NRDC ISSUE PAPER
May 2007

Nanotechnology's Invisible Threat

Small Science, Big Consequences

Natural Resources Defense Council

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Acknowledgments

The author would like to thank the following contributing authors for helping to write and review sections of this report: Ramya Chari, Elizabeth J. Dederick, Sarah Faulkner, Michael Helbing, Kristin Kulinowski, Georgia Miller, Elliott Negin, Rye Senjen, and Patrice Simms.

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Executive Summary

From mascara to tennis balls to baby wipes, tiny nanomaterials are hidden in many of the products we use every day. Although there is much more we'd like to know about how exposure to nanomaterials affects human health and the environment, preliminary studies demonstrate that some nanomaterials are likely to be harmful. The current approach to chemical regulation cannot be relied upon to prevent harm from nanomaterials; it is slow, costly, and fails to prevent exposures to known hazardous chemical pollutants. It is crucial that government regulation and public debate catch up with this rapidly advancing technology.

Nanotechnologies are the engineered convergence of biology, chemistry, and informatics on a nanoscale—that is, involving materials measured in billionths of a meter. The products of these efforts are called nanomaterials, consisting of nanoparticles (having one or more dimensions of 1 to 100 nanometers) and the grouping of these particles into structures that may be larger than nanoscale. Nanoscale materials dissolve in different ways, take on different magnetic properties, react differently to chemicals, or reflect light differently from the way they would at normal size. The very qualities that make nanomaterials commercially desirable can also make them more toxic than their normal-size counterparts. Because they are so small—the head of a pin is about 1 million nanometers across[1]—nanomaterials can be extremely mobile; they may pass easily into the bloodstream when inhaled or swallowed, and possibly when applied to the skin. Once inside the body, they seem to have access to most or all tissues and organs, including the brain. It is unknown whether nanomaterials can pass from a pregnant woman's blood circulation to the fetal circulation, or through breast milk to a nursing infant. While the potential toxicity of intentionally engineered nanoscale materials is still being explored, studies on the health effects of unintentional nanoscale air pollutants are relevant. These data demonstrate that inhalation of nano-size chemical pollutants is associated with asthma attacks, heart disease, strokes, and respiratory disease.[2]

The U.S. Environmental Protection Agency (EPA) has thus far authorized commercialization of 15 new nanoscale chemicals, though only limited information is available to the public because of statutory protections afforded to manufacturers who claim that even basic data are "confidential business information."

Even the names of the nanoscale materials and the names of the manufacturers are being withheld.[3] Precautionary regulation of these still-untested and potentially harmful nanomaterials must move quickly to catch up to the technologies that are generating them and to ensure safety for consumers and workers in advance of commercialization. NRDC proposes a three-part framework for regulating nanomaterials based on a precautionary approach to managing toxic chemicals:[4]

- **Prohibit the unsafe or untested use of nanomaterials.** Because preliminary data demonstrate the potential for toxicity, unsafe or untested nanomaterials should not be used in a manner that may result in human exposures or environmental releases over the life cycle of the material.
- **Conduct full life cycle environment, health, and safety impact assessments as a prerequisite to commercialization.** Robust testing is urgently needed to identify potential risks early in development, across the life cycle of the material. The results of testing should be made available to the public.
- **Facilitate full and meaningful participation by the public and workers in nanotechnologies development and control; consider the social and ethical impacts of nanotechnologies.** The potential of nanotechnologies to transform the global social, economic, and political landscape means we must move the decision making out of corporate boardrooms and into the public realm.

Despite the as yet unknown effects of nanotechnologies on human health, manufacturers already are incorporating nanomaterials into hundreds of consumer products, making nanomaterials the future of chemistry. Products as diverse as sunscreen, skin lotion, and house paint already contain nanomaterials. Given that early nanotoxicology studies suggest that nanomaterials have the potential to be harmful, until we know the risks, these products should be presumed dangerous to consumers and to the workers who are exposed to them during product development, production, use, and disposal. Labor unions and environmental justice advocates have joined together to call on the EPA to move quickly to fully disclose hazards and take protective action to prevent harm to workers and their families from nanomaterials.[5]

Chapter 1
Nanotechnologies: The Small Science with Big Consequences

Nanomaterials—too small to be seen with the naked eye—are engineered to take advantage of properties specific to their tiny size. They are already finding uses in hundreds, possibly thousands, of consumer products. With the proliferation of nanomaterials in consumer applications, there is an immediate need for a precautionary regulatory framework for consumer products that contain engineered nanomaterials. Existing regulations do not protect the public from unsafe exposures; new approaches are required.[6]

Who Uses Nanotechnologies?

