



Implications of Nanotechnology for Environmental Health Research

Lynn Goldman and Christine Coussens, Editors,
Roundtable on Environmental Health Sciences,
Research and Medicine

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IMPLICATIONS OF NANOTECHNOLOGY FOR ENVIRONMENTAL HEALTH RESEARCH

Lynn Goldman and Christine Coussens, *Editors*

Roundtable on Environmental Health Sciences, Research, and Medicine

Board on Health Sciences Policy

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Willing is not enough; we must do.”*

—Goethe



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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was overseen by **Melvin Worth**, Scholar-in-Residence, Institute of Medicine, who was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

The Institute of Medicine's Roundtable on Environmental Health Sciences, Research, and Medicine was established in 1988 as a mechanism for bringing the various stakeholders together to discuss environmental health issues in a neutral setting. The members of the Roundtable on Environmental Health Sciences, Research, and Medicine come from academia, industry, and government. Their perspectives range widely and represent the diverse viewpoints of researchers, federal officials, and consumers. They meet, discuss environmental health issues that are of mutual interest (though sometimes very sensitive), and bring others together to discuss these issues as well in a neutral setting. The purpose is to foster dialogue and discussion across sectors and institutions, and to illuminate issues, not resolve them. To allow full and candid participation by all members, the Roundtable identifies approaches, but does not make recommendations or endorse courses of action. The Roundtable's twelfth meeting examined the environmental health issues surrounding the emergence of nanotechnology. This discussion continued the theme established by previous Roundtable workshops, looking at rebuilding the unity of health and the environment. This workshop summary captures the discussions and presentations by the speakers and participants, who identified the areas in which additional research was needed, the processes by which changes could occur, and the gaps in our knowledge. The views expressed here do not necessarily reflect the views of the Institute of Medicine, the Roundtable, or its sponsors.

The timing of this meeting is important as society prepares for nanotechnology. Presently, we have a number of nanotechnology products that are on the market. Others are close to market or still in development. What this means is that, in the next decade, we will have an onslaught of products that hold great promise for revolutionizing how we manufacture products, communicate with each other, and treat disease. With this new technology come a number of uncertainties. At the beginning of this year, there were a few reports from a number of organizations that questioned the safety of some of these products for health and

the environment. These reports did not call for a moratorium on nanotechnology, but they did suggest that the field of environmental health must now take a critical look at this emerging technology and develop a research agenda for addressing critical issues related to the impact of nanotechnology on health and the environment. The role of the environmental health scientist is not to question whether a technology should be developed, but rather to create a framework so that, as these technologies come to market, scientists and policy makers will be in a better position to put policies in place to safeguard environmental health and inform the public of any risks involved.

Why now, when there is little evidence that nanotechnology will have toxic effects? With previous emerging technologies, such as genetically engineered foods and genomics, there have been uncertainty and concern about health risks. Scientists and policy makers point to the misstep that occurred when genetically engineered foods were introduced to the market. The public questioned their safety, and the technology stumbled as environmental health research was put in place to better answer the questions. Even today, the Institute of Medicine is involved in looking at some of the issues surrounding genetically engineered foods and will likely continue to do so for the foreseeable future.

The field of nanotechnology may be at risk in a number of ways, and speakers during the workshop considered scenarios where nanotechnology could be a liability or an asset depending on how the various products enter the marketplace and the extent of unintended consequences. During the meeting, the need for open communication was discussed in greater detail as some speakers and participants suggested that trust is very important. Enforcement of regulations and solid research planning are crucial if scientists and policy makers are going to have the answers about the implications of nanotechnology.

At the moment, the funding for research and development of the science is outpacing the research on related environmental health issues. With the resources available, the field needs to examine the technology so that the science is in a better position to answer basic questions. A research agenda will need to be developed to ensure that the right questions are being asked and that the research effort is coordinated. There needs to be flexibility in the program to respond to emerging challenges as they occur. Complicating the research is the lack of a nomenclature for the field. Currently, the science is based on the size of nanoparticles, but doesn't take into account the basic chemical structure, such as titanium or carbon, or the surface coating of the nanoparticles. It remains to be determined whether these particles are new chemicals or not. The discussion at this meeting could not begin to answer the questions, but certainly pointed to a need for a research agenda for the field.

As we reflect on the meeting, we are reminded that the public is an important part of the process. Nanotechnology holds great promise for the health and environment, but we need to ensure that our knowledge of any risks develop at a

similar rate as our knowledge of the technology. By knowing about the risks and how to address them, environmental health scientists will be better able to serve the public.

Paul G. Rogers,
Chair

Lynn Goldman
Vice Chair

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Summary

Nanotechnology is often described as an emerging technology—one that not only holds promise for society, but also is capable of revolutionizing our approaches to common problems. Nanotechnology is not a completely new field; however, it is only recently that discoveries in this field have advanced so far as to warrant examination of their impact upon the world around us.

The value of nanomaterials in many technology areas is very high because of their versatile properties. As a result, the investment in nanotechnology by the U.S. government has had a very steady growth; in 2004 investment from a range of different federal agencies reached nearly \$1 billion, noted Kenneth Olden, National Institute of Environmental Health Sciences. Industrial investment in this area is also growing steadily. Today some nanomaterials are already being used commercially. For example, some companies are using TiO₂ nanoparticles in sunscreen lotions because they provide transparency to a sunscreen, and are believed to be less toxic than the organic molecules currently used as UV absorbers in many sunscreen formulations. Nanomaterials can also be found in sporting equipment, clothing, and telecommunication infrastructure. The future of nanotechnology is boundless, according to some speakers. Some of the items that exist today were a topic of science fiction a decade ago and have the potential to transform our society very quickly, said Douglas Mulhall, author of *Our Molecular Future*.

