Nanomaterial Health Effects—Part 2: Uncertainties and Recommendations for the Future

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ABSTRACT
In this paper, we summarize some of the key data gaps, uncertainties, and unknowns that need to be addressed to develop adequate risk assessments for nanomaterials. We make recommendations to take timely and appropriate public health precautions. We also briefly discuss nanotechnology applications for food and food packaging, and describe the University of Wisconsin-Madison’s Nanotechnology in Society Project.

INTRODUCTION
Nanotechnologies, the manipulation and creation of materials and devices at the nanometer scale, are expected to bring a host of benefits to society in coming decades.1 Materials with 1 or more dimensions <100 nanometers, called “nanomaterials,” have properties that make them attractive for a variety of applications, including high strength, conductivity, durability, and reactivity. Hundreds of products containing nanomaterials are already on the market, including paints, sunscreens, sporting goods, textiles, and components of computers, cell phones, and other electronics. Biomedical and pharmaceutical researchers, moreover, are developing novel nanomaterials and “nanobio” devices that combine nanomaterials with biological substances for a variety of medical applications. Economic analysts estimate that sales of products incorporating nanotechnology will total $2.6 trillion by 2014—as big as the information and telecom industries combined and 10 times bigger than the biotechnology industry.2

Unfortunately, because of their small size, nanomaterials have very high surface-to-volume ratios, which makes them more reactive—and potentially more toxic—than larger materials.3 Numerous toxicological and epidemiological studies on existing fine and ultrafine (or nano-sized) particulates, such as those found in air pollution and some workplaces, demonstrate that exposures to materials in this size range can cause significant public health problems, such as pulmonary and cardiovascular disease.4 Consequently, scientists and governments worldwide have raised concerns about the widespread production and use of engineered nanomaterials, and are beginning to develop risk assessments and policies to address these concerns.5 At this point, however, relatively few studies have been done on engineered nanomaterials, so significant uncertainties and data gaps face risk assessors. In this paper, after briefly reviewing toxicological studies on engineered nanomaterials, we outline some of the key data gaps that need to be addressed in order to develop comprehensive risk assessments and risk management strategies that adequately protect public health.

A BRIEF REVIEW OF STUDIES ON ENGINEERED NANOMATERIALS
In the last issue of the Wisconsin Medical Journal, we outlined the key toxicological studies on engineered nanomaterials and nano-sized particulates in air pollution.6 Below, we briefly review some of these studies. Animal and cell culture studies that have been done on engineered nanomaterials show that they can have significant toxic effects similar to those associated with ultrafine particulates.7 Nanoscale titanium dioxides used in sunscreens and cosmetics have been associated

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with pulmonary effects such as lung inflammation, pulmonary damage, and fibrosis. Carbon nanotubes used in electronics, pharmaceuticals, and a variety of other applications, have fibrous structures similar to asbestos, and animal and cell culture studies show that they can cause significant pulmonary effects comparable to and in some cases stronger than those caused by carbon black and silica.

Quantum dots—nano-sized particles used or being developed for use in electronics, biomedical imaging, and surveillance—are typically made of cadmium or lead, which are well-known toxins. Toxicological and pharmaceutical studies show that protective coatings of quantum dots can degrade in light and oxidative conditions, releasing these toxic metals into cells and organisms and causing toxic effects.

Fullerenes, or “buckyballs,” are soccer-shaped balls of carbon (usually 60 carbons, but sometimes more) that are used in catalysts, copolymers and composites, lubricants, drugs and drug delivery systems, cosmetics, health care products, and sporting goods. Animal and cell culture studies suggest that they can have both beneficial (anti-oxidizing) properties and harmful (oxidizing) properties depending on the chemical and light conditions. Due to their anti-oxidant properties, they show promise as treatments for cancer, AIDS, and bacterial infections, or to facilitate delivery of these treatments in the body. Other studies, however, suggest that because they are very lipophilic and have strong oxidizing properties in certain conditions, fullerenes can cause DNA damage, lipid peroxidation, and leaky cell membranes.