More and more companies are entering the nanotechnology field—there are more than 1,600 nanotechnology companies in the United States by one account.[7] Many notable companies with diverse product lines are incorporating nanotechnologies into their products and applications. For example, Burlington Industries, Inc. has developed a water-repellent cotton material; DaimlerChrysler Corporation has developed a chip-resistant paint for its automobiles; and GE Water Technologies is using nanotechnologies to improve its water filtration systems.[8]

Nanotechnologies have also found applications in pharmaceuticals and medical equipment, sporting goods, electronics, computers, and imaging technology.[9] Nanomaterials are used in Behr Premium Plus Kitchen and Bath Paint, Blue Lizard Baby sunscreen, Dockers® Go Khaki® slacks, FresherLonger™ Miracle Food Storage, TX Express Laptop Computers, Turtle Wax® F21™ Super Protectant Wax, and the First Response® Home Pregnancy Test.[10] A 2006 report by Friends of the Earth identified more than 100 cosmetic and personal care products that claim to include nanomaterials, including toothpaste, shampoo, sunscreen, lipstick, perfume, and skin lotions.[11] The Woodrow Wilson Center Project on Emerging Nanotechnologies identified nearly 400 consumer products with nanomaterial components.[12] Nanotechnology is a rapidly growing field: More than $50 billion of nano-enabled products were sold worldwide in 2006, with the United States holding approximately 6,800 nanotechnology-related patents.[13]

Health Risks of Nanomaterials

The warning bells are ringing: People are beginning to raise serious questions about the possible impact of nanomaterials on human health. The small size of nanoparticles can give them greater access to body tissues and organs than larger particulates.[14] In addition, animal studies have demonstrated that some inhaled nanomaterials pass easily from the nose directly into the brain via olfactory neurons, and from lungs into the bloodstream.[15] There is some conflicting evidence from animal studies that ingested nanomaterials may pass through the gut wall, and dermally applied nanomaterials may be absorbed through the skin, with both routes providing entry into the lymphatic and blood circulation.[16] A 2004 report by Swiss Reinsurance Company warned that nanomaterials seem to have "almost unrestricted access to the human body."[17]

Once within the body, the larger surface area of nanomaterials per unit of mass makes them more chemically reactive than their normal-scale counterparts, and therefore more likely to interact with biological molecules. This is particularly likely where the size and shape or other characteristics of a nanomaterial mimic biologically active components of the body's systems, such as immune molecules, DNA-binding proteins, or cell components. Cell studies indicate that some nanomaterials may interact with cell DNA, cause inflammation and oxidative damage, and impair cell function.[18] Engineered modifications to nanomaterials, such as surface coatings, can alter a material's solubility, chemical activity, toxicity, and other properties, providing an opportunity to reduce the risks associated with a material early in its design.[19]

Although there is a paucity of toxicity data specific to engineered nanomaterials, the hazards of nano-size air pollutants are well documented. Particulate matter less than 10μm (10,000 nm) has been linked to increased lung cancer and cardiopulmonary disease.[20, 21, 22, 23, 24] While all particulate air pollution is hazardous, smaller inhaled particles have long been known to be more damaging to body tissues than larger particles, inducing inflammation and tissue damage.[25, 26] The risks are especially high among individuals with pre-existing heart and lung ailments, including asthma and chronic obstructive pulmonary disease, suggesting that the millions of people with these conditions may be especially vulnerable to the hazards of inhaled nanomaterials.[27, 28]

In light of these threats, it is imperative that the government move quickly to establish health and safety standards for workers who manufacture these products, consumers who use them, and the environment that absorbs the waste. In a laudable local effort, the Berkeley, California, City Council unanimously supported an ordinance to amend its hazardous materials law to compel researchers and manufacturers to report what nanotechnology materials they are working with and how they are being handled.[31]

Late Lessons from Asbestos

In the early twentieth century, reports began to surface about the health hazards of a material not widely understood at the time: asbestos. By the 1930s, asbestos was being linked to deaths; as of 2004, the cumulative financial liabilities from the substance were projected at more than $200 billion.[29] In the United States, we still have more than one death per hour—approximately 10,000 per year—as a legacy from past and continuing exposure to asbestos. The global death rate is estimated to be 10 times higher.