Nanoparticles fall into three major groups: natural, incidental, and engineered, noted Vicki Colvin, Rice University. Naturally occurring nanomaterials such as volcanic ash, ocean spray, magnetotactic bacteria, mineral composites and others exist in our environment. Incidental nanoparticles, also referred to as waste particles, are produced as a result of some industrial processes. The third category of nanoparticles is engineered nanoparticles—these are the particles associated with nanotechnology. Engineered nanoparticles are subclassified by the type of basic material and/or use: metals, semiconductoris, metal oxides, nanoclays, nanotubules, and quantum dots. Within each category the shapes,

sizes, and surface coatings further determine structure and function of these molecules. Each such material has been specifically designed for function, such as the fullerene C₆₀, which is used for fuel cell applications. Very little is known about engineered nanoparticles and how they interact with cells or human organisms, noted Colvin.

BENEFITS AND POTENTIAL NEGATIVE IMPACT OF NANOTECHNOLOGY

Nanotechnology has direct beneficial applications for medicine and the environment, but like all technologies it may have unintended effects that can adversely impact the environment, both within the human body and within the natural ecosystem. While taking advantage of this new technology for health, environmental, and sustainability benefits, science needs to examine the environmental and health implications.

Recently, nanotechnology has received considerable attention from the media. Most of the initial reports have been positive; however, scientists should not forget that not all nanomaterials will be benign, said Kenneth Olden, National Institute of Environmental Health Sciences. Therefore, it is very important to identify the negative aspects of the technology before we introduce it to the marketplace. During the workshop, many speakers and participants spoke of the paucity of data for engineered nanoparticles and cautioned against solely relying on the research of natural and incidental nanoparticles.

Determining toxicity can be complicated because not all engineered nanoparticles are more toxic than fine-sized particles of the same chemical composition. The surface coatings of particles, exposure to UV radiation, and dispersion properties can change the behavior of the particles, noted Eva Oberdörster of Southern Methodist University. For example, in pulmonary studies, whether particles aggregate and then disaggregate once they reach the lung fluids as well as the process for generation of nanoparticles, for example, fumed versus precipitated silica seems to be relevant. David Warheit, of the DuPont Company, suggested that developing a working hypothesis for determination of particle toxicity will depend on the capacity of the particles to cause cell and lung injury, promote inflammation, inhibit macrophage function, and persist in the lung. Finally, Warheit observed that species differences complicate research; for example, rats appear to be particularly sensitive to particle-induced pulmonary toxicity.

Some current hypotheses suggest that some engineered nanoparticles may be more toxic (inflammatory) than other fine-sized particles of identical chemical composition, noted Warheit. This concept is based primarily on a system evaluation of three particle types: titanium dioxide, carbon black, and diesel particles. However, he noted that the current hypotheses are based on a paucity of data.

John Froines of UCLA raised the question whether the research that scientists are doing on airborne particulate matter related health effects has relevance

to understanding potential issues with respect to nanotechnology. He suggested that there are areas where there are significant differences, but there are also places where there are commonalities. For example, most of the ultrafine particles from diesel emissions are in the 10 nanometer range, classifying them as nanoparticles. He suggested that a number of biochemical processes may be similar in both the air pollution particles and the engineered particles.

U.S. GOVERNMENTAL INVOLVEMENT IN ENSURING SAFETY

The potential health and environmental effects of nanoparticles and nanomaterials today raise public concern about nanotechnology. Health and environmental agencies in the United States have the responsibility to provide leadership to ensure the thorough assessment of safety and environmental effects of the new technologies.

Government policy makers need to ensure that nanotechnology is developed as a safe consumer product, said David Rejeski of Woodrow Wilson International Center for Scholars. Because many of the existing governmental regulatory frameworks are 30 to 40 years old—conceived when nanotechnology did not yet exist—they may not be adequate today. Yet, new frameworks have not been proposed.

NIH is working to develop some effective, high output, more informative, and less costly systems and has identified several areas for research in nanomedicine, said William Suk of NIEHS. One of its primary objectives is to obtain a comprehensive database and develop quantitative ways of measuring nanomaterials. The National Institutes of Health defines nanomedicine as the integration between nanotechnology and nanoscience. NIH is planning to support research on biological systems and molecules such as proteins, DNA, and RNA and how these molecules interact with each other as well as with environmental agents. The other need that NIH has identified—with the help of about 100 scientists—is to develop the mathematical and analytical tools to interpret measurements. Unfortunately, there are no models and tools yet to quantify the responses in such systems and to interpret what they mean. Thus, mathematicians and chemists need to get involved in the effort to understand the significance of these variations, changes, and readouts in terms of biological processes and subsequent effects on organisms.

Barbara Karn of the Environmental Protection Agency stated that by 2008, the total global demand of nanoscale materials, tools, and devices is projected to be about \$29 billion. To ensure that universities and research centers in the United States can perform the highest quality research in this rapidly growing area of technology, the EPA has plans to fund research in the areas of health and environmental effects of manufacturing nanomaterials, exploring topics such as their bioavailability and bioaccumulation. At the same time, there are very real prospects for the use of nanotechnology to extend into the realm of environmental

protection and remediation of contaminated sites or other environmental problems. Thus the EPA also plans to fund research on use of nanotechnology to develop new methods for treatment and remediation.

Likewise, NIOSH is concerned with identifying occupational health risks from nanoparticle exposure and considering how to control the risks, whether through reducing risk or reducing the impact. However, to be in a position to assess risk, additional information is needed regarding toxicity of the materials, how they interact biologically in the body, and what the health effects are resulting from toxicity. Additionally, scientists need to know about the exposures and the potential exposure routes (i.e. whether the material is inhaled, ingested, or absorbed cutaneously), noted Maynard.

