect. 111:5.

Frink, C.R., Waggoner, P.E., Asubel, J.H. 1996. Nitrogen Fertilizer: Retrospect and Prospect. Proc. Natl. Acad. Sci., pp. 1175-1180.

Georgia Tech. 2005. March 2005 press release http://gtresearchnews.gatech.edu/newsrelease/adhesive.htm; Abstract posted at:

http://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.abstractDetail/abstract/6352/report/0

Global Environment & Technology Foundation. 2000. Final Report: The US EPA Environmental Management System Pilot Program for Local Government Entities. http://www.epa.gov/owm/iso14001/emsrepor.pdf

Helz, G., Zepp, R.G., Crosby, D.G. (eds.) 1994. Aquatic and Surface Photochemistry, Lewis Publishers, CRC Press, Boca Raton FL., 552 pp.

Hughes L., Cass G., Gone J., et. al. 1998. Physical and Chemical Characterization of Atmospheric Ultrafine Particles in the Los Angeles Area. Env. Sci. and Tech. 32(9):1153-1161.

Health Effects Institute, Communication 9, August 2001. www.healtheffects.org/pubs-comm.htm

Hohr D., et al. 2002. The Surface Area Rather Than the Surface Coating Determines the Acute Inflammatory Response After Instillation of Fine and Ultrafine TiO2 in the Rat. Int. J. Hyg. Environ. Health 205:239-244.

Holker, V. et al. 2005. Cardiovascular Responses in Unrestrained WKY Rats to Inhaled Ultrafine Carbon Particles. Inhal. Toxicol. 17:29-42

Howard, C.V. 2003. Nano-particles and Toxicity, Annex to No Small Matter II: The Case for a Global Moratorium, Size Matters!, ETC Group Occasional Paper Series, 7(1). Available online at http://www.etcgroup.org/documents/Occ.Paper_Nanosafety.pdf

Health and Safety Executive (HSE) 2004. Nanoparticles: An Occupational Hygiene Review. Research Report 274. http://www.hse.gov.uk/research/rrhtm/rr274.htm

Hu, J., Lo, I.M., Chen, G. 2004. Removal of Cr(VI) by Magnetite Nanoparticle. Water Sci. Technol. 50(12):139-46.

Huang et al. 2003. J. Nanopart. Res., Aug. 2003.

Ignatovich, F.V., Novotny, L. 2003. Experimental Study of Nanoparticle Detection by Optical Gradient Forces. Rev. Scientific Instruments 74(12): 5231-5235. http://www.pacificnanotech.com/nanoparticles_nanoparticles.html

Institute for Defense and Government Advancement. 2004. Lightweight Materials for Auto and Air 2004. Emerging Technology for Lighter, More Efficient Vehicles. Presentation by Phillip J. Bond. http://www.idga.org/cgi-bin/templates/document.html?topic=329&event=4671&document=39562

Iden R. 2002. The "Eyes and Fingers" of Nanotechnology: Analysis Leads the Way to the Nanocosm. Presentation at Journalists and Scientists in Dialogue: Nanotechnology in Chemistry - Experiences Meets Vision, Oct. 28/29, 2002. Mannheim http://www.corporate.basf.com/en/innovationen/felder/nanotechnologie/analytik.htm?getasset=file1&name=Analytik_Text_Iden_e.pdf& http://www.corporate.basf.com/en/innovationen/felder/nanotechnologie/analytik.htm?getasset=file1&name=Analytik_Text_Iden_e.pdf&id=V00--i_QD6sSvbcp2SU

International Life Sciences Institute (ILSI) Research Foundation/Risk Science Institute, Principals for Characterizing the Potential Human Health Effects From Exposure to Nanomaterials: Elements of a Screening Strategy. Particle Fibre Toxicol. 2:8

International Organization for Standardization. 2005. TC207. Environmental Management. Frequently Asked Question. http://www.tc207.org/faq.asp?Question=9999

International Organization for Standardization. 2002. Environmental Management. The ISO 14000 Family of International Standards. http://www.iso.org/iso/en/prods-services/otherpubs/iso14000/index.html

Ivanov, V., Tay, J.H., Tay, S.T., Jiang, H.L. 2004. Removal of Micro-Particles by Microbial Granules used for Aerobic Wastewater Treatment. Water Sci. Technol. 50(12): 147-154.

Jia, G.J. et al. 2005. Cytotoxicity of Carbon Nanomaterials Environ. Sci. Technol. 39:1378-1383.

King, D.W., Lounsbury, H.A., Millero, F.J. 1995. Rates and Mechanism of Fe(II) Oxidation at Nanomolar Total Iron Voncentrations. Environ. Sci. Technol. 29(3): 818-824.

Kocum, C., Zareie, M.H., Ozer, F., Piskin, E. 2000. Observation of Nanoparticles and Film Formation by Scanning Tunneling Microscopy: Methyl Methacrylate/Butyl Methacrylate Nanoparticles Prepared by Microemulsion Polymerization. Colloid Polymer Sci. 278(6): 587-590.

Koropchak, J.A. et al. 1999. Nanoparticle Detection Technology. Anal. Chem. 71(11): 386A-394A.

Kozlovski, V., Brusov, V., Sulimenkov, I., Pikhtelev, A. and Dodonov, A. 2004. Novel Experimental Arrangement Developed for Direct Fullerene Analysis by Electrospray Time-of-Flight Mass Spectrometry. Rapid Comm. Mass Spec. 18(7): 780-786.

Kreyling, W.G., Semmler, M., Erbe, F., Mayer, P., Takenaka, S., Schulz, H., Oberdorster., G, Ziesenis, A. 2002. Translocation of Ultrafine Insoluble Iridium Particles From Lung Epithelium to Extrapulmonary Organs is Size Dependent But Very Low. J. Toxicol. Environ. Health A 65:1513-1530

Laitner, John A. "Skip". 2004. How Far Energy Efficiency? In Proceedings of the 2004 ACEEE Summer Study on Energy Efficiency in Buildings. Washington, DC: American Council for an Energy Efficient Economy.

Laitner, John A. "Skip". 2005a. Extreme Energy Efficiency: Possible? Profitable? Necessary! Presentation to the AAAS Annual Meeting, Washington, DC. Available online: http://www.ornl.gov/sci/eere/aaas/abtracts.htm.

Laitner, John A. "Skip," Marilyn A. Brown. 2005. Emerging Industrial Innovations to Create New Energy Efficient Technologies. Proceedings of the 2005 ACEEE Summer Study on Energy Efficiency in Industry. Washington, DC: American Council for an Energy Efficient Economy (forthcoming in July 2005).

Lam, et al. 2004.Pulmonary Toxicity of Single-Walled Carbon Nanotubes in Mice 7 and 90 Days after Intratracheal Instillation. Toxicol. Sci. 77:126-134.

Lecoanet, H.F., Bottero, J.Y., Wiesner, M.R. 2004. Laboratory Assessment of the Mobility of Nanomaterials in Porous Media. Environ. Sci. Technol. 38:5164-5169.

Lecoanet, H.F., Wiesner, M.R. 2004. Velocity Effects on Fullerene and Oxide Nanoparticle Deposition in Porous Media. Environ. Sci. Technol. 38, 4377-4382.

Li, Y.I. et al. 1999. Short Term Inflammatory Responses Following Intratracheal Instillation of Fine and Ultrafine Carbon Black in Rats. Inhal. Toxicol. 11:709-731.

Lin, Y. Lin, P. Liu, M. J. Meziani, L. F. Allard, and Y.- P. Sun. 2002. Hot-Fluid Annealing for Crystalline Titanium Dioxide Nanoparticles in Stable Suspension. J. Amer. Chem. Soc. 124:11514-11518.

Lockman P.R. et al. 2004. Nanoparticle Surface Charges Alter Blood-Brain Barrier Integrity and Permeability. J. of Drug Targeting 12 (9-10):635-641.

Lovern, S.B., Klaper, R.D. *Daphnia magna* mortality when exposed to titanium dioxide and fullerene (C60) nanoparticles. In press. Environ. Toxicol. Chem..

Luther, W., ed. 2004. Technological Analysis, Industrial Application of Nanomaterials - Chances and Risks. Future Technologies Division, VDI Technologiezentrum GmbH, Düsseldorf, Germany.

Lloyd, SM, Lave, LB, and Matthews, HS. 2005. Life Cycle Benefits of Using Nanotechnology to Stabilize Platinum-Group Metal Particles in Automotive Catalysts. Environ. Sci. Technol. 39:1384-1392.

Lyon D.Y., Fortner J.D., Hughes, J.B. and P.J. Alvarez. 2005. Impact of a C60 Water Suspension on Bacteria. 229th American Chemical Society Meeting, San Diego, CA March 2005.

Mackay, D., Shiu, W.Y., Ma, K.C. 2000. Henry's Law Constant (Chapter 4), in Boethling, R.S.; Mackay, D. (eds.) Handbook of Property Estimation Methods for Chemicals, Environmental and Health Sciences, Lewis Publishers, CRC Press, Boca Raton, FL.

Madan, T., Munshi, N., De, T.K., Usha Sarma, P., Aggarwal, S.S. 1997. Biodegradable Nanoparticles as a Sustained Release System for the Antigens/Allergens of Aspergillus fumigatus: Preparation and Characterization. Int. J. Pharm. 159, 135-147.

Malakoff. 1998. Death by Suffocation in the Gulf of Mexico. Science. 10 July 1998.
USGS (2001). The Quality of Our Nation's Waters: Nutrients and Pesticides.

Malik, N. et al. 2000. Dendrimers: Relationship Between Structure and Biocompatibility In Vitro, and Preliminary Studies on the Biodistribution of 125I-Labeled Polyamidoamine Dendrimers In Vivo. J. Control. Release 65:133-148.

Masciangioli, T, Wang, W-X, 2003. Environmental Technologies at the Nanoscale. Environ. Sci. Technol. March 1, 2003. 102A-108A.

Maynard, A.D., Baron, P.A., Foley, M., Shvedova, A.A., Kisin, E.R., and Castranova, V. 2004. Exposure to Carbon Nanotube Material: Aerosol Release During the Handling of Unrefined Single-Walled Carbon Nanotube Material. J Toxicol Environ Health A 67: 87-107.

McKim J., Schmieder, P, Veith, G. 1985. Adsorption Dynamics of Organic Chemical Transport Across Trout Gills as Related to Octanol-Water Partition Coefficient. Government Reports Announcements and Index, Issue 17, NTIS report number PB85-198315, 12 p.

McMurry, P. H. 2000. A Review of Atmospheric Aerosol Measurements. Atmospheric Environ. 34 (12-14):1959-1999

Montiero-Riviere, N.A., Nemanich, R.J., Inman, A.O., Yunyu, Y.W., Riviere, J.E. 2005. Multi-walled carbon nanotubes interactions with human epidermal keratinocytes. Toxicol. Lett. 155(3): 377-384

Muller, J., Huaux, F., Moreau, N., Misson, P., Heilier, J-F., Delos, J., Arras, M. Fonseca, A., Nagy, J. B., Lison, D. 2005. Respiratory toxicity of multi-wall carbon nanotubes. Toxicol. Appl. Pharmacol. 207: 221-231.