Insurer Lloyds of London compared nanotechnologies now in development and the asbestos issue of the last century in a June 2006 news release, stating that "some nanotubes, are similar in form and size to asbestos fibres….There are indications that certain nanomaterials are potential health hazards….The danger is most probably of a chronic nature and it could be some time before it manifests itself."[30]

The preliminary data on the toxicity of nanoparticles sound an early warning to those intending to manufacture or market products containing nanomaterials. The asbestos example is an important lesson on the need for a comprehensive regulatory structure before new and potentially toxic substances are introduced into widespread use.

Nanomaterials Pose Hazards

The dangers associated with nanomaterials extend beyond human health. Where their uses result in widespread releases to the environment, nanomaterials such as carbon nanotubes, nanoscale silver ions, zero-valent iron, and cerium oxide may also pose risks to the environment.

- Nanoscale silver ions act as an antimicrobial biocide, a substance that can kill or inhibit the growth of microbes. Nanoscale silver is used in numerous commercial products—including washing machines, clothing, kitchen utensils, wound dressings, and food storage containers—from which, either during normal use of the product or through degradation after the product is discarded, nanoscale silver ions are likely to wash into the waste stream. Once these ions are released into the environment, their biocidal activity is harmful to beneficial microbes such as some bacteria and fungi, potentially causing disturbances in critical ecosystems and ecological food webs.[32] In November 2006, the EPA announced its intention to regulate nanoscale silver as a pesticide, but only in products that advertise its use as a biocide.[33] This loophole has already encouraged some companies to remove references to nanosilver from their advertising and labels, without removing it from the product. With more than 40 consumer products already containing nanosilver, the EPA needs to close this loophole and review nanosilver, whether or not the manufacturer acknowledges its use.[34]
- Multiple studies have shown that carbon nanotubes cause irreversible, progressive lung damage when inserted into the airways of test rodents.[35]
- Nanoscale zero-valent iron can be used as a cleanup technology for carcinogens such as trichloroethylene, arsenic, and lindane.[36] Its potential impacts on the environment is unknown.
- Nano-cerium oxide particles are added to diesel fuel to decrease toxic diesel emissions and increase fuel efficiency. Inhalation of normal-scale cerium oxide in test mice induced cell damage that the researchers suggested is likely to lead to cancer. At the nanoscale, cerium induced cell damage in human lung cells exposed in a petri dish.[37] In contrast, another group reported that nano-cerium oxide reduced levels of reactive oxygen species.[38] Such opposing results may be explained by another study reporting that the ability of nano-cerium oxide to pass into cells was dependent on the particle size and agglomeration state, suggesting that these and other properties must be considered when assessing the risks to human health from exposure to nanomaterials.[39]

Until the safe use of nanoscale materials is assured, these data, while preliminary, provide strong support for removing them from consumer products where significant human exposures are likely, and preventing further uses of nanoscale materials where those uses may result in widespread environmental releases over the product lifetime.

Chapter 2
The Need for Precautionary Regulation of Commercial Nanomaterials

The potential for widespread human and ecological exposure to nanomaterials coupled with early indications of the damage these materials could cause to people, wildlife, and ecosystems warrants swift regulatory action. The Louisville Charter for Safer Chemicals, endorsed by more than 50 groups and individuals dedicated to the protection of human health and the environment, has called for a precautionary approach to the regulation of toxic materials to prevent harm, even when uncertainty remains regarding the exact nature and magnitude of the harm.40 Governments must act preemptively to protect people from the potential dangers of nanomaterials, even though the exact health and ecological impacts are still undetermined.

Regulatory Red Tape Blocks Protections

The current approach to chemical regulation is slow and costly, and it is designed to accept a level of harm as if it were a necessary cost of progress. Unfairly, this regulatory approach aims to strike a balance between public and private interests by weighing evidence of a health harm against the potential economic harm to industry (often exaggerated by industry economists) if the product were to be strictly regulated or banned. In addition, the lack of adequate oversight and enforcement of existing regulations renders the existing system even less effective. This approach has failed for 30 years to prevent human and environmental exposures to harmful industrial chemicals. For example, petroleum refineries in the United States self-reported releasing 3 million pounds of cancer-causing chemicals into the air in 2004 (the most recent year for which data are available).[41]

As evidence of the failure of current chemical regulatory structures to prevent harm, in 2006 the Government Accountability Office (GAO), the investigative arm of Congress, reported that "EPA has used its authorities to require testing of fewer than 200 of the 62,000 chemicals in commerce when EPA began reviewing chemicals under TSCA [the Toxic Substances Control Act] in 1979."[42] Further, the report noted

"The potential danger to human beings and the environment is literally incalculable if we don't understand how nanotechnology can interact with our bodies and our world."