Across the federal government, the agencies are coordinating work on nanotechnology through the National Nanotechnology Initiative (NNI). One of the NNI's goals is to establish research programs to understand the social, ethical, health, and environmental implications of the technology, according to Clayton Teague of the National Nanotechnology Initiative. This goal is being addressed by working groups, center of excellence, and NNI-sponsored workshops. One such working group, the National Science Technology Council's Subcommittee on Nanoscale Science, Engineering and Technology (NSET), was established in August 2003 to ensure effective communication among the research and regulatory agencies, and to identify specific research needs to support the regulatory decision making for nanoscale materials. Further, the NNI is encouraging inter- and multi-disciplinary research on these issues through centers of excellence and through discussions at a series of NNI-sponsored workshops on toxicology of materials, risk characterization and communication, and risk mitigation, noted Teague.

CANADIAN PERSPECTIVE

U.S. policy makers and scientists are not the only ones looking into the potential of nanotechnology. The Canadian government anticipates that nanotechnology will produce lasting social change and economic benefits to the country and also is investing in the development of these technologies. However, the use of these new technologies may pose risks to the environment and human health and are not well understood. To be able to answer the questions posed to them by the public, the Canadian government wants to know the downsides of the new technologies and also how to risk-manage these issues, observed Paul Glover, Health Canada. To risk-manage these issues they need to be put into perspective. Informing people about nanotechnology is critical and challenging, said Glover. Nanomaterials involve multiple substances and mixtures over varying periods of time with varying levels of intensity. Therefore, a substance-by-substance risk assessment approach may not be effective. Assessing the risk of nanotechnology is more complex. According to Glover, scientists will need to

update their risk assessment methodologies to create a multidisciplinary approach including industry; different levels of government; different types of researchers in chemistry, physics, and biology; and research regulatory scientists.

THE RIGHT TIME TO PLAN FOR NANOTECHNOLOGY

Today, we are at the optimal time to begin to study the impact of nanomaterials on human health, said Vicki Colvin of Rice University. We are looking at the birth of a new industry and beginning to address risk in a way that has not been done with any other developing technologies before, that is, well before large amounts of these materials are introduced into the environment or onto consumers. That provides us a unique opportunity to shape a new, emerging area with a lot of knowledge about environmental health issues that we would ultimately face and avoid the problems that have plagued chemistry in the past.

There is a need for increased levels of cooperation between the industries involved, public interest groups, and government parties to find economically viable solutions while still protecting the environment and health, asserted John Balbus, Environmental Defense. This is not a small goal, as it is important that nanotechnology development is done right the first time. Modern history has produced a number of technological advances that had such great promise for revolutionizing society; however, Balbus noted that these advances sometimes occurred at the expense of safety. For nanotechnology, the question is how does the science move forward in a way that best protects the public and gets health and safety right the first time. David Rejeski of Woodrow Wilson International Center for Scholars echoed many of these ideas and suggested that unlike genetically modified organisms where only a segregated sector is involved and risk prevention is more manageable, the impacts of nanotechnology will not be confined to one sector, but will be seen across multiple sectors and multiple products. He further suggested that policy makers need to start thinking about voluntary agreements with industry on the responsible use of nanotechnology and push the development of more models that bring together universities, NGOs, and industry to develop principles and best practices. Finally, Balbus noted that the process for conducting research and determining policy directions needs to be an open process with opportunities for public comment.

1

Preparing for Nanotechnology: Health, Policy, and Emerging Issues¹

In recent years, nanoparticles (particles in the size range of 0.1 nm to 500 nm) have received considerable attention from both science and industry as new information about these particles and their potential societal benefits. Nanoparticles fall into three major groups: natural, incidental, and engineered (see Table 1-1), noted Vickie Colvin, Rice University. Naturally-occurring nanomaterials such as volcanic ash, ocean spray, magnetotactic bacteria, mineral composites, and others are ubiquitously present in the environment. Incidental nanoparticles are often by-products produced as a result of industrial processes. The third category of nanoparticles is engineered nanoparticles. These are materials that have been specifically designed for function, such as fullerene C₆₀, which is used for fuel cell applications.

Nanotechnology is a broad description that is given to processes and technologies used to produce materials which are purposely engineered through the manipulation of atoms. The central tenet of nanotechnology is that almost any chemically stable structure that does not violate existing physical law can be built. By utilizing the basic properties of atoms, scientists have been able to precisely fabricate structures to create less bulky, stronger products and applications.

There are four basic categories of nanoscale materials that are being sold as commercial products and materials that may need to be regulated. The metal oxides—such as ceramics from oxides of zinc, iron, cerium, and zirconium; chemical polishing agents from semi-conductor wafers; scratch resistant coatings for glass; and cosmetics and sunscreens—are the biggest group of current commercial nanomaterials. Another group of nanomaterials used in commerce is nanoclays. Nanoclays are naturally-occurring plate-like clay particles that

¹This chapter was prepared by staff from the transcript of the meeting. The discussions were edited and organized around major themes to provide a more readable summary and to eliminate duplication of topics.