Nagaveni, K., Sivalingam, G., Hegde, M.S., Madras, G. 2004. Photocatalytic Degradation of Organic Compounds over Combustion-Synthesized Nano-TiO2. Environ Sci. Technol. 38, 1600-1604.

National Research Council. 1983. Risk Assessment in the Federal Government: Managing the Process. National Academy of Sciences, Washington, D.C. 192 pp.

National Research Council. 1994. Science and Judgment in Risk Assessment, National Academy of Sciences, Washington, D.C.

Nanotoxicology Workshop: Developing Experimental Approaches for the Evaluation of Toxicological Interactions of Nanoscale Materials, University of Florida, Nov. 3-4, 2004. www.nanotoxicology.ufl.edu

National Nanotechnology Initiative. 2000. The Initiative and Its Implementation Plan. www.nano.gov/html/facts/whatIsNano.html

National Nanotechnology Initiative. 2004. National Nanotechnology Initiative Strategic Plan, Goal 4: Support Responsible Development of Nanotechnology. http://www.nano.gov/NNI_Strategic_Plan_2004.pdf

Nemmar A. , Hoylaerts, M.F., Hoet, P.H.M., Vermylen, J., Nemery, B. 2003. Size Effect of of Intratracheally Instilled Particles on Pulmonary Unflammation and Thrombosis. Toxicol. Appl. Pharmacol. 186: 38-45.

Nigavekar, S.S. et al. 2004. 3H Dendrimer Nanoparticle Organ/Tumor Distribution. Pharm. Res. 21 (3):476-483.

Niimi, A. Oliver. , B. 1988. Influence of Molecular Weight and Molecular Volume on Dietary Adsorption Efficiency of Chemicals by Fishes. Can. J. Fish. Aquat. Sci. 45(2):222-227.

National Institute for Occupational Health and Safety. 2004. Nanotechnology Workplace Safety and Health. http://www.cdc.gov/niosh/topics/nanotech/default.html

Nurmi , J.T. et al. 2005. Characterization and Properties of Metallic Iron Nanoparticles: Spectroscopy, Electrochemistry, and Kinetics. Environ. Sci. Technol. 39(5): 1221-1230.

Oberdorster, G., Oberdorster, E., Oberdorster, J. 2005. Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles. Environ. Health Perspect. 113(7): 823-839.

Oberdorster, E. 2004. Manufactured nanomaterial (fullerenes, C60) induce oxidative stress in the brain of juvenile largemouth bass. Environ. Health Perspect. 12(10):1058-1062

Oberdorster E. 2004. Toxicity of NC60 Fullerenes to Two Aquatic Species: Daphnia and Largemouth bass. American Chemical Society, Anaheim, CA, March 27-April 2004. Abstract IEC21

Oberdorster, G., Sharp, Z., Atudorei, V., Elder, A., Gelein, R., Kreyling, W., and Cox, C. 2004. Translocation of inhaled ultrafine particles to the brain. Inhal Toxicol 16: 437-445.

Oberdorster, G., Sharp, Z., Atudorei, V., Elder, A., Gelein, R., Lunts, A. et al. 2002 Extrapulmonary translocation of ultrafine carbon particles following whole-body inhalation exposure of rats. J. Toxicol. Environ. Health A 65: 1531-1543.

Oberdorster. 1996. Significance of Particle Parameters in the Evaluation of Exposure-Dose-Response Relationships of Inhaled Particles." Inhal. Toxicol. 8 (Suppl. 8):73-89.

Oberdorster G. et al. 1994. Correlation Between Particle Size, In Vivo Particle Persistence, and Lung Injury. Environ. Health Perspect. 102(Suppl 5):173-179.

Organization for Economic Cooperation and Development. 2001. Environmental Strategy for the First Decade of the 21st Century. Adopted by OECD Environment Ministers. 16 May 2001. http://www.oecd.org/dataoecd/33/40/1863539.pdf

Organization for Economic Cooperation and Development 2001. OECD Environmental Outlook. (http://www1.oecd.org/publications/e-book/9701011E.PDF)

Opperhuizen, A., Velde, E., Gobas, F., Llem, D.,Steen, J. 1985. Relationship between bioconcentration in fish and steric factors of hydrophobic chemicals. Chemosphere 14(11/12):1871-1896.

Pickering, K.D.; Hote, E.M.; Wiesner, M.R. 2005. Reactive Oxygen Species Generated by Clustered Fullerene in Aqueous Solution. ACS Meeting Abstracts, 229th ACS National Meeting, San Diego, CA, March 13-17, 2005. Abstract available online: http://oasys2.confes.com/acs/229nm/techprogram/P848711.HTM

Pickering, K.D.; Wiesner M.R. 2005. Fullerol-Sensitized Production of Reactive Oxygen Species in Aqueous Solution. Environ. Sci. Technol. 39(5): 1359-1365.

Preining, O. 1998. The Physical Nature of Very, Very Small Particles and its Impact on Their Behaviour. J. Aerosol Sci. 29(5/6): 481-495.

Reguera, G., McCarthy, K.D., Mehta, T., Nicoll, J.S., Tuominen, M.T., Lovley, D.R: 2005. Extracellular Electron Transfer Via Microbial Nanowires. Nature 453(23): 1098-1101.

Renwick, L.C. et al. 2001. Impairment of Alveolar Macrophage Phagocytosis by Ultrafine Particles. Toxicol. Appl. Pharmacol. 172:119-127.

Roberts, D.W. et al.. 2005. Localization of Intradermally Injected Quantum Dot Nanoparticles in Regional Lymph Nodes. Society of Toxicology Annual Meeting, New Orleans, LO, 2005, Abstract.

Rupprecht & Patashnick Co., Inc. 2005. TEOM Series 7000 Source Particulate Monitor. Web site May 2005, http://www.rpco.com/products/cemprod/cem7000/index.htm

Sayes, C.M. et al. 2004. The Differential Cytotoxicity of Water Soluble Fullerenes. Nano Letters 4(10):1881-1887, 2004

Schwarzenbach, R.P., Gshwend, P.M., Imboden, D.M., (eds.) 1993. Sorption: Solid-Aqueous Solution Exchange (Chapter 11) in Environmental Organic Chemistry, Wiley-Interscience, New York.

Science Daily Magazine. 2005. Probing the promise and perils of nanoparticles. http://www.sciencedaily.com/releases/2005/03/050323133026.htm, posted 25 March 2005.

Sclafani, A. and Herrmann, J. M. 1996. Comparison of the Photoelectronic and Photocatalytic Activities of Various Anatase and Rutile Forms of Titania in Pure Liquid Organic and in Aqueous Phases. J. Phys. Chem. 100:13655-13661.

Sgro, L. A., Basile, G., Barone, A. C., et. al., .2003. Detection of Combustion Formed Nanoparticles. Chemosphere 51(10): 1079-1090.

Shvedova A.A., et al. 2005. Unusual Inflammatory and Fibrogenic Pulmonary Responses to Single Walled Carbon Nanotubes in Mice. Am. J. Physiol. Lung Cell Mol. Physiol. doi:10.1152/ajplung.00084.2005. http://ajplung.physiology.org/cgi/search?andorexactfulltext=and&resourcetype=1&disp_type=&sortspec=relevance&author1=shvedova&fulltext=&pubdate_year=2005&volume=&firstpage=

Shvedova, A.A., Castranova, V., Kisin, E.R., Scwegler, B-D., Murray, A.R., Gandelsman, V.Z., Maynard, A., Baron, P. 2003. Exposure to Carbon Nanotube Material: Assessment of Nanotube Cytotoxicity using Human Keratinocyte Cells. J. Toxicol. Environ. Health A. 66(20): 1909-1926

Song Zhao, G.X. 2002. Catalysis l. Today 75, 3B15.

Spurny, K.R. 1998. On the Physics, Chemistry and Toxiology of Ultrafine Anthropogenic, Atmospheric Aerosols (UAAA): New Advances. Toxicol. Lett. 96,97, 253-261.

Stapleton, PJ, Glover, MA and Davis, SP. 2001. Environmental Management Systems: An Implementation Guide for Small and Medium-Sized Organizations. 2nd Ed. NSF International. http://www.epa.gov/owm/iso14001/wm046200.htm and http://www.epa.gov/owm/iso14001/ems2001final.pdf

Steinfeldt, M., Petschow, U., Haum, R. Gleich, A. v.. 2004. Nanotechnology and Sustainability. Discussion Paper #65/04. Institute for Ecological Economy Research. Berlin. www.ioew.de

Sun, J.D.; Wolff, R.K.; Kanapilly, G.M. 1982. Deposition, Retention and Biological Fate of Inhaled Benzo(a)pyrene Adsorbed onto Ultrafine Particles and as a Pure Aerosol. Toxicol. Appl. Pharmacol. 65(2): 231-244.

Sun, J.D.; Wolff, R.K.; Kanapilly, G.M., McClellan, R.O. 1984. Lung Retention and Metabolic Fate of Inhaled Benzo(a)pyrene Associated with Diesel Exhaust Particles. Toxicol. Appl. Pharmacol. 73(1): 48-59.

Swiss Report Reinsurance Company. 2004. Nanotechnology: Small Matter, Many Unknowns. www.swissre.com

Tinkle S. et al. 2003. Skin as a Route of Exposure and Sensitization in Chronic Beryllium Disease. Environ. Health Perspect. 111:1202-1208.

TSI Inc. 2005A. Model 3089 Instrument Brochure: Nanometer Aerosol Sampler. TSI web site May 2005, http://www.tsi.com/products/nas.aspx

TSI Inc. 2005B. Model 3091 Fast Mobility Particle Sizer Spectrometer. TSI web site May 2005,http://www.tsi.com/products/fastmobilitycpc.aspxhttp://www.tsi.com/products/fastmobilitycpc.aspx

TSI Inc. 2005C.. Model 3800 Instrument Brochure: Aerosol Time-of-Flight Mass Spectrometers with Aerodynamic Focusing Lens Technology (2005), TSI web site May 2005, http://www.tsi.com/http://www.tsi.com/products/massspec.aspx

TSI Inc. 2005D. Model 3550 Instrument Brochure: Nanoparticle Surface Area Monitor, TSI web site June 2005, http://www.tsi.com/documents/3550_PN2980333.pdf

Tungittiplakorn, W., Cohen, C., Lion, L.W. 2005. Engineered Polymeric Nanoparticles for the Bioremediation of Hydrophobic Contaminants. Environ. Sci. Technol. 39:1354-1358.

Tungittiplakorn, W.; Lion, L.W.; Cohen, C.; Kim, J.Y. 2004. Engineered Polymeric Nanoparticles for Soil Remediation. Environ. Sci. Technol. 38: 1605-1610.

Turpin B.J., Saxena P. 2000. Andrews E. Measuring and Simulating Particle Organics in the Atmosphere: Problems and Prospects. Atmospheric Environ. 34(18): 2983-3013.

United Kingdom Royal Society. 2004. The Royal Society and the Royal Academy of Engineering. Nanoscience and Nanotechnologies: Opportunities and Uncertainties. http://www.nanotec.org.uk/finalreport.htm

United Kingdom Department for Environment, Food, and Rural Affairs (DEFRA). 2002. Guidelines for Environmental Risk Assessment and Management. http://www.defra.gov.uk/environment/risk/eramguide/02.htm

U.S. Department of Agriculture. 2003.. Nanoscale Science and Engineering for Agriculture and Food Systems. Report Submitted to Cooperative State Research, Education, and Extension Service. Norman Scott (Cornell University) and Hongda Chen (CSREES/USDA) Co-chairs.