— Rep. S. Boehlert (R-NY), September 2006

that public access to information, even by state agencies and foreign governments, is often denied because of confidential business information provisions.[43]

Unfortunately, it is unclear whether the United States will regulate nanomaterials as new substances, thereby triggering increased regulatory scrutiny, or capitulate to industry demands to treat nanoscale materials as though they were identical to their normal-scale counterparts, thereby defaulting to the regulations already established for the normal-scale material. This approach would ignore the growing body of evidence showing that along with extremely small size comes unique properties that potentially impart unique hazards. Moreover, such an approach would directly contradict the explicit recommendations of a 2004 report by the United Kingdom's Royal Society and Royal Academy of Engineering, which acknowledged the need to assess nanoscale materials as distinct from normal-scale.[44] It is unclear what statutory authorities regulators may rely upon and what products a governance structure would apply to.

Next Steps for Effective Regulation

The need for policy-relevant research addressing the health and environmental effects of nanomaterials has been broadly acknowledged by both the public and private sectors.[45] Scientists have called for an effective regulatory response to their increased use in consumer products and in environmental applications such as water treatment.[46] But thus far the U.S. government's response to the potential risks has been woefully inadequate, despite the recommendations of the U.S. House Science Committee. The committee, chaired by Rep. Sherwood Boehlert (R-NY), held hearings on research needs in September 2006, with the chairman declaring in open remarks that "the nanotechnology industry, which has enormous economic potential, will be stymied if the risks of nanotechnology are not clearly understood and addressed. And, of course, the potential danger to human beings and the environment is literally incalculable if we don't understand how nanotechnology can interact with our bodies and our world."[47]

It is illustrative that just 4 percent of the total $1.05 billion in federal nanotechnology funding for fiscal year 2006 was allocated to research on health and environmental effects, and another 4 percent to social implications and education.[48] It is somewhat heartening that the allocation of funding to the EPA almost doubled, from $5 million in 2006 to a proposed $9 million in 2007. However, this represents only 0.7 percent of the total federal nanotechnology budget of $1.2 billion across the federal agencies, and how much of this EPA will spend on relevant risk-related research is unclear. What is clear is that commercial exploitation of nanomaterials far outpaces research on their potential dangers to living systems. For this reason, public interest groups and industry together have challenged the federal government to "dedicate at least $100 million annually, sustained for several years" to policy-relevant risk-related research.[49, 50]

Nanotechnologies provide the government with an opportunity to make a fresh start and develop a precautionary regulatory framework for a new generation of chemicals and substances, some of which will almost certainly be harmful.

A voluntary pilot program now under consideration by the EPA will request that industry participants submit data on material characterization, toxicity, exposure potential, and risk management practices.[51, 52] While this program may act as a stopgap to fill the regulatory breach, it would involve only those companies that volunteer to participate, and would gather data regarding only those products that participating companies choose to disclose. Companies with the riskiest products, as well as those with poor business ethics—that is, those most likely to need government oversight—are least likely to participate. A coalition of

more than 20 public interest groups including NRDC, Friends of the Earth, Greenpeace, the Sierra Club, and ETC Group insist that a voluntary program without a mandatory regulatory component will not be able to address potential risks.[53]

The reliance on voluntary stewardship initiatives has left a regulatory void that could harm both human health and the economic stability of the nanotechnology industry. Nonetheless, the EPA appears unwilling to commit to comprehensive, enforceable regulations.

Chapter 3
A Framework for Regulation of Commercial Nanomaterials

There is strong and unprecedented consensus among insurers, investors, environmental groups, worker protection groups, and public health experts about the need for precautionary regulation of nanomaterials, independent safety testing, and public access to risk information. NRDC has developed a preliminary framework to guide regulation of the burgeoning nanotechnology field.

The preliminary regulatory framework proposed here is based on the Precautionary Principle, which was described in a 1998 Wingspread conference as follows: "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically."[54] Components of this approach require:

- taking preventive action in the face of uncertainty;
- shifting the burden of protection onto those responsible for the potentially harmful activities;
- considering alternatives to possibly harmful activities; and
- increasing public participation in decision making.