TABLE 1-1 Major Groups of Nanoparticles

Natural	Anthropogenic	
	Incidental	Engineered
Volcanic ash	Combustion products	Carbon nanotubes
Ocean spray	Frying, cooking	Quantum dots
Biogenic magnetite:	Sandblasting	Sunscreen pigments
<i>Protoctists, Mollusks,</i>	Mining	Fullerenes
<i>magnetotactic bacteria,</i>	Metal working	Semiconductor wires
<i>Arthropods, fish, birds,</i>	Biomaterial degradation	
<i>human brain, [meteorite]</i>	>10,000 peer-reviewed publications	~ 50 overall
Forest fire smoke		
Mineral composites		
Ferritin (12.5 nm)		
lipoprotein particles		
<i>(1-75 nm, plasma)</i>		
Clouds		
>500 peer-reviewed publications		

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improve strength, harness, heat resistance and flame retardancy of materials and are used to produce barrier films in plastic beverage bottles, paper juice cartons, and tennis balls. The third group is nanotubes that are used in coatings to dissipate and minimize static electricity in fuel lines and hard disk handling trays; they can also be found in electrostatically paintable car exterior components, flame-retardant fillers for plastics, and field emitter sources in flat panel displays. The fourth group is quantum dots used in exploratory medical diagnostics and therapeutics and self assembly of nanoelectronic structures.

ISSUES IN NANOTECHNOLOGY INVOLVING ENVIRONMENTAL HEALTH SAFETY

Today the public is more educated, involved, and concerned about new technologies and industrial processes and their potential effect on human health and the environment than it was 50 or 60 years ago, said Kenneth Olden of the National Institute of Environmental Health Sciences. The potential health and environmental effects of nanoparticles and nanomaterials today raises public concern about nanotechnology. Health agencies in the United States have the responsibility to provide leadership to ensure the thorough assessment of safety and environmental effects of the new technologies as well as to communicate openly and clearly about the issues. Some of the new technologies, such as

genetically modified foods, are not well accepted by the public worldwide because health agencies did not involve and educate the public and policy makers in the beginning when the technology was being developed, stated Olden. Scientists and the government need to learn from this experience and ensure that this does not happen with other emerging technologies, observed Olden.

Recently, nanotechnology has received considerable attention from the media. Most of the initial reports have been positive because of its potential applications

in molecular medicine and communication. However, we should not forget that given the nature of nanoparticles, not all nanomaterials will be benign. Therefore, it is very important to identify the negative aspects of the technology before we introduce it to the marketplace. Otherwise, it would set us back for a number of years, said Olden.

Toxicology research on nanotechnology (engineered nanoparticles) has

no history so we will have to start from scratch. We are just at the beginning of this effort and it will take a lot of thoughtful consideration and planning to achieve positive results without wasting time and resources, concluded Olden. Such effects are beginning and are described in Chapter 4.

Most of the initial reports (in the media) have been positive; however, we should not forget that given the nature of nanoparticles, not all nanomaterials will be benign.

—*Kenneth Olden*

NANOTECHNOLOGY: POLICY IMPLICATIONS

Policy makers must ensure that nanotechnology is developed as a safe consumer product, said David Rejeski of Woodrow Wilson International Center for Scholars. Many of the governmental regulatory frameworks we have today were conceived 30–40 years ago, when nanotechnology did not yet exist and therefore do not specifically address the unique properties of nanomaterials. One issue is that people do not always trust the government to enforce the regulations, said Rejeski. What matters to the protection of public health and the environment is not regulation *per se* but the enforcement of regulation. Unlike genetically modified organisms (GMOs) where only a segregated sector is involved and risk prevention is more manageable, the impacts of nanotechnology will not be confined to one sector, but will be seen across multiple sectors and multiple products. Given the large investments in applied research it is not unreasonable that we could see 30–50 new nano-products appearing every month as more and more research bears fruit and companies drive toward commercialization. Rejeski suggested that nanotechnology development could encounter four plausible near-term scenarios that could make nanotechnology either a liability or an asset. He called these scenarios: “tipping scales,” “nano Bhopal,” “Hollywood wins,” and “old Europe.”

"Tipping scales" and *"nano Bhopal."* Nanotechnology is planned disruption: it is all about the search for novelty. If we have the ability to extract radically new properties and behaviors from existing chemicals and substances, we need to be careful about asserting that we can use past knowledge to predict future consequences. Policy makers have to bear in mind that nanotechnology is being developed globally, and not only in industrialized countries but also in developing countries that do not have strict regulations even for conventional chemicals. Therefore, there is a good possibility that an accidental exposure or release may happen in a developing country, a small business, or a research lab. Such an accident does not have to be on the scale of the 1984 Bhopal chemical plant disaster that occurred in India to attract global press coverage and provide a public backlash against nanotechnology. This scenario cannot be ruled out and it must be addressed. Many small businesses are receiving large amounts of venture capital investment and their main goal is to get product to market as fast as possible. If they cut corners in this process, mistakes could happen and tip the scale to the negative side of the public's perception of the entire industry (not just the specific technology involved). One way to guard against this kind of scenario is to use transnational corporations to encourage the responsible development and use of nanotechnology across their entire supply chain. Today, the scales of public opinion for or against nanotechnology could tip either way, said Rejeski, because the benefits of nanotechnology are not yet widely appreciated by the public and the negative consequences have received more press coverage.

Many of the governmental regulatory frameworks we have today were conceived 30–40 years ago, when nanotechnology did not yet exist and therefore do not specifically address the unique properties of nanomaterials.

—David Rejeski

"Hollywood scenario." Policy makers have to think of deeper social messages people receive from films, books, and games about what to trust and distrust in society and what and how things may go wrong with science and technology. Mad scientists have been the object of movie fiction since we have had movies and nanotechnology has been a major theme for science fiction writers for decades. Hollywood has already produced films where nanotechnology plays a role (Spiderman II and Agent Cody Banks) and the video game industry recently released NanoBreaker for the PlayStation 2, a game where the player must deal with nanotechnology which has gone out of control. The cumulative impact of the messages conveyed in the movies and other media is not necessarily positive, yet it can reach millions of people in a few weeks. One message embedded in many of the plots of these movies and video games is that technology can "bite back," often after we have integrated it into our lives. While scientists tend to dismiss these media representations as nonsense, the plots are memorable and

may seem more realistic to people who are generally uninformed about the technologies and underlying science. In the end, it is the story, or narrative, that sticks, not the intricacies of the science.