U.S. Department of Energy. 2005. National Renewable Energy Laboratory Nanoscience & Nanotechnology: Meeting 21st Century Energy Challenges.

U.S. Department of Energy 2005. May 26, 2005 Press Release. http://www.energy.gov/engine/content.do?PUBLIC_ID=17978&BT_CODE=PR_PRESSRELEASES&TT_CODE=PRESSRELEASE

U.S. Department of Energy 2005. EIA Country Analysis Brief. United States of America. Short Term Energy Outlook. http://www.eia.doe.gov/emeu/cabs/usa.html

U.S. Environmental Protection Agency. Innovation Action Council. 2005. .Presentation by Jay Benforado. June 30, 2005.

U.S. Environmental Protection Agency Federal Register Notice. March 14, 2005. Request for Nominations, Ad Hoc Integrated Nitrogen Research Committee of the Science Advisory Board.

U.S. Environmental Protection Agency. 2005. Office of Waste Management. Environmental Management Systems/ISO 14001 – Frequently Asked Questions. http://www.epa.gov/owm/iso14001/isofaq.htm

U.S Environmental Protection Agency. 2005a. EPA SW-846 Methods on Line. http://www.epa.gov/SW-846/main.htm

U.S. Environmental Protection Agency. 2005. Office of Pollution Prevention and Toxics. 12 Principles of Green Chemistry. http://www.epa.gov/greenchemistry/principles.html

U.S Environmental Protection Agency. 2004. Office of Research and Development. Air Quality Criteria for Particulate Matter. Vol. 1, Chapter 2. http://cfpub2.epa.gov/ncea/cfm/recordisplay.cfm?deid=87903

U S Environmental Protection Agency. 2004. Air Quality Criteria for Particulate Matter. Report Number EPA/600/P-99/002a,bF. October. http://cfpub.epa.gov/ncea/

U.S. Environmental Protection Agency. 2003. Office of Water. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000) Technical Support Document Volume 2: Development of National Bioaccumulation Factors.

U.S. Environmental Protection Agency. 2000. Science Policy Council. Risk Characterization Handbook. EPA 100-B-00-002; http://www.epa.gov/osa/spc/htm/2riskchr.htm.

U.S. Environmental Protection Agency. 1986. Health Effects Assessment for Asbestos. Washington, D.C., EPA/540/1-86/049. NTIS PB86134608.

U.S. Environmental Protection Agency , Office of Solid Waste and Emergency Response. 1999. EPA Federal Facilities: Issuance of Final Guidance: Ecological Risk Assessment and Risk Management Principles for Superfund Sites. http://www.epa.gov/swerffrr/documents/eco_risk_superfund.htm

U.S. Environmental Protection Agency. 1998. Guidelines for Ecological Risk Assessment. EPA/630/R095/002F. http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=12460

U.S. Environmental Protection Agency. 1996. Health Effects of Inhaled Crystalline and Amorphous Silica., EPA/600/R-95/115

U.S. Environmental Protection Agency. 1996. OSWER National Risk-Based Priority Panel. http://www.epa.gov/superfund/programs/nrbpp/index.htm

Utsunomiya S., Ewing R. 2003. Application of High-Angle Annular Dark Field Scanning Transmission Electron Microscopy, Scanning Transmission Electron Microscopy-Energy Dispersive X-ray Spectrometry, and Energy-Filtered Transmission Electron Microcopy to the Characterization of Nanoparticles in the Environment. Environ. Sci. Technol. 2003, 37, pp.786-791. http://www.geo.lsa.umich.edu/relw/groupmembers/satoshi/homepage2/EST-haadf03.pdf

Wang, L., Wang, L.Y., Zhu, C.Q., Wei, X.W., Kan, X.W. (2002). Preparation and application of functionalized nanoparticles of CdS as a fluorescence probe. Analytica Chimica Acta 468(1): 35-41.

Warheit D.B. et al. 2004.. Comparative Pulmonary Toxicity Assessment of Single-wall Carbon Nanotubes in Rats. Toxicological Sciences 77:117-125.

Wiesner, M.R., 2003. Environmental Implications of Nanotechnologies. Environmental Engineer 39(3): 8-11.

Wilson, F.J., Jr., Hiller, F.C., Wilson, J.D., and Bone, R.C. 1985 Quantitative deposition of ultrafine stable particles in the human respiratory tract. J. Appl. Physiol. 58: 223-229.

Wilson W.E., Chow J. C., Claiborn C., et al. 2002. Monitoring of Particulate Matter Outdoors. Chemosphere 49(9):1009-1043.

World Resources Institute. 2000. The Weight of Nations: Material Outflows from Industrial Economies. .

Wu, J., Boyle, E., Sunda, W., Wen, L-S. 2001. Soluble and colloidal iron in the oligotrophic North Atlantic and North Pacific. Science, 293: 847-5-849.

Wong. C.P. et al March 2005 press release http://gtresearchnews.gatech.edu/newsrelease/adhesive.htm; Abstract posted at: http://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.abstractDetail/abstract/6352/report/0

Yang, L., Watts, D.J. 2005. Particle surface characteristics may play an important role in phytotoxicity of alumina nanoparticles. Toxicol. Lett. 158:122-132.

Zepp, R. G., Sheldon, W.; Moran, M.A. 2004. Dissolved Organic Fluorophores in Southeastern US Coastal Waters: Correction Method for Eliminating Rayleigh And Raman Scattering Peaks in Excitation-Emission Matrices. Marine Chem. 89(1-4):15-36.

Zhang, W. 2003. Nanoscale Iron Particles for Environmental Remediation: An Overview. J. Nanoparticle Res. 5: 323-332.

Zitko V. 1981. Uptake and excretion of chemicals by aquatic fauna. pages 67 to 78 in Stokes PM (ed.) Ecotoxicology and the Aquatic Environment. Pergamon Press.

Conversation with Hongda Chen. May, 2005. Dr. Chen expressed great interest in nano-fertilizers, and asked to be kept abreast of any work in this area, though he is not funding it.

Appendix A: Glossary of Nanotechnology Terms

Aerosol: A cloud of solid or liquid particles in a gas.

Array: An arrangement of sensing elements in repeating or non-repeating units that are arranged for increased sensitivity or selectivity.

Biomimetic: Imitating nature and applying those techniques to technology.

Buckyballs: see fullerenes

Catalyst: A substance, usually used in small amounts relative to the reactants, that modifies and increases the rate of a reaction without being consumed or changed in the process..

Dendrimers: artificially engineered or manufactured molecules built up from branched units called monomers. Technically, a dendrimer is a branched polymer, which is a large molecule comprised of many smaller ones linked together.

Diamondoid: Nanometer-sizes structures derived from the diamond crystal structure.

Electron beam lithography: Lithographic patterning using an electron beam, usually to induce a change in solubility in polymer films. The resulting patterns can be subsequently transferred to other metallic, semiconductor, or insulating films.

Engineered/manufactured nanoparticles: Engineered/manufactured refers to those nanoparticles that do not occur naturally but are purposefully made. These are in contrast to incidental particles such as combustion ultrafine particles or occupational fumes like beryllium or welding fumes.

Exposure assessment: The determination or estimation (qualitative or quantitative) of the magnitude, frequency, duration, route, and extent (number of people) of exposure to a chemical, material, or microorganism.

Fullerenes/C_{60}: Pure carbon molecules composed of at least 60 atoms of carbon. Because a fullerene takes a shape similar to a soccer ball or a geodesic dome, it is sometimes referred to as a buckyball after the inventor of the geodesic dome, Buckminster Fuller, for whom the fullerene is more formally named.

Intentionally produced nanomaterials: Nanomaterials that do not occur naturally but are purposefully made. These include both deliberate engineering of particles by certain chemical and/or physical processes (referred to as "bottom-up" production) to create materials with specific properties not displayed in their macro-scale counterparts, as well as the use of such manufacturing processes as milling or grinding ("top-down" production) to produce nano-

sized particles that may or may. These are in contrast to incidental particles such as combustion ultrafine particles or occupational fumes like beryllium or welding fumes.

Manufacturing processes: General term used to identify the variety of processes used in the production of the part. Processes may include plastic injection molding, vacuum forming, milling, stamping, casting, extruding, die-cutting, sewing, printing, packaging, polishing, grinding, metal spinning, welding, and so forth.

Metallocenes: a compound consisting of a group of atoms bound to a metal, where the group includes two pairs of carbon atoms.

Nano-: a prefix meaning one billionth.

Nanometer: one billionth of a meter.

Nanobiology: A field of study combining biology and physics which looks at how nature works on the nanometer scale, particularly how transport takes place in biological systems. The interaction between the body and nanodevices are studied, for example, to develop processes for the body to regenerate bone, skin, and other damaged tissues.

Nanochemistry: A discipline focusing on the unique properties associated with the assembly of atoms or molecules on a nanometer scale. Chemistry dealing with individual molecules where quantum effects can be significant, and new methods of carrying out chemical reactions are possible.

Nanodevice: Functional nanoscale components.

Nanoelectronics: Electronics on a nanometer scale, whether by current techniques or nanotechnology; includes both molecular electronics and nanoscale devices resembling today's semiconductor devices.

Nanomaterial: Materials with basic structure of the nanometer size.

Nanometer: one billionth of a meter.

Nanoparticle: Free standing nanostructured material, consisting of between a few hundred to hundreds of atoms.

Nanoscale: having dimensions measured in nanometers.

Nanoscience: the interdisciplinary field of science devoted to the advancement of nanotechnology.

Nanostructures: structures at the nanoscale; that is, structures of an intermediate size between molecular and microscopic (micrometer-sized) structures.

Nanotechnology: Research and technology development at the atomic, molecular or macromolecular levels, in the length scale of approximately 1 - 100 nanometer range; creating and using structures, devices and systems that have novel properties and functions because of their small and/or intermediate size; and the ability to control or manipulate on the atomic scale.

Nanotube: Tubular structure, carbon and non-carbon based, with dimensions in nanometer regime.

Nanowire: High aspect structures with nanometer diameters that can be filled (nanorods) or hollow (nanotubes) and can be made from conducting or semiconducting materials.

$PM_{0.1}$: Particulate matter less than 0.1 micrometers in diameter

$PM_{2.5}$: Particulate matter less than 2.5 micrometers in diameter

PM_{10}: Particulate Matter less than 10 micrometers in diameter

Quantum dot: Semiconductor materials that have typical dimensions between nanometers and a few microns and emit varying colors of light depending on their size and composition.

Self-Assembled Monolayers on Mesoporous Supports (SAMMS): nanoporous ceramic materials that have been developed to remove contaminants from environmental media.

Self-assembly: The ability of objects to assemble themselves into an orderly structure. Routinely seen in living cells, this is a property that nanotechnology may extend to inanimate matter.

Self-replication: The ability of an entity such as a living cell to make a copy of itself.

Superlattice: nanomaterials composed of thin crystal layers. The properties (thickness, composition) of these layers repeat periodically.