Our proposed framework for regulation of nanomaterials incorporates a precautionary approach that closely parallels the Louisville Charter for Safer Chemicals.[55] Much of this framework is also consistent with the recommendations of Friends of the Earth,[56] as well as aspects of voluntary programs being considered by the EPA and by industry for reporting information pertaining to nanomaterials (see page 5).[57, 58]

Prohibit the untested or unsafe use of nanomaterials. This includes preventing or limiting the manufacture, import, processing, distribution in commerce, use, and disposal of nanomaterials until such materials are tested and can be shown to be used safely. This approach must assume worst-case exposure scenarios in order to prevent unsafe human exposures and releases to the environment, and it must be flexible, iterative,

and responsive as new robust and reliable information becomes available. Such a precautionary regulatory approach places the burden on the manufacturer to provide evidence of safety prior to widespread use, rather than on regulators to prove harm. This would drive policy-relevant research that informs risk management decisions in a timely manner, and would support the innovation of sustainable and socially beneficial materials and technologies.

Conduct full life cycle environment, health, and safety impact assessments as a prerequisite to commercialization.

- Assess nanomaterials as new substances, since nanoscale size may impart unique hazard profiles.
- Develop a research agenda that provides the needed information for risk management decisions and protective policies; risk managers, consumer and worker representatives, and regulators should be involved in the development of a research agenda.
- Develop a flexible, adaptive testing framework, one that is grounded in the precautionary principle while allowing innovative evaluation criteria.
- Conduct independent testing to develop life cycle hazard and toxicity profiles.
- Build life cycle exposure profiles that are application specific, and identify the critical properties and/or specific applications of nanomaterials that may contribute to risks.
- Develop testing approaches to identify hazards. A testing strategy should consider the bioavailability, application, and exposure scenarios relevant to a nanomaterial's life cycle. Possible elements of a testing strategy are outlined in Appendix B. As with traditional risk assessments, the information needed to address the risks associated with nanomaterials will include:
    - — relevant exposure media (air, food, water, soil, skin contact);
    - — relevant routes of exposure (inhalation, ingestion, absorption);
    - — exposure characteristics such as frequency and duration;
    - — information regarding exposed populations;
    - — data on vulnerable populations such as children or the elderly;
    - — potential for biopersistence and/or bioaccumulation; and
    - — implications of interactions with other chemicals/substances.
- Target impact assessment specifically to nanomaterials. Traditional approaches to predicting toxicity of materials based on their mass or structure may not be useful for nanomaterials.[59, 60] Nanomaterial-specific assessment should consider:
    - — appropriate potency estimates (e.g., expressed as an effect per number of particles or per unit surface area, rather than the traditional "per mass" basis);
    - — appropriate application-specific physicochemical characteristics;
    - — whether the particles are bound or free; and
    - — what medium the particles are found in, whether they are coated or not, the surface charge, the amount of surface area available for chemical interactions, the particle size and shape, and the presence of impurities.
- Establish risk management practices along the supply chain for each application/use, including production, manufacture, use, and disposal of nanomaterials and products containing nanomaterials. Specific risk management practices may include: worker training, use of available engineering controls, provision of personal protective equipment, product labeling, customer education, waste management best practices, monitoring of workplace exposures, monitoring of environmental releases, and medical monitoring of workers.[61, 62, 63]

- Evaluate efficacy and compliance with risk management practices.
- Require substitution of safer materials and processes where available.[64]

Facilitate full and meaningful participation by the public and workers in nanotechnologies development and control; consider the social and ethical implications of nanotechnologies. The potential of nanotechnologies to transform the global social, economic, and political landscape makes it essential that the public participate in decisions regarding the introduction and management of these new technologies to ensure that public values and preferences inform the development of this transformative new technology. It is essential that such public participation directly inform public policy development and nanotechnology decision making, rather than being limited to a one-way process in which government and the scientific community "educate" the public. Public preferences should also inform the allocation of public funding for nanotechnologies research and development; commercially oriented research should not be at the expense of public interest research. Consideration of nanotechnology's broader social implications and ethical issues should occur at each stage of the development process. Social impact and ethical assessment, alongside the expression of community preference, should guide the allocation of public funding for research; new nanoproducts should be subject to a social impact and ethical assessment as part of the regulatory approval process prior to their commercialization; and social science analysis of nanotechnology's implications should take place in real time alongside toxicological analysis. Meaningful public participation will require transparency of both scientific and social issues, and will require rapid public access to credible information.