**NANOTECHNOLOGY RISK ASSESSMENT DATA GAPS**

Risk assessment is the process of determining whether exposure to a substance will lead to negative health effects. The typical risk assessment process includes hazard identification, dose-response assessment, exposure assessment, and risk characterization. Risk characterization, typically the last step in the risk assessment process, requires information from the first 3 steps. Risk management uses the results of a risk assessment to develop policies and communication strategies to identify and reduce risks as well as to communicate with people who might be at risk. Unfortunately, in the case of nanomaterial risks, there are significant risk characterization data gaps, making comprehensive risk assessments for nanomaterials—and therefore risk management—difficult. Below, we briefly outline some of these risk characterization data gaps.

**Material Characterization and Toxicological Data**

Several recent government and industry reports identify research gaps that need to be filled to address hazard identification and dose-response steps of risk assessment. Most of these reports focus on gaps related to material characterization, dose and exposure characterizations in toxicological studies, and other methodological issues such as (1) characterizing the wide variety of nanomaterials being produced more precisely, (2) characterizing adhesion, diffusion, agglomeration, and aggregation behaviors of various nanomaterials, (3) determination of dose-response curves and toxicological modes of action of specific nanomaterials, and (4) better understanding of potential routes into the body for specific nanomaterials.

There are also many methodological uncertainties about what parameters of nanomaterials are most critical to measure for risk assessments and how to best measure them. Scientists and regulators agree that the parameters typically used to characterize potentially toxic materials—such as mass and volume—may not be the most relevant parameters to measure for nanomaterials. Studies suggest that particle number, size, shape, surface area, surface chemistry, and solubility are all relevant to nanomaterials’ toxicities, but most scientists agree that “biologically available” surface area is probably the most critical parameter, and an increasing number of studies suggest that surface chemistry is important as well. However, scientists have not yet agreed on the definition of “biologically available” surface area or how to best measure it. Complicating matters, many existing studies report mass, or are unclear about what parameters they measured, so it can be difficult to weigh the relevance of the findings and compare studies. Because many regulatory health standards and safety control systems tend to be mass-based, moreover, switching to other kinds of measurements may make it difficult to compare findings to current standards.

**Potential Effects of a Wider Range of Nanomaterials and Exposure Routes**

There are large gaps in the kinds of materials addressed in studies and the types of exposures considered. To date, only a small proportion of nanomaterials being produced have been addressed in publicly available toxicological studies. Few studies, for example, address potential health impacts of many of the unique engineered nanomaterials currently in consumer products or in development for use in these products. Few published toxicology studies address the poten-
Nanotechnologies and Food Safety

Several emerging nanotechnologies promise to improve food safety and food quality. Scientists are developing nano-sensors that could be used in food packaging to detect pathogens or pesticides, or to monitor temperature, pH, and other food characteristics. Nanomaterials are also being used to improve the flavor and nutritional value of foods and drinks. For example, nano-sized materials that release flavors, colors, and/or nutrients at specific times or places are being developed for food packaging, food, drinks, and “nutraceuticals.” Food companies are developing nanoparticles designed for “smart” drinks and foods that they say could be programmed to be the desired color or taste.12

According to the consultant firm Helmut Kaiser, around 200 companies worldwide are currently active in nanofood research and development, and the nanofood market is expected to rise to $20 billion by 2010. Several kinds of nanomaterials are already on the market in foods or food production. Radio frequency identification chips, which are based on nanotechnologies, are being used to track food products, livestock, and pets. The Forbes “Top Nano Products of 2005” list includes a “fat-busting” canola oil with nanocapsules, and chocolate chewing gum with nanocrystals that give it a creamier texture and more intense chocolate flavor.