Unintentionally produced nanomaterials: Nano-sized particles that occur naturally in the environment, such as viruses or volcanic ash, and nanoparticle byproducts of human activity such as diesel exhaust particulates, occupational fumes like beryllium or welding fumes, or other friction or airborne combustion byproducts.

Appendix B: Principles of Environmental Stewardship Behavior

What does a good environmental steward do?
(based on statements by environmental stewards and others)

Exceeds required compliance. An environmental steward views environmental regulations only as a floor, not a target.

Protects natural systems and uses natural resources effectively and efficiently. An environmental steward considers and reduces the household, community, farm or company's entire environmental footprint. A steward safeguards and restores nature at home and elsewhere. A steward follows the pollution prevention hierarchy of acting first to prevent pollution at its source. A steward uses less toxic, more environmentally benign materials, uses local resources and conserves natural resources whenever possible. A steward reuses and recycles materials and wastes and seeks sustainability.

Makes environment a key part of internal priorities, values and ethics, and leads by example. Environmental stewards make decisions through their own volition that will prevent or minimize environmental harm. They anticipate, plan for, and take responsibility for economic, environmental and social consequences of actions. A steward approaches business strategies, policy planning, and life as an integrated dynamic with the environment. A steward acts in innovative ways, using all available tools and creating or adding value. A steward adopts holistic, systems approaches.

Holds oneself accountable. An environmental steward measures the effects of behavior on the environment and seeks progress. A steward applies an understanding of carrying capacity to measure progress and update objectives to achieve continuous improvement, often using indicators, environmental assessments, and environmental management systems.

Believes in shared responsibility. An environmental steward recognizes obligations and connections to all stakeholders- shareholders, customers, communities at home and elsewhere. For a company, this means being concerned with the full life cycle of products and services, beyond company boundaries, up and down the supply chain (including consumers and end-of-life). For a community, this means to protect the environment for all members and takes responsibility for effects on downstream air pollution, and effects of wastes disposed elsewhere. A steward operates with transparency. They encourage others to be collaborative stewards.

Invests in the future. An environmental steward anticipates the needs of future generations while serving the needs of the present generation. Their actions reflect possible changes in population, the economy and technology. A steward guides the development of technology to minimize negative environmental implications and maximize potential environmental stewardship applications. A steward values and protects natural and social capital. They seek

preventative and long-term solutions in community development, business strategy, agricultural strategy, and household plans.

Appendix C: Additional Detailed Risk Assessment Information

C1 Environmental Fate of Nanomaterials - Additional Details on Information Currently Available

C1.1 Fate of Nanomaterials in Air

Although most nanomaterials do not demonstrate high vapor pressures indicative of volatile chemicals, when released to the atmosphere nanomaterials behave like a gas or vapor demonstrating Brownian motion. Several processes influence the fate of airborne nanomaterials in addition to their initial dimensional and chemical characteristics: the length of time the particles remain airborne, the nature of their interaction with other airborne particles or molecules, and the distance that they may travel prior to removal. The processes important to understanding the potential atmospheric transport of nanosized particles are diffusion, agglomeration, wet and dry deposition, and gravitational settling.

Particles with aerodynamic diameters in the nanoscale range (<100 nm) follow the basic laws of gaseous diffusion when released to air. The rate of diffusion is inversely proportional to particle diameter, while the rate of gravitational settling is proportional to particle diameter (Aitken et al., 2004).

Airborne particles are classified by size and behavior into three groups or modes: the coagulation mode (diameters <80 nm), the accumulation mode (diameters >80 nm and <2 μm), and the coarse mode (diameters >2 μm) (Bidleman, 1988; Preining, 1998; Spurny, 1998). Particles in the coagulation mode are short-lived because they rapidly coagulate to form larger particles. Particles in the coarse mode are subject to gravitational settling.

Particles in the accumulation mode remain suspended in air for the longest time. Their main modes of physical removal from the air are wet and dry deposition. Dry deposition velocities, and in turn particle deposition rates, are at a minimum for particles with diameters of 300-500 nm; larger particles deposit faster due to increased gravitational attraction, and smaller particles deposit faster due to increased Brownian diffusion (Atkinson, 2000; Bidleman, 1988). For example, nanoparticles form naturally from the condensation of gases from combustion (as in forest fires or vulcanism). The initial particles, which are about 10 nm in diameter, rapidly coalesce to form aggregates of about 100 nm, which can remain suspended in the air for days or weeks (Royal Society, 2004; Dennenkamp et al., 2002). Wet deposition of particles is dependent on that particle's washout ratio, the ratio of the chemical's concentration in the aqueous phase to its concentration in air. Values of W typical for particle-associated chemicals have been correlated to residence times of about 20 days in air based on a constant precipitation rate of 1 meter per year (Atkinson, 2000).

Deposited nanoparticles are typically not easily resuspended in the air or re-aerosolized because of the action of van der Waals and other weak forces (Colvin, 2003;

Aitken et al., 2004). For example, in an experiment to test the ready suspension of carbon nanotubes, samples of single-walled carbon nanotubes and samples of fumed alumina were agitated at a variety of speeds and the particle sizes of the resultant aerosol were measured. It was found that the bulk of the nanotubes was aerosolized as clumps greater than 1 μm, and the fraction of suspended particles <0.5 μm decreased rapidly over time (within 15 minutes). Significant amounts of particles with sizes <100 nm were generated only under vigorous agitation, but the particles were not characterized. For comparison, the fumed alumina was aerosolized at concentrations about 100 times that of the carbon nanotubes (Baron et al., 2003). Carbon nanotubes are known to clump together due to the action of van der Waals forces along the length of the tubes. Because physical particle size is a critical factor affecting the properties of nanomaterials, maintaining particle size during the handling and use of nanomaterials is a priority. Current research is underway to produce carbon nanotubes that do not form clumps either via functionalizing the tubes themselves, or by treatment with a coating or dispersing agent (Royal Society, 2004; Colvin, 2003), so future materials may be more easily dispersed.

The atmospheric chemistry of nanomaterials has not been described in the literature. Many nanosized particles are reported to be photoactive (Colvin, 2003), but their susceptibility to photodegradation in the atmosphere has not been studied. It is generally assumed (though not always true) that organic compounds are unreactive with respect to oxidants such as hydroxyl radicals when bound to particles in the atmosphere; however no studies have examined the reactivity of the particle itself. Reactivity to atmospheric oxidants such as ozone or photochemically produced hydroxy radicals will depend on the chemical nature of the nanoparticle, and general statements are not possible at this time. Although not volatile as vapors, nanosized particles can be suspended in the atmosphere long enough for photooxidation to be possible. Nanomaterials are known to readily adsorb a variety of materials, and many act as catalysts. No studies are currently available that examine how nanosized adsorbants and chemicals sorbed to them might influence their respective atmospheric chemistries.

C1.2 Fate of Nanomaterials in Soil

The fate of nanomaterials released to soil will vary depending upon the physical and chemical characteristics of the nanomaterial. Nanomaterials released to soil can be strongly sorbed to soil due to their high surface areas, and therefore be immobile. On the other hand, nanomaterials are small enough to fit into smaller spaces between soil particles, and might therefore travel farther than larger particles before becoming trapped in the soil matrix.

The strength of the sorption of any engineered/manufactured nanoparticle to soil will be dependent on its size, chemistry and the conditions under which it is applied. For example, iron (Fe^0) colloids tend to agglomerate and adhere to soil surfaces. Other studies have demonstrated the differences in mobility of a variety of insoluble nanosized materials in a porous medium. Based on their adherence to the model medium, their mobilities were estimated for a sandy soil aquifer. Mobilities (as distance for $C/C_{int} = 0.1\%$, where C_{int} is the initial aqueous concentration and C is the aqueous concentration at a particular distance from

the initial point) ranged from 14 meters for fullerol to 0.1 meter for C_{60} aggregate, anatase and ferroxane. Some interesting contrasts were observed: single walled carbon nanotubes (0.07-1.1 x 80-200 nm) were about 100 times more mobile than C_{60} aggregates (aggregate size 160 nm); the C_{60} aggregates showed the same mobility as anatase (TiO_2, 198 nm) and ferroxane (303 nm); finally, smaller particles of silica (57 nm) were about 10 times more mobile than larger silica particles (135 nm) (Lecoanet et al., 2004). The mobility of the materials investigated in these studies does not appear to be dependent on the velocity of the aqueous solution through the sorbant medium. (Zhang, 2003; Lecoanet and Wiesner, 2004).

The properties of the soil environment can affect nanomaterial mobility. For example, the mobility of mineral colloids in soils and sediments is strongly affected by zero point of charge (ZPC). Most mineral colloids have a surface charge that depends on pH of the environment. Above ZPC surface is negatively charged, below ZPC it is positive.

Surface photoreactions provide pathway for nanomaterial transformation on soil surfaces. Humic substances, common constituents of natural particles, are known to photosensitize a variety of organic photoreactions, including those mediated by singlet oxygen, a reactive, excited form of dioxygen. Singlet oxygen photo production occurs on soil and other natural surfaces that are exposed to sunlight. Studies of nanomaterial transformations in field situations are complicated by the presence of naturally occurring nanomaterials of similar molecular structures and size ranges. Iron oxides are one obvious example. Also titanium oxide concentrates in soils from rock form quantitatively, so dependably so that the titanium concentration ratios in soil to rock often are used to infer how many feet of rock are needed to form each foot of soil.

More research is needed to assess the mobility of nanomaterials in soils. A side-by-side comparison of nanomaterials with micron-sized or bulk material of the same composition would be useful to assess how the size of the material influences its mobility. Basic research is also needed to determine the mobilities of novel materials that have no corresponding bulk material. An example of this would be fullerenes and nanotubes. Although some comparisons to soot, carbon black, or graphite are possible, fullerenes and nanotubes exhibit novel properties, and it is not well understood how these properties may affect soil adsorption and desorption.

C1.3 Fate of Nanomaterials in Water

The aqueous solubility/dispersability of nanomaterials will vary depending upon the nanomaterial in question. At nanoscale dimensions, the distinction between a dissolved solute and a suspended colloid is not readily defined. Some functionalized carbon nanostructures, such as fullerols, are claimed to be water soluble, and nanosized particles of water-soluble polymers are being investigated for a variety of uses. Insoluble particles will be subject to diffusion, dispersion, agglomeration, and settling in water. As is the case for airborne particles, waterborne nanoparticles are expected to settle more slowly than larger particles of the same material.

Dispersed insoluble nanoparticles can be stabilized in hydrophobic microenvironments provided by naturally-occurring colloids made up of humic acids and other organics, which would also delay settling from the water column. Insoluble materials may also form stable colloidal suspensions in water. For example, researchers at Rice University have reported that although C_{60} is insoluble in water, it spontaneously forms aqueous colloids containing nanocrystalline aggregates. Dubbed nano-C_{60} or n-C_{60}, these aggregates have diameters of about 50 nm and carry a negative charge on their outer surfaces. The size of the aggregates depends on the pH of the water and the speed of mixing when C_{60} is introduced to water. The concentration of the suspensions can be as high as 100 ppm, but are more typically in the range of 10-50 ppm. The stability of the particles and suspensions are sensitive to salts content. At salt concentrations typical of groundwater, n-C_{60} suspensions are stable for months. In simulated seawater, they sink to the bottom within hours. (CBEN, 2005; Fortner et al., 2005). The researchers also observed that while C_{60} will not partition from an organic solution (toluene) into water, n-C_{60} does not readily partition from water into toluene. n-C_{60} can also become resuspended in water after the original aqueous suspension has been evaporated; however, the conditions (such as the presence of soil) for this experiment were not reported (European Commission, 2004).