The regulatory agencies must facilitate public access to critical information with the following measures:

- Developing an inventory of publicly accessible data for each application regarding physical properties, hazards, potency (dose-response), exposure potential, and any existing risk management practices or other protective measures.
- Labelling consumer products that contain nanomaterials.
- Following workplace "Right to Know" rules for all products and processes that involve nanomaterials.[65] These rules "require chemical manufacturers or importers to assess the hazards of chemicals which they produce or import, and all employers to provide information to their employees about the hazardous chemical to which they are exposed" through such measures as labels, material safety data sheets, and training.[66] Disclosure should include chemical identities, toxicity information, appropriate hazard warnings, safe disposal information, and risk mitigation practices.
- Establishing a national, publicly available tracking system for all engineered nanomaterials.[67] This will facilitate global information sharing among governments, business sectors, workers, and communities.

Appendix A
Toxicity Studies

The fledgling science of "nanotoxicology" is particularly vulnerable to misinterpretation because toxicity testing methods for nanomaterials are not standardized, and because the toxicity of nanomaterials may depend on variable material characteristics such as the amount and type of contamination of the test material, the size and shape of the test material, and the surface modifications of the test material. For example, a test sample of a nanomaterial may have different contaminants depending on what methods were used to produce the material. Surface modifications may alter a material's solubility, bioavailability, surface charge, and aggregate state, all of which may alter its toxicity. It is therefore important that readers take caution not to extrapolate the results of any study inappropriately. As with all scientific inquiry, our confidence is strengthened when consistent results are supplied by multiple lines of evidence drawn from multiple, well-conducted studies. The studies selected for mention here are all from published, publicly available, peer-reviewed scientific literature. Readers should refer to the complete articles for details, including study limitations.

Metal-Based Nanomaterials

Nanomaterials can be made from metal atoms. Examples include nanoscale gold, nanoscale silver, silicon nanowires, reactive metal oxides such as nanotitanium dioxide, and quantum dots.

Aluminum and alumina (aluminum oxide) nanoparticles currently are used in scratch- and abrasion-resistant coatings on commercial products such as safety glasses, car finishes, and flooring. In humans, exposure to normal-scale aluminum has been shown to disrupt bone formation and remodeling, induce microcytic anemia, and cause brain damage in patients with impaired kidney function.[68] It impairs parathyroid function in both humans and test animals.[69] It has been suggested that it plays a role in the progression of Alzheimer's disease in humans, although these data are still inconclusive.[70] Because of the potential for adverse effects, federal agencies have attempted to limit both human and environmental exposures to normal-scale aluminum.[71] Regarding nanoscale aluminum and alumina (aluminum oxide), there are very few toxicity studies. Braydich-Stolle et al. reported aluminum nanoparticles (30 nm) to be cytotoxic to a mouse spermatogonial stem cell line in vitro, causing dose-dependent significant cell membrane leakage and cell death by a mechanism of apoptosis.[72] In plants, alumina nanoparticles were reported to stunt the root growth of corn, cucumbers, cabbage, carrots, and soybeans after a 24-hour exposure (2 mg/ml) to the particles in water.[73] These data suggest that nanoscale aluminum and alumina may harm plants and animals.

Semiconductor nanocrystals, or quantum dots, are made of a metal core composed of a variety of metal complexes, often cadmium and selenium. The core is surrounded by a shell that makes it easier for the "dot"

to access the body and interact with biological tissues (biocompatible). Normal-scale cadmium and cadmium compounds, including cadmium oxide, are classified as known human carcinogens by the EPA and by the International Agency for Research on Cancer, part of the World Health Organization, based on evidence from human (occupational) studies and from laboratory animal studies.[74] A review of toxicity studies on quantum dots has yielded conflicting results. A recent review of available data reports that longer exposure times lasting several days were generally found to be toxic to cells, whereas shorter exposures of several hours or less generally led to no observed toxicity.[75] Despite a lack of understanding of the risks, and some evidence of toxicity, quantum dots are commercially available for medical imaging and electronics.

Nanoscale silver ions are used increasingly as a germ-killing agent in consumer products, including refrigerators, washing machines, pillows, slippers, food storage containers, and athletic clothing. Most of these uses will almost certainly result in environmental releases of silver over the lifetime of the product. Although the literature is inconclusive with regard to these particles' impact on human health, nano-scale silver has been reported to be toxic to rodent cells grown in a petri dish.[76] At normal scale, silver has long been known to be toxic to fish and invertebrates, and highly toxic to aquatic organisms and microbes.[77] At the nanoscale, silver is even more potent as an antibacterial agent than at normal scale, suggesting that the widespread release of nanoscale silver ions into the waste stream will almost certainly have a negative impact on ecosystems by damaging beneficial microbes in the environment and adversely affecting complex food webs.