As the nanofood market grows, some concerns are arising about potential health risks related to using nanoparticles in foods and food packaging. In February 2006, the Institute of Food Science & Technology, a UK-based organization, issued a statement arguing that more safety data should be gathered before nanoparticles are used in foods and packaging. They proposed that safety and toxicological data be provided by companies and be made publicly available, and that foods containing nanoparticles be labeled. The UK’s Food Standards Agency is beginning a research program exploring the health and safety implications of using nanoparticles in foods. The US Food and Drug Administration (FDA), however, is not treating nano-sized materials as novel substances at this point, and is likely to place many nanomaterial food and food packaging additives in the “generally recognized as safe” category—particularly those made from materials that are not considered “new” (e.g., carbon nanotubes, which are made of carbon). Generally, the FDA regulates products, not materials, and does not regulate most products unless they are shown to cause harm in use. For more information about nanomaterials in food and government regulations, see www.lafollette.wisc.edu/research/Nano/nanorisk/food.html.

The types of health outcomes considered in studies to date are extremely limited. Toxicological studies have only examined a small number of short-term and small-scale health effects of single nanomaterials, usually on the lungs. Given that a body of existing research on existing nanomaterials demonstrates the capacity of this class of materials to cause pulmonary effects, and inhalation is likely to be a significant route of exposure in certain contexts (e.g., the workplace), the focus on pulmonary outcomes is logical. However, given that engineered nanomaterials can migrate out of the lungs into the bloodstream, and other types of exposures (e.g., dermal, ingestion) are also likely, what systemic effects might they have in other tissues and whole organisms over the long-term? Lead and cadmium used in quantum dots are known reproductive and developmental toxins, and a few recent studies suggest that various other kinds of nanomaterials may cause reproductive or development effects. Will engineered nanoparticles used in materials and products contribute to reproductive or developmental problems over the long term? Further, given that most people are likely to be exposed to a variety of engineered and incidentally-produced nanomaterials at the same time, what might the interactive effects of exposures to multiple engineered nanomaterials be?

Addressing these questions would require long-term studies on a wider range of materials and exposure contexts, and more importantly, interdisciplinary research models that include toxicological, epidemiological, ecotoxicological, engineering, socioeconomic, and public health considerations. Toxicological studies typically dose lab animals with relatively large amounts of single substances over short periods of time. While they provide critical information about the potential toxicities of materials, they may not be well suited to predict long-term health effects in humans, who are likely to be exposed to much lower levels of complex mixtures of substances over longer periods of time.15
Current and Future Workplace and Public Exposures

In the case of nanomaterial risk assessment, as with many other environmental pollutant risk assessments, by far the largest and most important data gaps are related to the lack of real-time exposure assessments, which are essential components of risk characterization. Exposure assessment refers to the identification and characterization of the populations exposed, and determines the magnitude and duration of the exposures. Real time exposure assessments require monitoring in actual exposure contexts, and are unfortunately often the most neglected aspects of risk assessments.13

Although several studies have noted that the potential for human exposures to engineered nanomaterials is significant, little is known about exposures to engineered nanomaterials in workplaces or via consumer products. As of late 2005, an estimated 1645 nanotechnology companies were operating in the United States.2 Nanomaterial production levels, currently estimated as in the thousands of tons per year, are increasing dramatically.1,2 Concerns about occupational exposures to fullerenes and carbon nanotubes were raised as early as the 1990s, and more recently, several toxicologists and occupational health specialists have again raised concerns about occupational exposures to carbon nanotubes as production levels increase. Based on their experimental findings, one group of researchers speculated that using the current Occupational Safety and Health Administration permissible exposure limit (PEL) for carbon nanotubes (based on graphite), workers exposed to nanotube dust at a fraction of the PEL concentration would develop serious lung lesions.16 Other public health researchers propose that given recent findings on carbon nanotubes’ toxicity and likely levels of nanotube exposures in production facilities, surveillance of workers for fibrosis is warranted.17 Several scientists have concluded their production facilities, surveillance of workers for fibrosis should be conducted, and protocols should be developed for the monitoring of surface area emissions.6

Real-time exposure assessments are essential for toxicological studies, risk characterization, and risk management and communication. Exposure data from “real-world” contexts would help toxicologists select relevant doses for future studies. Exposure data could also help health and safety experts track changes in exposure levels through time, develop appropriate safety precautions if necessary, and would greatly aid any epidemiological studies done in the future. Although surface area monitoring is necessary and the equipment is not available at many facilities, the National Institute of Occupational Safety and Health proposes that surface areas of nanoparticles found in workplaces could be estimated using currently available technologies such as those used to monitor existing ultrafine particulates. Further, the first priority in exposure control is prevention or containment of hazardous workplace emissions at their source,11 so identifying sources of nanomaterial emissions in workplaces seems prudent at this point, to identify potentially problematic emission sources and design safety control strategies. While better nanomaterial monitoring techniques are being developed, workplace emission sources could be identified using aerosol number concentrations.11