No studies have been published investigating the sorption of nanomaterials to soil and sediment particles in the water column. One report states that nanosized particles tend to sorb to sediment and soil particles and are immobilized due to their high surface area to mass ratio (Oberdorster et al., 2005). However, the source cited in that paper (Lecoanet and Wiesner, 2004) illustrates that the rate of sorption to porous media from aqueous solution depends on the nature of the particles. The Lecoanet and Wiesner study used artificial media to mimic soil and sediment environments. Due to their high surface area to mass ratios, nanosized particles have the potential to sorb to suspended soil and sediment particles as described in the Oberdorster paper. Although the rate of removal of engineered/manufactured nanomaterials by sorption has not been investigated, it is likely that various heterogeneous processes on environmental surfaces are important in the fate of nanomaterials. In the case of abiotic processes, both thermal and photochemical reactions in particle/water systems are likely involved in nanomaterial transformations. As used here, the term "abiotic" refers to processes that do not involve direct participation of metabolically active organisms. By this definition, abiotic processes include reactions involving chemicals of biological origin, such as extracellular enzymes or iron porphyrins.

Certain organic and metallic nanomaterials likely will be reduced in anaerobic sediments. From past studies, it is known that several types of organic compounds are generally susceptible to reduction in anaerobic sediments: chlorinated hydrocarbons, nitroaromatic compounds, N- and O-alkylated organic compounds, azo compounds, and quinones, among others. Complexation by natural organic ligands such as humic colloids can facilitate redox reactions that transform metals in anaerobic sediments, e.g., the reduction of iron oxides in anaerobic sediments. Functional groups in the humic substances such as quinones facilitate reduction by acting as an electron shuttle from reducing substances in the bulk water (see Nurmi et al. 2005 and references therein).

Particles in the upper layers of aquatic environments, on soil surfaces, and in water droplets in the atmosphere are exposed to sunlight. Light-induced photoreactions often are an important fate in such environments. Research has demonstrated environmentally significant abiotic photoreactions involving particle surfaces (Helz et al. 1994). Also, heterogeneous photoreactions on metal oxide surfaces are increasingly being used as a method for drinking water, wastewater and groundwater treatment. Past research has focused on heterogeneous photoreactions of iron oxides that apparently involve direct photolysis of inner sphere surface complexes of iron with various ligands. These photoreactions initially involve the reduction of iron (III) to iron (II). In addition, iron complexes can be reduced by superoxide ions that are produced by photochemical processes in sunlit environments.

Indirect photoreactions involving particles have also received considerable attention during the past few years. Most of this research can be subdivided into two broad areas: reactions involving reactive intermediates produced by surface photolysis, such as semiconductor-type mechanisms, and reactions involving electronically excited surface species. Heterogeneous organic photocatalysis involving particles with semiconducting properties has received considerable attention recently. Semiconductors such as titanium dioxide and zinc oxide have been shown to effectively catalyze both the reductions of halogenated chemicals and oxidation of various other pollutants and heterogeneous photo-catalysis has been used for water purification in treatment systems.

The fate of nanosized particles in wastewater treatment plants is not well characterized in the literature. Wastewater is subjected to multistep processes in treatment plants, including screening to remove debris, gravitational removal of large particulates, combination, and agitation with and digestion by activated sludge, settling, filtration, and chemical treatment (Cl_2 and SO_2) to destroy pathogens. Chemicals in a wastewater treatment plant are removed from the effluent via volatilization, sorption to sludge, biodegradation, and in some cases, chemical reaction. The most likely processes to affect nanosized particles are sorption and chemical reaction. The ability of either of these to immobilize or destroy the particles will depend on the chemical nature of the particle and the residence times in each of the compartments of the treatment plant. As noted earlier in the section on soils, the ZPC and thus sorption, coagulation and mobility of mineral colloids is strongly affected by pH. It has been demonstrated that the sorption of different nanomaterials to model soils from aqueous solution can vary considerably (Lecoanet et al., 2004). It is therefore impossible to say that all nanomaterials will be captured by sorption to sludge in wastewater treatment. Current research in this area includes the production of microbial granules that are claimed to remove nanoparticles (fluorescent microspheres, 100 nm) from simulated wastewater (Ivanov et al., 2004). Further research is needed to determine the ability of various nanosized particles to adsorb to activated sludge in order to characterize the fate of nanomaterials in wastewater treatment plants. Nanomaterials that escape sorption may be removed from the effluent via settling. As discussed earlier, the rate of gravitational settling of nanomaterials in fluids, whether the fluid is air or water, will be dependent on particle diameter, and the smaller particles will settle more slowly.

C1.4 Bioavailability and Bioaccumulation of Nanomaterials

The bioavailability of specific nanomaterials in the environment will depend in part on the particle. Complexation of metallic nanomaterials may have important interactive effects on biological availability and photochemical reactivity. For example, the biological availability of iron, is dependent on its free iron concentrations in water, and the free iron concentrations are affected by complexation or, in the case of metal oxides, by redox transformations. Complexation reduces biological availability by reducing free metal ion concentrations and dissolved iron is quantitatively complexed by organic ligands. Solar UV radiation can interact with these processes by inducing direct photoreactions of the complexes, by enhancing redox reactions between the ligands and metal oxides, or by indirect photoreactions in which photochemically-produced reactive oxygen species react with the complexes.

C1.5 Potential for Interactions Between Nanomaterials and Other Organic or Inorganic Contaminants

Engineered/manufactured nanomaterials are being created and studied because their small sizes, high surface areas, and novel electrical properties affect their interactions with other chemicals and with cells, tissues, and organisms. Two of the types of effects under study for possible exploitation are sorption and reaction.

C1.5.1 Sorption research- Detailed description of current information

Several studies investigating the sorption of pollutants to nanosized materials have recently been reported in the literature.

1. The sorption of naphthalene to C_{60} from aqueous solution was compared to activated carbon (Cheng et al., 2004). Not surprisingly, the investigators observed a correlation between the surface area of the particles and the amount of naphthalene adsorbed from solution. Activated carbon with a surface area of about 1000 m^2/g had the highest measured solid-water distribution constant of $10^{5.17}$ mL/g. Large aggregates of C_{60} (20-50 μm) had a surface area of 0.07-0.17 m^2/g, and a distribution constant of $10^{2.39}$ mL/g. Small aggregates of C_{60} (1-3 μm) were reported to have a surface area >10 times that of the large aggregates, and had a measured distribution constant of $10^{4.28}$ mL/g. The authors apparently did not investigate "nano-C_{60}", crystalline aggregates on the order of 50 nm in diameter.

2. Nanoparticles made of an amphiphilic PEG-modified polyurethane-acrylate polymer (80 ± 15 nm) have been shown to mobilize phenanthrolene (PHEN) from contaminated sandy soil (Tungittiplakorn et al., 2004). The particles have the ability to enhance PHEN desorption and transport it in a manner similar to that of surfactant micelles, but unlike surfactants, the nanoparticles do not sorb to the soil surface. In order to be effective, surfactants must be present at concentrations at or above the critical micelle concentration. Sorption to soil reduces the effective aqueous concentration of surfactants and disrupts the formation of micelles. However, the activity of the nanoparticles is not dependent on maintaining a particular concentration, and therefore provides a more stable environment for the

solubilization of PHEN from soils. In addition, the nanoparticles can be altered to optimize their affinities for particular pollutants by modifying the chemical identity of the polymer. In a followup study, the rate of PHEN biodegradation was measured in aqueous media in the presence and absence of both the nanoparticles and a sandy aquifer soil (Tungittiplakorn et al., 2005). The presence of the nanoparticles increased the initial rate of mineralization of radiolabeled PHEN (measured as $^{14}CO_2$), both with and without the soil. These studies show that these nanoparticles not only enhance the mobility of PHEN, but also increase its bioavailability.

3. Preliminary results report that arsenic irreversibly adsorbs to 15-20 nm magnetite crystals dispersed in water. The arsenic can then be removed from the water by magnetic attraction of the magnetite. This system is being investigated as a purification technique for arsenic-laden drinking water (CBEN, 2005). Another investigator reports that 10 nm magnetite crystals adsorbs Cr(VI) from wastewater (Hu et al., 2004).

4. The adsorption and desorption of volatile organic compounds (VOCs) from ambient air by fullerenes has been investigated. In this study, 9 VOCs were adsorbed to fullerene tubes and later desorbed and recovered with little loss of the adsorbed gas (Chen et al., 2000).

5. Inhalation exposures of benzo(a)pyrene sorbed to ultrafine aerosols of Ga_2O_3 (Sun et al, 1982) and diesel exhaust (140 nm) (Sun et al:, 1984) were studied in rats. The studies showed that when compared to inhalation of pure benzo(a)pyrene aerosols, material sorbed to the gallium oxide had increased retention in the respiratory tract, and increased exposure to the stomach, liver, and kidney.

C1.5.2 Research involving reaction of nanomaterials with environmental contaminants-Detailed description of current information

Many groups are currently investigating the use of nanomaterials for the destruction of persistent pollutants in the environment. Some examples are listed below.

Iron (Fe^0) is a mild reducing agent, and has been used to dechlorinate halogenated solvents, such as tetrachloroethylene, in the environment. Nanoscale iron particles have been demonstrated to be effective in the *in situ* remediation of soil contaminated with tetrachloroethylene. The nanosized iron particles were able to flow with the groundwater and remained active for 4-8 weeks. Reaction times were rapid, with 99% reduction of tetrachloroethylene occurring in a few days. A wide variety of additional pollutants are claimed to be transformed by iron nanoparticles in laboratory experiments, including halogenated (Cl, Br) methanes, chlorinated benzenes, certain pesticides, chlorinated ethanes, polychlorinated hydrocarbons, TNT, dyes, and inorganic anions such as nitrate, perchlorate, dichromate, and arsenate. Further investigations are underway with bimetallic nanoparticles (iron nanoparticles with Pt, Pd, Ag, Ni, Co, or Cu deposits) and metals deposited on nanoscale support materials such as nanoscale carbon platelets and nanoscale polyacrylic acid (Zhang, 2003).

2. Nanosized clusters of C_{60} were shown to generate reactive oxygen species in water under UV and polychromatic light. Clusters with a mean diameter of 100 nm were more active than clusters with a larger diameter of 300 nm (Pickering et al., 2005). Similar colloids have been reported to degrade organic contaminants and act as bacteriocides (Boyd et al., 2005). Fullerol ($C_{60}(OH)_{24}$) has also been demonstrated to produce reactive oxygen species under similar conditions (Pickering and Wiesner, 2005).

The examples cited in this section illustrate how nanomaterials have been demonstrated to alter the partitioning behavior of chemicals between environmental compartments and between the environment and living organisms. Furthermore, several nanoscale materials are reactive toward chemicals in the environment, generate reactive species, or catalyze reactions of other chemicals. These properties are currently under study for use in waste remediation operations. However, the potential also exists for nanomaterials to affect unforseen changes if released to the environment in large quantities.