“Old Europe.” In general, European environmental NGOs and activists are more aggressive, radicalized, and media savvy, and have, to date, promoted a more cautious approach to new technologies than their American counterparts, said Rejeski. Much of the negative feedback against GMOs came from Europe, and the movement against nanotech in Europe may also evolve in a similar way. Rejeski stated that the European Union has developed and refined the *precautionary principle* over a number of years. This model rests on the premise that society needs to “learn and act,” in contrast to the United States approach to new technologies, which is more to “act and then learn.” Many European countries, as well as the European Union and Commission, also have rigorous technology assessment systems in place. In contrast, the U.S. Congress eliminated the Office of Technology Assessment (OTA) in 1995, which could have played an important role in evaluating genomics, nanotechnology, and other new science. According to Rejeski, it is important to have an office like OTA that can operate at the interface of science and public policy. This interface is traditionally underdeveloped and understaffed by government, but crucial to the development of new technologies in ways that are socially and environmentally responsible. In concluding, Rejeski suggested that policy makers need to start thinking about voluntary agreements with industry on the responsible use of nanotechnology and push the development of more models that bring together universities, NGOs, and industry to develop principles and best practices. It is very important to start this process today not two years from now, said Rejeski.

2

The Promise of Nanotechnology¹

Nanotechnology is often described as an emerging technology—one that not only holds promises for society but is capable of revolutionizing our approaches to common problems. Nanotechnology is not a completely new field; however it is only recently that discoveries have advanced so far as to warrant examination of their impact upon the world around us. Nobel laureate Richard P. Feynman, in his famous speech to the American Physicist Society in 1959, said “in the year 2000, when they look back at this age, they will wonder why it was not until the year 1960 that anybody began seriously to move in this direction.”

PRODUCTS OF TODAY

The value of nanomaterials in many technology areas is high because of their versatile properties. Investment in nanotechnology in the United States government has had a very steady growth; in 2004 we are approaching the \$1 billion a year in investment from many different federal agencies, said Olden. Industrial investment in this area is also growing steadily. It is said that the future of nanotechnology is potentially boundless if we can avoid the pitfalls. Some of the items that exist today were a topic of science fiction a decade ago and have the potential to transform our society very quickly, said Douglas Mulhall, author of *Our Molecular Future; How Nanotechnology, Robotics, Genetics, and Artificial Intelligence Will Transform Our World*. Today, some of the nanomaterials are already being used in commerce. For example, Proctor and Gamble is using titanium dioxide (TiO₂) nanoparticles to provide transparency in sunscreen

¹This chapter was prepared by staff from the transcript of the meeting. The discussions were edited and organized around major themes to provide a more readable summary and to eliminate duplication of topics.

lotions, as a less toxic alternative to the organic molecules currently used as UV absorbers in many sunscreen formulations. Other nanomaterials are incorporated in sporting equipment, clothing, telecommunication infrastructure, and fuel cells.

The future of nanotechnology is potentially boundless if we can avoid the pitfalls. Some of the items that exist today were a topic of science fiction a decade ago.

—*Douglas Mulhall*

Other examples of current nanotechnologies are three-dimensional printing with nanoparticles, high speed computing driven by nanotechnology, and computer-assisted design software with generic algorithms that learn by themselves. Three-dimensional printers were invented in the 1990s and commercialized in 2000 and are already being used to make products such as surgical models. Surgical models have the potential to match the exact needs of an individual patient while allowing surgeons to eliminate the need for exploratory surgery when they are doing reconstructive work.

Today it is technologically feasible to manufacture programmable nanofilters that eliminate the pressure requirement for desalinization and reduce the expenses by 99 percent, meaning the end of water shortages in arid regions. It could also potentially alter regional environments and convert deserts to forests by removing large amounts of fresh water from the oceans, postulated Mulhall.

With the invention of solar paint and principal solar cells based on nano-engineered organic plastics, fossil fuel dependence may begin to recede. Another nanotechnology-based invention is extremely strong materials called nanostructured aerogels. These materials are inexpensive and they could make structures resistant to earthquakes and hurricanes, which will have significant societal benefits, said Mulhall.

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ENVIRONMENTAL APPLICATIONS FOR NANOTECHNOLOGY

Some of the greatest potential uses or applications for nanotechnology in the environment are sensors, treatment, remediation, and green nanotech manufacturing and engineering, stated Barbara Karn of the Environmental Protection Agency. These applications can be further categorized as either reactive to existing environmental problems or proactive in anticipating and preventing future problems.

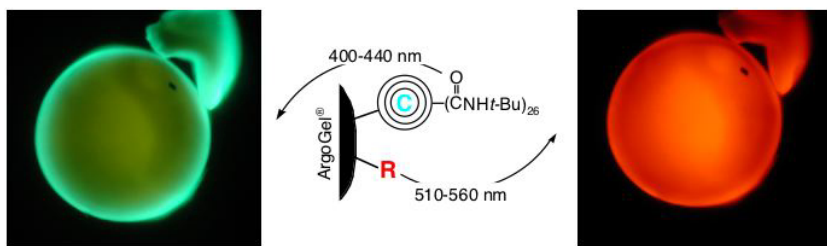
Reactive Applications

Reactive applications involve sensors, treatment, and remediation. Diverse research is being conducted on the use of nanoparticles as sensors to allow for accurate, real-time simultaneous sensing of a variety of compounds, often at extremely low concentrations and in hostile environments. Karn discussed a number of research projects sponsored by the Environmental Protection Agency that are aimed at developing applications for nanotechnology.