Current and Future Production Levels and Emissions

Broader public exposures to nanomaterials will depend on the types of nanotechnology consumer products on the market, the types of nanomaterials included in these products, and the nature and levels of emissions from nanotechnology labs and industries. There are many unanswered questions about these issues. What are the current and projected levels of nanomaterial production? Many environmental pollutants (e.g. dioxins, mercury, phthalates) are additives or byproducts of industrial processes. Unfortunately, nanomaterial products on the market, production levels, and emissions are not systematically tracked by any government agencies. What kinds of emissions do nanomaterial production processes involve? Will they add significantly to incidentally-produced nanoparticles?
in air pollution? What sorts of substances are added to nanomaterials during production, and are they likely to leach out of these materials at any point in their life cycle? Is the public likely to be exposed to harmful levels of these materials now or in the future? Without this information, it will be difficult to anticipate current or future public health effects.

**Ecotoxicological Effects**

Understanding potential environmental and public health exposures and effects will also require addressing ecotoxicological questions. Many analysts predict that the most significant releases of nanomaterials will occur during disposal and recycling. Because they are so reactive, nanomaterials are likely to interact with other natural and synthetic materials (including other nanomaterials) when they enter the environment. Some biomedical nanomaterials are specifically designed to target certain tissues or cells, and others (e.g., fullerenes) are strong anti-microbials. Other nanomaterials, such as silver nanoparticles, are being added intentionally to clothing and textiles to give them antibacterial properties. How might these materials affect ecosystems if they enter the environment through waste streams, and how might these changes affect human and ecological health over the long term? Where might non-biodegradable nanomaterials, such as carbon nanotubes, accumulate? If they end up in incinerators, what types of materials will result from their combustion? Modeling some of these potential processes could help scientists and policymakers anticipate ecosystem and public health impacts of emerging nanotechnologies. Ongoing monitoring of nanomaterial facilities would provide critical baseline data and track changes in nanomaterial emissions through time. Moreover, testing nanomaterials for degradation and leaching byproducts, emissions and ecosystem monitoring, and comprehensive ecotoxicological studies could provide early warnings of potential problems.

**CONCLUSIONS**

Significant data gaps challenge nanotechnology risk assessors. Scientists and regulators need to characterize the wide range of nanomaterials being produced, standardize definitions for nanomaterials, and understand their complex behaviors in different media. Much is unknown about the dose-response curves and toxicological modes of action of specific nanomaterials and how these materials might enter the body. Moreover, a variety of broader, longer-term data gaps need to be addressed. Novel nanomaterials already on the market have not been studied for toxicological effects. There is no systematic information available about nanomaterial production levels, exposures in workplaces or labs, and exposures related to consumer products. Little is known about emissions from nanomaterial production facilities or the fates of these emissions in the environment. Many of these data gaps will need to be filled to develop comprehensive and protective risk assessments and risk management strategies for nanotechnologies.

Addressing these data gaps, ultimately, requires funding for research and risk assessments. Unfortunately, relatively little government money has been allotted in the US National Nanotechnology Initiative to address these gaps. More funding is needed to address the toxicological, epidemiological, ecotoxicological, and occupational safety data gaps outlined above. Without filling these data gaps, risk assessments will be difficult and risk management strategies are likely to be inadequate. Even though there are still significant data gaps about exposure monitoring methodologies and materials characterization, potential workplace exposure issues should be addressed as soon as possible in order to develop appropriate health and safety measures. Workers in nanomaterial industries and researchers in academic institutions should take available safety precautions while data gaps are being addressed. Similarly, nanomaterial facilities should take steps to prevent releases of engineered nanomaterials into air, water, and soil.

**REFERENCES**

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