C2 The Environmental Detection and Analysis of Nanomaterials

C2.1 Overview

The challenge in detecting nanomaterials in the environment is compounded not only by the extremely small size of the particles of 100 nanometers or less but also by their unique physical structure and chemical characteristics

Particle analytical techniques can generally be classified as ensemble or single-particle techniques. With ensemble techniques, a signal from an individual particle cannot be isolated. Instead, ensemble techniques receive signals from multiple particles simultaneously. Laser light diffraction is a commonly employed ensemble technique. In contrast with ensemble techniques, single-particle techniques isolate and identify signals from individual particles. Statistical information for groups of particles can be obtained by processing data from many different individual particles. A common example of a single-particle technique is optical imaging combined with image processing to measure and analyze particles. In general, morphological information, such as shape and aspect ratio, as well as surface information, such as texture and roughness parameters, cannot be obtained using ensemble techniques. Only single-particle techniques that look at individual particles can supply such information. Physical parameters for each particle in a set of particles are recorded to generate a statistical distribution for the entire set of particles.

The following sections describe some of the technologies/methods available for the analysis of nanoscale particles in the environment . The review is subdivided into several sections starting with sampling methods and followed by methods used to measure nanoparticle mass/mass concentrations, surface area, particle count concentration, size, physical structure (morphology), and chemical composition.

C2.2 Sampling

Aerosol nanomaterials can be collected by sampling technologies that isolate particles based upon aerodynamic mobility or electrical mobility. The aerodynamic mobility of a particle is dependent upon the shape, density and size of the particle. For larger size nanoparticle fractions of 50 to 100 nm, cascade impactors have been use to isolate and collect nanoparticles based upon aerodynamic mobility. Cascade impactors consist of a collective series of inertia-based impactors and are limited to fractionating nanometer particles in size ranges of no less than approximately 50 nanometers (McMurry, 2000). With decreasing particle size, the lack of mass and inherent diffusion properties of nanoparticles inhibits the use of inertia-based collection technologies like impactors and cyclones for sample separation and collection (McMurry, 2000). Studies by Cabada et. al.(2004) and Hughes, et. al. (1998) employed the use of a cascade impactor (referred to as a micro-oriface uniform deposit impactor (MOUDI)) to collect nanoparticles in a size range of 56 to 100 nm onto filters for mass and chemical analyses. The sizes of nanoparticles fractions isolated based upon aerodynamic properties are referred to as "the aerodynamic diameter." However, in general, the use of inertia-based sample collection technology for aerosol sampling does not collect sufficient nanomaterial mass to perform gravimetric analysis or many chemical analysis methods (like atomic absorption spectroscopy).

Differential mobility analyzers (DMAs) based upon particle electrical mobility are used to separate and collect aerosol nanometer fractions ranging from 2 to 100 nanometers. Before entering the DMA chamber, the sub-micron particles from an aerosol sample obtain an equilibrium-charge distribution resulting in a known ratio of positives, negative and zero charged particles (Fuch's equilibrium charge distribution). In the DMA the aerosol sample flows around a negatively charged inner cylinder. The electrical mobility of nanoparticles is dependent upon particle shape and size. Negatively charged particles are repelled by the inner cylinder to the outer walls of the DMA. Neutral particles are exited with the excess air. Positively charged particles are attracted to the negative inner cylinder. The electrical mobility of the positively charged particles is inversely related to size. Only positively charged particles within a narrow range of electric mobility have the correct trajectory to exit the DMA through an open slit. Specific nanoparticle size fractions are separated and exited out of the DMA by altering the voltage on the negatively charged inner cylinder. The size of nanoparticles fraction isolated based upon electrical mobility is referred to as the "electrical diameter." Commercial samplers are available that use electrostatic precipitation to collect particle fractions exiting a DMA directly onto a substrate that can be used for electron microscopic analyses (TSI, 2005A).

The material composition of the filter/substrate used to collect the nanometer fraction varies depending upon the type of physical and chemical analyses to be conducted. Composition materials include nylon, Teflon, quartz fibers and aluminum (USEPA, 2004; Turpin, 2000). Where trace metals analyses are involved as in the assessment for quantum dot nanoparticles, high purity filters must be used in order to avoid sample contamination during trace metal analyses.

For the analysis of soil, water and sediment samples, ultrafiltration (Wu et al., 2001; Wiesner, 2003) and ultracentrifugation (Colfen, 2004) have been used to isolate nanoparticle fractions. In the case of soil, sediment, and turbid water samples, a series of filtrations with progressively smaller filter or membrane sizes can be helpful. However, the effective pore size of the filter can be decreased during filtration by the accumulation of particles, i.e., by a "clogging" effect. This effect depends on the volume of samples as well as the nature and concentration of the particles.

The many challenges of sampling for nanoparticles include the agglomeration of nanoparticles with nanoparticles and other particulate matter forming agglomerates far greater in size than 100 nanometers. In the case of atmospheric particles, the surface absorption of water and volatile chemicals can affect size separation efforts, as can the loss of semi-volatile nanomaterials due to volatilization during sample collection and/or analysis and the loss of nanomaterials during sampling and analysis due to the development of static charges on the particles.

C2.3 Mass Analysis of Atmospheric Particles

As stated previously, bulk sampling and mass analysis of aerosol particle between 1 and 100 nm is challenging due to the lack of mass and diffusion properties. Success has been noted by Cabada et. al. (2004) who employed the use of an inertia-based impactor to collect nanoparticles between 56 nm and 100 nm onto Teflon filters for analysis using a high-precision microbalance. The actual time of collection required to obtain a sample with sufficient mass for accurate gravimetric measurement (sensitivity of $\pm$ 1 μg (McMurry, 2000) will vary depending upon the concentration of nanoparticles in the atmospheric environment being sampled. The accuracy of nanoparticle gravimetric analyses can also be significantly impacted by the amount of moisture occluded to particles and the surface absorption of semi-volatile organic compounds. It must also be noted that in cases where the nanomaterials of interest include chemical complexes that are semivolatile, mass loss can be experienced due to particle volatilization resulting from elevated sample inlet temperatures used to drive off sample moisture and extreme pressure gradients created during collection using impactor-based systems.

Real-time aerosol particle mass concentration analysis instruments have been developed in support of the EPA Air Quality Program (USEPA, 2004). These technologies were designed for the real-time mass analysis of particles in sizes ranging up to 10 microns. These instruments include the TEOM (Tapered Element Oscillating Microbalance, Rupprecht and Patashnick, 2005) and the Continuous Ambient Mass Monitor (CAMM). The detection technologies employed in particle mass analysis instruments include Beta gauges, piezoelectric crystals and harmonic oscillating elements (McMurry, 2000). An assessment of these mass concentration analysis instruments needs to be made as to their applicability to analyzing the mass concentration of nanometer-sized particles. Descriptions of these technologies are available from the 2004 EPA Air Quality Criteria for Particulate Matter (USEPA, 2004).

An approximate sample mass concentration for nanoparticles can be calculated by isolating the desired nanoparticle size fraction of interest, obtaining a particle count concentration, and multiplying by a known or approximate particle density. Available technologies for nanoparticle size fractioning and particle counting are described in the following.

C2.4 Size Separation, Number Concentrations, Surface Area and Physical Structure

Air particulate analysis technologies have evolved and are capable of analyzing aerosol samples for nano-sized particle concentrations in real time or near real time. These technologies are designed for field use and require minimal or no attention once they are in operation.

Aerosol grab samples are taken through a size-selective inlet where an impactor or a cyclone removes unwanted larger particles based upon inertia properties (Koropchak, J.A. et al., 1999; McMurry, 2000). Particles exiting the particle separation chamber are electrostatically charged. The particles are then passed though a bipolar ion neutralizer that brings the charge level to the aerosol particles to a Fuch's equilibrium charge distribution. At this point only a fraction of the particles retains a positive or negative charge. As explained in section A2.2 on sampling, DMA technology is capable of separating nanoparticle fractions in the 2 to 100 nm range by exploiting the different electrical mobility of various size fractions of nanoparticles.

In order to obtain particle concentration data, the output of the DMA must proceed to a particle-counting instrument. One of the most widely used type of instruments for particle counting is the condensation particle counter (CPC), an instrument capable of detecting particles as small as 3 nanometers (Koropchak, J.A. et al., 1999; McMurry, 2000). Condensation particle counters are also referred to as condensation nuclei counters (CNCs) or Aitken Nuclei Counters (ANCs). CPCs operate by supersaturating a vapor (water, isopropyl alcohol, or butyl alcohol) about the particles from an incoming sample stream. This results in the formation of a droplet some 100 to 1000 times larger than the initial particle size. The formed condensate droplets are then passed through an optical detector where the light attenuation is measured, results being reported as a concentration. Hand-held battery-powered CPCs are commercially available at relatively low costs. The supersaturation required to activate particles increases with decreasing particle size. Particles at approximately 3 nanometers in size require supersaturation levels of several hundred percent. At these high supersaturation levels, vapors can undergo self-nucleation resulting in particle counting errors (McMurry, 2000). Another technology used for particle counting is a cloud condensation counter (CCN). In contrast to CPCs, cloud condensation counters use only water as the vapor generation fluid and are operated at supersaturation levels much lower than CCN. CCN techniques are capable of detecting particles down to 40 nanometers (McMurry, 2000).

More sophisticated instruments are commercially available that combine DMA with particle counting technology into one instrument. These instruments, which are referred to as scanning mobility particle size analyzers (SMPS), not only provide particle-counting data but

also measure aerosol particle size distribution from 10 nm to several hundred nanometers. Figure A1 provides a general schematic of the basic components of an SMPS. As stated previously, only particles within a narrow electrical mobility range and in turn size, are focused by the DMA onto an open slit exiting the DMA. From the exit slit, the particles flow into the CPC where they are counted. The approximate time for one scan (DMA set at a single negative potential) is a few minutes. This is the time needed to provide a count for the total number of particles at a certain particle size (as defined by electrical mobility). Additional particle size fractions can be quantified on a fraction-by-fraction basis by changing the electrical potential of the DMA thereby focusing the trajectory of another particle size onto the open slit leading to the CPC.

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

Optical particle counters (OPCs) using lasers as light sources can detect nanoparticles down to approximately 50 nanometers (McMurry,2000). These technologies use a photodetector to measure the amount of scattered light by individual particles. The photodetector produces a voltage pulse based upon the scattered light that is proportional to particle size. The relationship between voltage pulse and particle size is dependent upon appropriate calibration curves. Accuracy of these techniques is challenging if the OPC is not calibrated using particles of similar physical properties (shape, refractive index and morphology).

Aerosol time of flight mass spectrometers (ATOFMS) can provide aerodynamic particle size characterization in near real time for particles as small as 10 nm (Chow 2002). In some designs, a two laser system is employed to access particle velocity which in turn is correlated to particle size (TSI, 2005C).