The research of Nongjian Tao at Arizona State University focuses on “lab on a chip” nanotechnology for on-site detection of ultratrace levels of heavy metal ions, including radioactive compounds, using a silicon chip which contains nanoscale electrodes separated by an atomic-scale gap. Thus, with the electrode position of only a few metal ions in this gap, the circuit can be completed, indicating the presence of various compounds.

Nanoscale sensors are also being investigated for detection of biological compounds such as algal toxins in the marine environment or mycobacteria present in drinking water. Robert Gawley of the University of Arkansas has developed fluorescent dendrimers displaying spatially resolved microdomains on polymer beads for the detection of different algal toxins. The binding of different toxins results in specific fluorescence wavelengths, depending upon the spatial resolution of the dendrimers on the polymer beads, which correlate to known toxins (Figure 2-1). This technology would be a less costly and time consuming alternative to current methods used to monitor shellfish populations,

Fluorescent Dendrimers



Spatially resolved microdomains on polymer beads

FIGURE 2-1 Depending upon the spatial resolution of the fluorescent dendrimers on polymer beads, the binding of different toxins results in a correlating specific fluorescence wavelength. SOURCE: Cardona, et al., 2002. © Helvetica Chimica Acta AG. Reprinted with permission.

which are especially sensitive to marine toxins such as those responsible for large fish kills on the Eastern seaboard.

Advances in nanodetection would allow not only for detection of microbial pathogens in drinking water, but also the quantization of these organisms, noted Karn. A piezoelectric microcantilever sensor is a method of detection and quantization being developed by Wan Shih of Drexel University, which involves the use of micron-scale cantilever arms coated with specific DNA strands. Test water is run through the piezoelectric cantilever sensor and when target molecules bind the cantilever becomes heavier, changing its rate of vibration and creating an electric current. Thus movement of the cantilever by just a few nanometers correlates with the number of molecules captured on its surface, allowing for detection and quantization of specific pathogens in the water.

Treatment and remediation are two other reactive applications made possible by nanotechnology research. Nanoscale molecules used in treatment and

remediation have the ability to access areas that larger molecules cannot, and can be coated to prevent reactivity with surrounding soil particles. In addition, the researchers are following the paths of these nanoparticles, so the fate and transport of these molecules as well as the clean-up efficiency is being studied, added Karn. For example, iron oxide

Nanotechnology will make possible great advances in our ability to retroactively solve environmental issues.

—Barbara Karn

particles encapsulated in a protein shell can be used for the reduction of heavy metals such as hexavalent chromium, a frequent groundwater contaminant. Karn pointed out that clean-up is where nanoscale makes an impact: for example, the smaller the radius of zero-valent iron particles, the more milligrams of trichloroethylene (TCE) are reduced per milligram Fe per hour. Iron particles with a radius of 1 μm can reduce 0.186 mg TCE/mg Fe/h. However, this same type of particle with a radius of 1 nm can reduce 186 mg TCE/mg Fe/h. The nanoscale particle is three orders of magnitude smaller, but its rate of TCE reduction is three orders of magnitude greater than that of the microscale particle.

Research varies in the approaches taken to reach the endpoint of treatment or remediation, said Karn. Some researchers attempt to surface-coat molecules to pull them together, and maybe detoxify them while others coat them so that the desired nanoparticle is isolated and collectable. Regardless of the strategy utilized, Karn proposes that nanotechnology will make possible great advances in our ability to clean up the environment.

Environmental Proactive Applications

Proactive applications mainly include green manufacture and green energy productions. Green energy can be produced using nanotechnology to create solar

and fuel cells as potential sources of commercially available alternative clean energy sources. Green manufacturing has two aspects: the use of nanotechnology in the design process to eliminate polluting waste products at their source and, alternately, the efficient production of nanomaterials themselves.

Green manufacturing improves catalysis specificity, producing more of the desired compounds and less waste and pollution. Researchers are exploring how to stabilize nanoparticles without harmful additives that would pollute water and soil. Often these processes require less time, sometimes hours instead of days, and can potentially significantly reduce the cost of making nanoparticles. Consumption of energy during the manufacturing processes can also be reduced, and Karn noted that many aspects of nanotechnology and its application in manufacturing are devoted to the research and production of cleaner and more efficient energy sources.

Green energy can be produced using nanotechnology to create solar and fuel cells as potential sources of commercially available alternative clean energy sources.

—Barbara Karn

Nanotechnology has a great future for providing solutions in the area of green energy applications, said Karn. New research is exploring the use of electrochemistry, nanoscale photosynthesis, micro fluidic biofuel cells, and photo electrochemical cells, among other endeavors, to address the growing need for safe, inexpensive, and renewable energy resources. For example, solid state lighting can be enhanced by the use of nanocrystals/polymer composites for light-emitting diodes (LED). This allows for brighter, more efficient, and less costly lighting for use in such equipment as traffic signals. Karn stated that use of LED technology could reduce the consumption of light energy up to 50 percent by 2020 in the United States alone. Reduction of carbon emissions by an estimated 28 million metric tons per year has obvious climate change and materialization implications. Economically, this translates to a savings of \$100 billion in fewer than 20 years (Bergh et al., 2001).