Reactive Metal Oxides

Nano-titanium dioxide (nano TiO_2) is a popular ingredient in some cosmetics and sunscreens because it blocks harmful ultraviolet rays and, unlike its conventional counterpart, it is transparent instead of white.[78, 79] It has a very high surface area and is more chemically reactive than conventional titanium dioxide. Its ability to generate reactive chemical species, particularly under ultraviolet illumination, has been exploited in products such as self-cleaning glass and low-cost solar cells. Unfortunately, in living cells reactive species are often toxic. A 1992 study reported that rodents that inhaled nano-titanium dioxide (20 nm) for three months under conditions simulating occupational exposures (six hours a day, five days a week) had significantly more lung inflammation and scar tissue compared with those that inhaled larger titanium dioxide particles (250 nm).[80, 81] Multiple laboratories have reported that nano-titanium dioxide particles are toxic to human and animal cells, and to aquatic organisms, in the presence of ultraviolet illumination (photoactivation), likely through the generation of toxic reactive oxygen species, making its use in sunscreen and skin cream unwise.[82]

A study of the impacts on freshwater aquatic environments reported a dose-dependent increase in damage to and death of water fleas (*Daphnea magna*) after 48 hours of exposure to nano-titanium dioxide (average of 10–20 nm diameter), whereas normal-scale titanium dioxide particles at the same concentration had no effect.[83] The same study reported that carbon fullerenes (buckyballs) were even more lethal than nano-titanium dioxide under identical experimental conditions. The authors emphasized the implications for harm to the ecosystem if toxic nanomaterials are allowed to pollute aquatic environments.

Nano-zinc oxide is popular in numerous cosmetics, lotions, and sunscreens because it blocks harmful ultraviolet light and, unlike its normal-scale counterpart, it is transparent instead of white.[84] Because zinc oxide is also a common workplace air pollutant, its risks have been documented as metal fume fever. In a 1997 study designed to evaluate occupational exposures, 13 adults reported fever, cough, and fatigue after two hours of inhaling normal-scale zinc oxide fumes (100-1,000 nm diameter) at the workplace allowable limit (TLV; 5 mg/m^3 8-hr time-weighted average).[85] A study of adult mice reported that gastrointestinal dosing (5 g/kg body weight) with either nano-zinc oxide or larger particles resulted in much more severe symptoms in the nano-treated group, including lethargy, vomiting, diarrhea, and two deaths due to obstruction of the intestines by aggregated nano-zinc oxide.[86] A study of guinea pigs reported that inhalation of 6 mg/m^3 of nano-zinc oxide particles (diameter of 50 nm) for three hours daily on six consecutive days, particularly when combined with sulfur dioxide exposure (1 ppm), significantly decreased lung function.[87] While workplace and laboratory animal studies are difficult to extrapolate to the general population, given differences in exposure parameters and in particle types, the results suggest that appropriate safety testing should be conducted before

introducing these materials into consumer products, particularly those where human exposure is likely. At this time, it is unknown what the health effects may be from the potential skin absorption of nano-zinc oxide in cosmetics.

Carbon-Based Nanomaterials

Carbon-based nanomaterials have desirable electrical, mechanical, and thermal properties, useful in developing strong, lightweight building and packing materials, in computers, and in aerospace engineering. However, the data thus far indicate that exposure to various carbon nanomaterials may be harmful to the brain, lungs, cardiovascular system, and immune system.[88] Carbon nanomaterials come in two basic shapes: spherical "buckyballs" and cylindrical single-walled or double-walled nanotubes. From these, structures can be formed that are highly varied in shape, function, and toxicity. Nanoscale carbon structures can also vary in purity, solubility, aggregation state, and even size. These characteristics can alter the toxic potential of the material. Conflicting study results are likely due to differences in the size, shape, surface coating, and aggregate state of the test samples. Research in this area provides opportunities to engineer nanomaterials in ways that minimize their hazard while enhancing their desirable properties.