Another technology for assessment of the size of particles in an aerosol stream involves the use of diffusion batteries. They are simple and rugged in design and can be used in hostile environments such as in-stack sampling (McMurry, 2000). Diffusion batteries are designed on the principal that as nanoparticle sizes decrease, the rate at which they deposit on nearby surfaces increases. With diffusion batteries, aerosol flows through a series of fine capillaries or fine wire-mesh screens where fine particulates are deposited on the surfaces. Based upon the rate of decay in aerosol concentration observed through the series of capillaries or screens, a particle size distribution can be calculated.

For water samples, particle size analysis of nanoparticles can be performed *in situ* by Dynamic Light Scattering (DLS) or Photon Correlation Spectroscopy (PCS). DLS uses scattered light to measure the diffusion rate of particles. Particle size is deduced from observed particle diffusion rates.

The technologies described above, although sensitive to the detection of particles only a few nanometers in size, are limited by their inability to distinguish single nanoparticles from a particle that consists of an agglomeration of smaller particles. In addition, there is a great deal of interest in the correlation of human toxicity and exposure to nanoparticle surface area versus nanoparticle number concentration and mass concentrations. Technology is available that provides data relative to total nanoparticle surface area. The Epiphaniometer is a device that may be applicable in assessing accurate particle sizes at the nanometer level (Aitken et. al., 2004). The Epiphaniometer passes aerosol samples through a charging chamber where lead isotopes created from the decay of actinium attach to particle surfaces. The particles are then passed through a capillary and onto a collecting filter. The amount of radioactivity measured in the collected sample is proportional to the amount of surface area allowing for an assessment of particle size. For a set mass, the smaller the particle size, the greater the surface area. More recently, the development by TSI of a nanoparticle surface area monitor based upon the diffusion charging of particles followed by electrometer detection provides data that correlates with the deposition of airborne nanoparticles in human respiratory systems (TSI, 2005D). These real time analyses are capable of assessing particles in the 10 nm to 1000 nm range.

For air, water, sediment or soil samples collected onto a filter or substrate, the physical characterization of nanoparticles on a particle-by-particle basis can be obtained through the use of scanning electron microscopy (SEM) and transmission electron microscopy (TEM) techniques (Kocum et al, 2000; Lin et al., 2002; Nurmi et al., 2005) These methods can provide detailed particle size, shape and structure, information that can be used to identify the type of nanoparticles in question (i.e. fullerenes, quantum dots, nanowires, etc.,). Samples are collected directly onto or re-deposited onto substrates supported by the SEM or TEM instrumentation. Sample particle loading must be controlled in order for effective analysis. In contrast to automated particle size aerosol characterization technologies like SMPS and FMPS, electron microscopic analyses are expensive, require sample collection and preparation and do not provide real-time data. However, in contrast to automated particle characterization technologies, both SEM and TEM provide definitive information concerning the physical characterization of nanoparticles. Physical structure and size characterization of single-particles can also be accomplished using a relatively new technology, atomic force microscopy (AFM) (Sgro, L.A., 2003). AFM uses the interaction of van der Waals forces between a microscopic probe tip and the nanoparticles in question lying on a substrate. AFM information includes the height and topology of the nanoparticle. Fluorescence techniques also can be used to characterize nanomaterials. Naturally-occurring organic colloids can be characterized by excitation-emission matrix (EEM) fluorescence spectroscopy (Zepp et al., 2004). Moreover, the fluorescence techniques have been used to characterize nanoparticles of cadmium sulfide (Wang et al., 2002).

C2.5 Chemical Composition

Instruments have been developed by academia and commercial entities that along with particle size, provide chemical profiles of nanometer aerosol particles in near real time (Chow, 2002). Samples are taken directly from the atmosphere and analyzed for particle size

and particle composition with no additional sample preparation by the analyst. Aerosol time of flight mass spectrometers (ATOFMS) are capable of analyzing single particles with sizes as low as 10 nanometers (Chow, 2002, TSI 2005C). In some designs, a two laser system is employed to access particle velocity which in turn is correlated to particle size. Lasers are also used to ionize the particles. The ionized particles then travel to a mass spectrometer for ion characterization. Some instruments employ a bipolar ion detector where both positive and negative ion mass spectra are obtained to characterize the chemical composition of the particle based on detected inorganic and organic chemical fragments from the particle. Portable ATOFMS instruments are commercially available for indoor-air quality monitoring (TSI, 2005C).

For off-line single-particle chemical analysis of collected samples, laser microprobe mass spectrometry (LAMMS) can provide chemical composition information including trace metals and organics analyses. Electron microscopy techniques like scanning TEM with energy dispersive x-ray diffraction (TEM EDX) are also capable of providing single particle chemical profiles on collected samples. An advancement in scanning TEM technology called high angle annular dark field (HAADF) TEM EDX has proven to be an excellent tool for the detection and analysis of nanoparticles containing metals, metals characteristic of quantum dots (Utsunomiya, Ewing 2003).

As stated previously, the information available from the bulk analysis of nanomaterials from environmental samples has limitations when one is trying to identify for a specific nanomaterial. For ensemble techniques signals generated by nanoscale materials that are not of interest can mask or augment the signals of nanomaterials of interest resulting in inadequate or erroneous data. Also, because of the lack of mass and diffusion properties of nanomaterials, depending on the specific nanoparticle size fraction being analyzed, particle concentration, and where applicable, sampling time, the available mass collected of the nanoparticle of interest may not be sufficient to use the technologies described below.

For the bulk analysis of metals from particulate samples collected from air, water, soil and sediment matrices, an array of analytical techniques are available. For samples in the solid state, chemical profiles can be obtained using energy dispersive X-ray fluorescence (EDXRF), proton induced X-ray emission spectroscopy (PIXE), and total X-ray reflection fluorescence (TRXRF) (Wilson 2002). Metal concentrations in water samples or acid-digested filters/substrates used to collect nanoparticles can be measured using graphite furnace atomic absorption spectrophotometry (GFAA) or, when higher concentrations are present, by inductively-coupled plasma-atomic emission spectrophotometry (ICP-AES) or inductively-coupled plasma mass spectrometry. High-resolution differential surface plasmon resonance (SPR) sensors have also been developed for analysis of heavy metals such as gold, copper and nickel (Forzani et. al. 2005). Less expensive techniques are available for measuring certain metals at low concentrations. A chemiluminescent technique can measure iron concentrations at the nanomolar level, for example (King et al 1995).

In the analysis for carbon-based nanoparticles like fullerenes, the distinction of carbon-based nanoparticles as "organic" (OC) versus "elemental" (EC) is important as a part

of the chemical characterization process. The general distinction of organic carbon versus elemental as well as carbonate nanomaterials can help support the identification of nanomaterials of concern. Bulk carbon-type analytical techniques applicable to collected nanoparticle samples are available. These methods include both wet chemistry techniques involving the acidification to convert carbonates to carbon dioxide and automated thermal analysis techniques to help distinguish organic versus elemental carbon (Wilson 2002). As described above, real time analysis of single-particles for organic composition (like fullerenes) can be done using an aerosol time of flight mass spectrometer (ATOFMS). Laser microprobe mass spectrometry (LAMMS) is capable of providing single particle off-line organic analysis.

For the analysis of organic nanomaterials in samples of water, sediment or soil, a procedure similar to the following can be used. Methods for trace organic analyses are available from EPA (USEPA 2005a) and other sources. Samples are analyzed directly (usually not possible) or are extracted. Sometimes an appropriate internal standard is added to the sample before it is extracted. Extraction procedures are:

(a) Water - In the case of water, the techniques of liquid/liquid extraction (water extracted by some organic solvent that is immiscible with water) or a form of solid phase extraction are typically used. Solid phase extraction is the presentation of an adsorbent such as polystyrene divinylbenzene in a convenient vehicle for the extraction of analytes from water. The water sample flows through the adsorbent where the analyte of interest absorbs to the solid phase absorption bed. A solvent is required to flush the analytes from the adsorption bed.

(b) Sediments or soils - The most widely used extraction tool for sediments or soil is the Soxhlet system. In this technique a solvent mixture is boiled to produce a vapor that is then condensed on a condenser and dripped onto an extraction thimble filled with sample. Once the thimble is filled with solvent, the solvent flushes over into the boiling region and the process repeats. This extraction process may involve procedures designed to speed it up or render it more efficient, e.g. accelerated solvent extraction, temperature-pressure-assisted solvent extraction, supercritical fluid extraction, SoxTec extraction, sonication extraction, and shakeout extraction.

Once the trace organic has been extracted into an organic solvent, it usually is cleaned up (e.g., by gel permeation chromatography and silica gel) to remove substances that can interfere with the analysis. Sometimes an appropriate internal standard and calibration curves are used. Then the extract usually is analyzed using a technique that separates the organic compound of interest from other interfering substances that may be included in the extract. Many separation techniques work similarly by having the mixture start at the beginning of a column of separating material and components of the mixture exit the column one at a time as some flowing material (liquid or gas) helps to move them through the column. Commonly used separation techniques are Gas Chromatography (GC), High Performance Liquid Chromatography (HPLC), and Capillary Electrophoresis (CE). The analysis also requires detection of the trace organic substance after separation. Mass Spectrometry (MS) is a widely used detection system, and Mass Spectrometry/Mass Spectrometry (MS/MS), and High

Resolution Mass Spectrometry (HRMS) also are now being widely used. Other less expensive (but less specific) detectors for gas chromatography include electron capture, flame, flame photometric, and limited-mass-range-scan detectors and HPLC can be coupled with ultraviolet-visible, diode array and fluorescence detectors. Detector responses depend on the nature of the organic analyte. Fullerenes are one common class of organic nanomaterials that can be measured using mass spectral techniques (Kozlovski et al. 2004). Matrix-assisted laser desorption/ionization mass spectral analysis is currently considered to be among the most sensitive techniques.

C2.6 Analytical Technology Needs

As described in the proceeding sections, technologies do exist capable of detecting nanomaterials in environmental samples. However, there are analysis related areas in need of significant research and development. Reference materials need to be developed along with application methodologies for nanoparticle that may pose significant health and environmental risks. These reference materials will allow one to access the accuracy of the analyses being conducted for nanomaterials. Surrogate materials must be made available to access matrix effects like sequestration during sample preparation. Surrogates are also needed to access degrees of particle agglomeration and the loss of semi-volatile nanoparticle fractions during particle separation and analysis processes due to volatilization as well as adhesion to vessel walls due to static and or other molecular forces. Standards methods of analysis need to be developed for both sample analysis and sample preparation techniques. In particular, sample preparation techniques need to be developed for bulk and single-particle analyses (qualitative and quantitative) of nanomaterials in water, sediment and soil matrices. These methods include the development of solid-phase column extraction techniques specific to the extraction of the nanoparticle of interest. The techniques presented for definitive single particle characterization like TEM EDX are labor intensive and require expensive instrumentation. A future alternative may well be the development of what is termed by BASF as chemical force microscopy or CFM (Iden, 2002). CFM utilizes cantilever probes that can be specifically designed to detect for the nanoparticles of interest. This technology could possibly provide real-time qualitative and quantitative detection of nanoparticles of interest for all matrices at a fraction of the cost of the technologies currently available. Perhaps nanotechnology is an answer unto itself when it comes to the rapid and accurate detection and analysis of nanomaterials in the environment.