The challenges facing researchers with regard to fuels in the realm of transportation are three-fold: how to produce the fuel, how to transport it to the location where it is needed, and how to store the fuel safely. These questions are especially pertinent to hydrogen fuels and were addressed in President Bush's State of the Union address. Aimed at putting an appreciable number of motor vehicles on the road that are powered by hydrogen fuel by 2020, the initiative allocates \$1.2 billion to research and production of these vehicles.

Nanotechnology may offer solutions in all these areas of concern, noted Karn. Nanomaterials may be used to create harder alloys and ceramics for cutting tools to increase the efficiency of manufacture. Motors may be made more efficiently by incorporating low-loss, high-performance magnets. The use of lightweight materials with low failure rates and surface tailoring of parts to

produce less friction and increase resistance to wear, would decrease fuel consumption while improving the safety of ground and air transportation. Finally, the use of nano catalysts will lead to cleaner, less costly, and environmentally friendly petroleum refining and the production of more efficient and productive batteries and fuel cells, said Karn.

Sustainability is a top consideration in the quest for new fuel sources, particularly with reference to the issue of global climate change. The harm to human health and the environment that the transportation systems produce is well known; thus, with the better catalysts, better kinds of tires, better, lighter materials that nanotechnologies can offer, this can help affect climate change by changing the kind and amounts of resources consumers use, said Karn. Lighter-weight materials lower the amount of fuel needed for transportation, more efficient electronics use less electrical energy, less production energy can be used with increased production efficiency, and fuels themselves can burn cleaner due to better filtration.

Research on Nanotechnology Life Cycles

Prospects for the use of nanotechnology also extend into the realm of environmental protection and remediation. Karn stated that by 2008, the total global demand of nanoscale materials, tools, and devices is projected to be about \$29 billion (Business Communication Company, 2004). To ensure that universities and research centers in the United States can perform the highest quality research in this rapidly growing area of technology, the EPA has plans to fund research in the areas of treatment and remediation, environmental implications, and the health and environmental effects of manufacturing nanomaterials, exploring topics such as toxicology, fate and transport, and bioavailability and bioaccumulation.

The EPA is especially concerned with the study of manufactured nanomaterials and their life cycle aspects, the role of industrial ecology, toxicology, and exposure. One EPA project examines the full life cycle of nanomaterials and researches the following:

- Where are the impacts of products that have nanomaterials in them?
- Where in the life cycle are their impacts going to fall?
- Are there any impacts in the use stage like automobiles; the disposal stage, like electronic equipment; or the extraction stage like some of our mining endeavors?
- How will the move to nanotechnology change a material's flow within a particular sector?

Scientists need to look where in the full life cycle the impacts from these products and processes may occur. Nanotechnology can offer direct beneficial applications to the environment, and society can take advantage of this for both

environmental and sustainability benefits. However, it is important to remember that this evolving technology can also have indirect effect on the environment. If solar paint has a persistence problem in the environment, but avoids the pollution created by fossil fuels, or if super-strong materials have similar problems, but help us to avoid the pollution that comes from whole communities being destroyed by a chemical spill, then researchers must be careful to weigh the implications concurrently with the benefits of developing nanotechnology applications, said Karn.

If solar paint has a persistence problem in the environment, but avoids the pollution created by fossil fuels, then researchers must be careful to weigh the implications concurrently with the benefits of developing nanotechnology applications.

—Barbara Karn

Nanotechnology has direct beneficial applications for medicine, public health, and the environment but it also has peripheral effects that can impact the environment, both within the human body and within the natural ecosystem. While taking advantage of this new technology for health, environmental, and sustainability benefits, the U.S. government also must examine the risks concurrently with development of new applications.

NANOTECHNOLOGY, HUMAN HEALTH, AND MEDICINE

NIH is supporting the development of effective, high output, informative, and less costly systems and has identified several areas for research in nanomedicine, which it defines as integration of nanotechnology and medicine. NIH is planning to support the research on biological molecules such as proteins, DNA, and RNA as well as research into how these molecules interact with each other and with environmental agents. One of its primary objectives is acquisition of a comprehensive database and development of quantitative nanomaterial measurements, said Olden. NIH researchers and independent scientists have identified the need for mathematical and analytical tools to quantify manipulations and interpret measurements of nanomolecules. Thus, mathematicians and chemists need to get involved in the effort to understand what these variations, changes, and readouts mean to biological processes.

Once an early biomarker of a disease or dysfunction is identified, then scientists can use targeted pharmaceutical or gene therapy to correct the faulty components.

—Kenneth Olden

Additionally, NIH is planning to develop very sensitive detection systems that would be able to detect a single cell or a few cells that are diseased or perturbation of a pathway. Once an early biomarker of a disease or dysfunction

is identified, then scientists can use targeted pharmaceutical or gene therapy to correct the faulty components, noted Olden.

Pebble Chemistry as an Example of a Medical Application of Nanotechnology

Nanotechnology, especially as it is applied to biological systems, is an intricate, interdisciplinary field, said Martin Philbert of the University of Michigan. Researchers have begun to build nanoparticles that are intrinsically biocompatible, that do not alert the immune system to their presence, and that can contain a variety of highly functional and highly specific elements that might be toxic but which are shielded from the biology by a shell. One example, the Probes Encapsulated by Biologically Localized Embedding (PEBBLE) was created as a nanoparticle platform with multi-functional capabilities (Figure 2-2).

Generally, PEBBLES are fluorescent dyes that are encased in a molecular shell, protecting cells from the dye and protecting the dye from cellular degradation or manipulation, stated Philbert. The presence and intensity of the fluorescence is directly proportional to the pathway or molecule that the sensor is measuring.