Carbon C60 (buckyballs) are soccer ball–shaped molecules of carbon atoms. A December 2005 study using detailed computer simulations suggested that, once inside body tissues, C60 could interact with cellular DNA, causing it to deform and almost surely preventing it from functioning normally.[89] This suggests that C60 may cause irreversible damage including cancer. If sperm and egg cells were to be affected, the damage could be inherited by the offspring of exposed individuals. Although C60 tends to be insoluble as single particles, it more often exists as crystalline aggregates. These aggregates have been reported to be toxic to bacteria, suggesting that they may have unintended impacts on ecosystems.[90] How the surface characteristics of C60, and all nanomaterials, are modified has been shown to greatly impact the material's toxicity, bioavailability, solubility, and other properties associated with toxicity.[91]

Carbon nanotubes form ropelike filaments that are long, thin, and insoluble, qualities associated with the cancer-causing effects of asbestos and other deadly fibers.[92, 93, 94] Five different research groups have reported that single-walled carbon nanotubes (SWCNTs) cause lung damage in test rodents: Government researchers reported dose-dependent rapid lung inflammation, rapid progressive fibrosis, and granulomas within seven days after a single dose of SWCNTs into the lungs of mice.[95] Cell damage increased in a dose-dependent manner within one day after exposure. One year earlier, in 2004, DuPont researchers had reported that in test rats, lung exposure to single-walled carbon nanotubes (1 mg/kg) resulted in acute lung toxicity, transient inflammation, and lung fibrosis after one week.[96] Also in 2004, a collaboration between the National Air and Space Administration (NASA) and the University of Texas reported dose-dependent granulomas and inflammation in mice that were administered a single dose of either 0.1 or 0.5 mg of single-walled carbon nanotubes into the lungs.[97] The authors calculated that this is roughly equivalent to a mouse inhaling nanotubes for about three and a half workdays (low dose) or 17 workdays (high dose) at the workplace allowable level for graphite (carbon) dust (15 mg/m^3 of total dust, and 5 mg/m^3 for the breathable fraction).[98] These authors warned that workers breathing nanotube dust at a fraction of the workplace allowable level "would likely develop serious lung lesions" within a short time.[99] It is important to note that in these studies the test substance was placed directly into the airways, whereas inhalation exposure may be less severe due to aggregation of nanoparticles into larger molecules.

Several studies have reported that carbon nanotubes were toxic to human or animal skin cells grown in petri dishes, while study results with C60 carbon buckyballs were conflicting.[100, 101]

Appendix B
Research Needs

It is essential that the right research be designed and conducted, in order to provide needed information to risk managers and regulators. Many of the generally agreed-upon elements of a tiered-testing strategy have been outlined in numerous documents by scientists from academia, nongovernmental organizations, and industry.[102, 103, 104, 105, 106] Most recently, a number of scientists from government, industry, and academia have outlined a research strategy that includes the development of monitoring methods and toxicity tests with proposed timelines reflecting feasibility and priority of scientific needs.[107] The points below borrow heavily from those referenced documents in an attempt to capture some consensus of scientific thought about what will be necessary to adequately manage the risks that nanomaterials pose:

- Develop monitors and sensor devices to measure the presence and identity of nanomaterials in air, water, soil, and biological tissues.
- Develop rapid screening tests for evaluating the potential toxicity, persistence, and bioaccumulation of nanomaterials. This will necessitate the identification of physical properties that may be relevant to toxicity in manufactured form, during use, in emissions, in wastes, in products, in environmental media, and in organisms. These properties are likely to include many of the following: chemical composition (including impurities), agglomeration state, physical form/shape, concentration, size distribution and/or surface area per unit mass, solubility, electrical state, reactivity, and stability.
- Describe the immediate (acute), short-term (subchronic), and long-term (chronic) toxicity related to both human and ecological health with consideration of pre-birth exposure, exposure during vulnerable life stages, and impacts on populations or ecosystems.
- Document the exposure potential across the life cycle of a nanomaterial, including production, use, and disposal. This includes data on the environmental fate and transport of the material over its life cycle as it is manufactured, commercialized, and discarded as waste material.

Appendix C
Proposed Structure for Health and Safety Testing

Conducting independent, credible, and rigorous risk research on rapidly emerging technologies is a challenge, but not a unique one. One possible model for funding and managing this research may exist in the research initiative of the National Institute of Environmental Health Sciences (NIEHS) and the Department of Energy (DOE) called the Electric and Magnetic Fields (EMF) Research and Public Information Dissemination (RAPID) Program (www.niehs.nih.gov/emfrapid/). A similarly styled Nano-RAPID Program would be a multiyear, federally coordinated effort to evaluate and research the effects of exposure to nanomaterials on biological systems, and to communicate these results to the public sector. The program would need to provide rigorous, credible health and safety information to the public, to industry, and to regulators. Research needs would be developed with opportunities for public and stakeholder participation, and all research protocols would be reviewed by relevant expert advisers. Funding would come jointly from the public and private sectors and be managed jointly by the relevant federal agencies with opportunities for the public and stakeholders to provide perspectives, identify research needs, and enhance mechanisms for communicating research findings to the public.

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