Table C1. Partial list of techniques available for the analysis of nanoparticles

TECHNIQUES	CHARACTERISTICS
Aerosol Time of Flight Mass Spectrometer (ATOFMS)	• Ensemble technique • Near real time aerosol analysis • Analysis of particles down to 10 nm in size • Potential inorganic and organic analysis • Potential particle size analysis
	• Single particle technique

TECHNIQUES	CHARACTERISTICS
Atomic Force Microscopy (AFM)	• Compositional and crystallographic information can also be obtained • Can be performed in liquid or gas media • Typical range: 1nm to 8mm
Cloud Condensation Nuclei Counter (CNC)	• Ensemble technique • Measures concentration of particles converted to cloud droplets • Detects particles as small as 40 nm • Uses supersaturated atmospheres consisting of water
Condensation Particle Counter (CPC) Also referred to as condensation nucleus counter (CNC) or Aitken Nuclei Counter (ANC).	• Ensemble technique • Measures total particulatele counts • Detects particles as small as 3nm • Uses supersaturated atmospheres consisting of water or isopropanol or butanol
Differential Mobility Analysis (DMA)	• Ensemble technique • DMA creates monodisperse stream of particle; relies on mass-based charge to isolate particles within a specified size range • Applicable to particles down to 2 nm
Dynamic Light Scattering (DLS)	• Ensemble Technique • Commonly used in chemical and pharmaceutical industries • Relies of Brownian motion of particles in a liquid medium to determine particle size • Typical range 1 nm to 5 um
Energy Dispersive X-ray Fluorescence (EDXRF)	• Ensemble technique • Provides qualitative and quantitative analysis for a series of heavier elements (metals) • Analysis of sample on a collected substrate.
Laser Microprobe Mass Spectrometry(LAMMS)	• Single particle technique • Compositional inorganic and organic information • Performed on nanoparticles collected on a substrate
Scanning Electron Microscopy (SEM)	• Single particle technique • Compositional information can be obtained • Requires high-vacuum conditions • Typical range: 50nm to 1cm
Scanning Mobility Particle Sizer (SMPS)	• Combines DMA with particle counting technology • Relies on mass-based charge to isolate particles within a specified size range

TECHNIQUES	CHARACTERISTICS
	• Typical range: >10nm
Transmission Electron Microscopy (TEM)	• Single particle technique • Compositional and crystallographic information can also be obtained. • Requires high-vacuum conditions • Typical range: 5nm to 500μm

C3 Human Health Effects Assessment - Additional Details on Studies Currently Available

C3.1 Toxicity and Hazard Identification of Engineered/manufactured Nanomaterials

Studies assessing the role of particle size on toxicity have generally found that ultrafine or nanosize range (<100nm) particles are more toxic on a mass-based exposure metric when compared to larger particles of identical chemical composition (Oberdorster et al. 1994; Li et al. 1999; Hohr et al. 2002). However, studies conducted by Lam et al. (2004) and Warheit et al.(2004) examining the pulmonary toxicity of carbon nanotubes, have provided evidence that engineered/manufactured nanomaterials can display unique toxicity that cannot be explained by differences in particle size alone. For example, Lam reported single walled carbon nanotubes (SWCNTs) displayed greater pulmonary toxicity than carbon black nanoparticles. Similar results have been obtained from comparative *in vitro* cytotoxicity studies which have reported the hierarchy of toxicity of engineered/manufactured carbon-based nanomaterials to be: SWCNT>MWCNT10>C60 fullerene based on an equal mass dose metric (Jia et al., 2005). Shvedova et al. (2005) reported unusual inflammatory and fibrogenic pulmonary responses to SWCNT suggesting that SWCNTs may injure the lung by new mechanisms. The investigators of these studies speculated that nanoparticle surface area, surface reactivity, or shape may regulate the toxicity of carbon nanomaterials. Sayes et al. (2004) has shown that surface hydroxylation of fullerenes dramatically decreased their *in vitro* cytotoxicity. In contrast, surface hydroxyl groups of nano-TiO_2 are responsible for their photoelectronic and photocatalytic properties and may also be responsible for their *in vitro* photocatalytic cytotoxicity (Cai et al., 1992; Sclafani and Herrmann 1996). Nemmar et al. (2003) demonstrated that surface charge was responsible for the pulmonary inflammatory and vascular thromobotic effects of polystyrene nanoparticles.. *In vitro* toxicological studies performed on quantum dots demonstrated that photoactivation and surface oxidation produced alterations in the surface chemistry of these nanomaterials leading to the release of Cd and subsequent hepatic cytotoxicity (Derfus et al. 2005). These studies demonstrate that nanoparticle toxicity is extremely complex and multi-factorial potentially being regulated by a variety of physicochemical properties such as size, shape, as well as surface properties such as charge, area, and reactivity.

C4 Ecological Effects - Additional Analyses

C4.1 Additional detailed analyses regarding the potential uptake and accumulation of nanomaterials in aquatic ecosystems

For consideration of potential effects in aquatic systems, it may be useful to sort nanosized particles into four classes, by their charge: neutral, anionic (negatively charged), cationic (positively charged), or amphoteric (having characteristics of both and acid and a base).

Based on general chemical behavior, it is expected that neutral nanosized particles based on carbon or silicon will have very high octanol-water partition coefficients (log K_{ow} values) and very low water solubilities, and will have great affinity for organic matter in the environment. These neutral nanoparticles may preferentially bind to organic matter rather than to gills because organic matter has a much larger surface area and is more prevalent in the environment than are aquatic organisms. Research verifying this hypothesis for the variety of nanomaterials is needed.

Anionic nanoparticles would be expected to be poorly absorbed by gill and gastrointestinal (GI) tract membranes since they would be repelled by the anionic charges commonly associated with these surfaces. Research verifying this hypothesis for a range of nanomaterials is needed.

Cationic and amphoteric particles may bind to membranes because of their cationic charge and to damage these membranes. However, this would be only be expected occur after the total organic carbon (TOC) in the environment was bound and neutralized. This mitigating effect of TOC in natural water can be significant for conventional chemicals and may be important for the effects of nanomaterials in aquatic ecosystems. For example, for specific non-nano-sized chemicals, 10 mg TOC/L decreases fish toxicity 100-fold over similar exposures at 2 mg TOC/L. The median TOC concentration in US surface waters is 6.8 mg TOC/L based on the Office of Water STORET database (Boethling and Nabholz, 1997). Therefore, there is likely to be significant attenuation of toxicity from cationic and amphoteric nanoparticles to aquatic organisms exposed in natural waters. Any laboratory-based toxicity studies need to accommodate the potential impact of TOC on nanoparticle toxicity. Based on the expected effects of TOC in the aquatic environment, effects values may require a TOC adjustment factor when implemented for regulatory purposes (Boethling and Nabholz, 1997). As noted above, research verifying the mitigating effects of TOC on nanomaterials is needed for a range of nanomaterials.

Science Daily Magazine (March 2005) reported that nanosized cationic dendrimers punch nanoscale holes in cell membranes in a manner analogous to polycationic polymers, while neutral polymers did not damage membranes. Engineering the dendrimer surface to make the dendrimers neutral may prevent or reduce this damage. Constituents of natural waters, such as TOC, may possibly also mitigate this effect.

It is likely that nanomaterials can accumulate and biomagnify in aquatic organisms. As an example of a conventional chemical in the nanometer size-range, 1,2,5,6,9,10-hexabromo-cyclododecane (molecular weight 642, cross-sectional diameter 1.08 nm, log Kow 7.8 (Cash and Nabholz, 2002)) has a measured log bioconcentration factor in rainbow trout-whole body of 13,085 from a mean water concentration of 0.18 µg/L (OPPTS data, note this bioconcentration factor was not measured at steady state). However, this chemical is not an engineered or manufactured nanomaterial; the behavior of these nanomaterials may or may not be the same. Studies are needed to develop predictive relationships for different classes of nanoparticles.

C4.2 Aquatic ecosystem effects

Toxicity studies for carbon black and suspended clay particles suggest that some suspended nanosized particles in the aquatic environment will have low toxicity to aquatic organisms (Table C2). Predictions are based on SARs for polynonionic polymers, SARs for neutral organic chemicals, SAR-nearest analog analysis for fullerenes, carbon black, and suspended clay particles.

Table C2
Predicted (P) and measured (M) toxicity values in mg/L (ppm) either in terms of soluble material or suspended particles

Organism	Endpoint			P/M	Material	source
Zebra fish	96-h LC50	>	800	M	carbon black	R1
Fish	96-h LC50	>	1000	M	clay	
Daphnid	24-h LC50	>	4500	M	carbon black	R1
Daphnid	48-h LC50	>	1000	M	clay	
Algae	72-h EC50	>	8000	M	carbon black	R1
Algae	96-h EC50[c]	>	1000	M	clay	
sewage microbes	3-h EC50	≥	640	M S,N	carbon black	R1
Fish	ChV	>	80	P	carbon black	ZF/ACR10
Fish	ChV	>	100	P	clay	F96/ACR10
Daphnid	ChV	>	100	P	clay	D48/ACR10
Daphnid	ChV		500	P	carbon black	R1
Algae	ChV	≥	8000	M	carbon black	O2
Algae	ChV[c]	>	300	M	clay	GAEC50/4
Sewage microbes	ChV	≥	640	M S,N	carbon black	R1

ACR = acute-to-chronic ratio
ChV = chronic value = geometric mean of lowest-observed-effect concentration (LOEC) and no-observed-effect concentration (NOEC)
C = based on inhibition of biomass by cells/mL
M = measured toxicity value
N = nominal concentration
O2 = inhibition of oxygen consumption or inhibition of respiration
P = predicted toxicity value using SAR
SAR = structure-activity relationship
S = static method

Predictions: SAR chemical class = polymer-nonionic->C84 nanotube; MW>10 000; log Kow >> 8 (P); solid with melting point unk but S << 0.001 mg/L at 25 C (P) but particles can be suspended in water > 100.0 mg/L (P); pH7.
Effective concentrations (EC) are based on 100% active ingredients and nominal concentrations, water hardness <150.0 mg/L as CaCO3, and TOC <2.0 mg/L.
R1 = MSDS for RAVEN-H20 = 80% carbon black, 15% water, 2.5% surfactant, and 2.5% surfactant
Data from Columbian Chemicals Co, 1800 West Oak Commons Court, Marietta GA 30062.

Recent reports suggest that nanomaterials may be effective bactericidal agents against both gram positive and negative bacteria in growth media. Lyon et al. (2005) reported EC_{50} values for fullerenes of 1 mg/L, or ~ 10 nM. Fortner et al. (2005) report that fullerenes aggregate to form crystalline structures of variable sizes (d = 25 to 500 nm and which were dependent upon water pH) that inhibit the growth (≥0.4 ppm) and decrease aerobic respiration rates (4 ppm) of bacteria. Fortner et al. (2005) also found that these nanocrystals may be more mobile in water than expected. It has to be emphasized that these aggregates were formed under very specialized conditions in the laboratory, in pure water, with tetrahydrofuran, and water sparged of oxygen. Their formation in natural water needs to be demonstrated. In addition, the bacterial assays were performed in growth media over 55 hours. The ability of these "nano-C60" aggregates to inhibit the growth and respiration of microbes needs to be demonstrated under more realistic conditions, for example, sewage microbes in sewage sludge effluent and natural communities of bacteria in natural lake and river water.