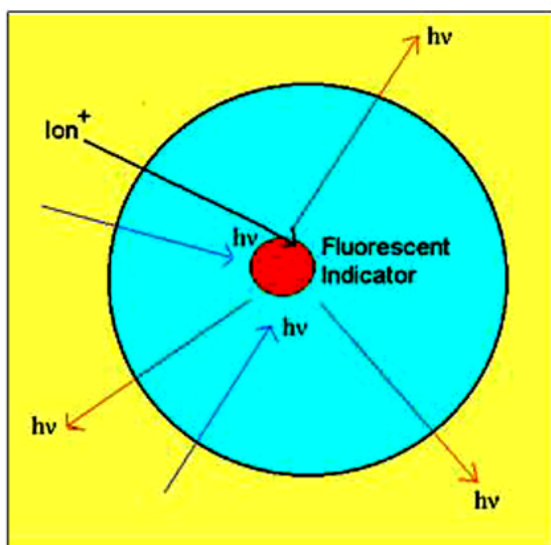


FIGURE 2-2 PEBBLES are fluorescent dyes that are encased in a molecular shell, protecting cells from the dye and protecting the dye from cellular degradation or manipulation. SOURCE Martin Philbert, unpublished. Reprinted with permission.

Currently, they are being used in research facilities and offer researchers the ability to measure real-time binding, translocation, and molecule production, instead of the widely used tools available for steady-state or endpoint measurements. However, they may have use for a wide range of research and medical needs.

PEBBLE Chemistry

The simplest iteration of a PEBBLE is a polymer shell that contains a fluorescent molecule, ranging in size from 20 nanometers to 600 nanometers in diameter. One 20 nanometer particle occupies 1 thousandth of a human motor neuron in the anterior horn of the spinal cord; thus, cells have a potentially tremendous capacity for the retention of a wide range of PEBBLES sensing and reporting on a variety of cellular pathways and processes.

Philbert stated that the analytical chemistry that can be performed within the conserved space of the cell is much more sophisticated. A dye can be incorporated that changes with time as a function of the analyte of interest. The system can also be constructed in a more complex fashion using ionophores. When irradiated with the appropriate wavelength of a laser, light is emitted and can be measured, allowing for an amazingly useful property where the measurement system is completely calibratable and the fluorescence is reversible, said Philbert.

PEBBLES as Stepping Stones to Understanding Cellular Processes

One aspect of nanoparticle research has focused on the use of nanoparticles as sensors of cellular activity. This can include extra cellular measurements, such as the presence of oxygen or nitrogen radicals in the extra cellular space and the presence of the molecules in the blood and tissue, or measurements at the subcellular level. Protein movement, oxidation or reduction reactions, and the production of super oxide ions within the cell may be tracked by the use of fluorescent nanoparticles. There are also design prototypes for measuring lead and mercury, and soon, according to Philbert, the ability to measure phosphorylation and other chemical reactions inside the cell will be possible.

The light emitted from individual nanoprobosc introduced into the volume of the cell can be viewed using confocal microscopy. The concentration of oxygen at each individual point is reported by a dot in the co-focal viewing field when observing the cell. The intensity of the light emitted by the dot indicates the concentration of oxygen at that point in the cell. With this new look at the cell, Philbert suggested that our assumptions about how oxygen enters the cell, diffuses through the cell, and is used in the cell may not be entirely correct.

Nanoparticles can also be used to track the movement of particular cellular compartments. Endosomes can take up the nanoparticle, and depending on surface charge, size, and other characteristics, transport them to the apical surface or the basal lateral surface of the cell.

The reason why scientists have attempted to go smaller and smaller is that they were trying to find out if there is a point at which the sensors that are being designed and placed into systems to measure biological activity begin affecting

or changing the very processes they are intended to measure. Once a molecule is below 100 nanometers, it begins interacting with proteins, potentially signaling proteins, and can result in entirely unintended consequences, which is why PEBBLES have been kept close to 100, and less than 200, nanometers. Thus while there are many advantages to keeping PEBBLES very small, scientists really do not know yet

With this new look at the cell our assumptions about how oxygen enters the cell, diffuses through the cell, and is used in the cell may not be entirely correct.

—*Martin Philbert*

what the interactions with proteins and other elements of the cell are going to be, said Philbert.

PEBBLES on the Path to Understanding Tumor Biology

One area of research, according to Philbert, focuses on targeting molecules to tumors for treatment and eradication. Coating a PEBBLE nanoparticle with a magnetically responsive metal allows researchers to target nanoparticles to specific locations within the body and to obtain a better image of tumors from magnetic resonance imaging (MRI). These MRI images reveal a significant contrast enhancement due to the presence of the nanoparticles within the tumor tissue, that is, nanoparticles allow for very good contrast from normal tissue, where the tumor becomes clearly visible to the observer (Figure 2-3).

Fine resolution of small tumors is not the only possibility within the same nanoparticle. Ruthenium (Sol Gel Ru-DNPs) can also be included within the

nanoparticle. When a laser is turned on, Sol Gel Ru-DNPs can produce a large amount of singlet oxygen only when it reaches the target, in this case a brain tumor called 9L gliosarcoma produced in the rat brain. Therefore, researchers can kill this clone of the gliosarcoma, which does not respond to chemotherapy or radiation therapy. Coupled with a fiber optic that is only a millimeter in diameter, the tumor can

The ultimate goal of this research is to create particles that are not going to interfere with the normal biology of the organism and are going to have very high therapeutic index.

—*Martin Philbert*

be stopped or at least reduced in size with time. Because the 9L gliosarcoma is extremely aggressive, if one or two cells are left, after some time the tumor will re-grow. However, with a single injection and only 10 minutes of laser irradiation

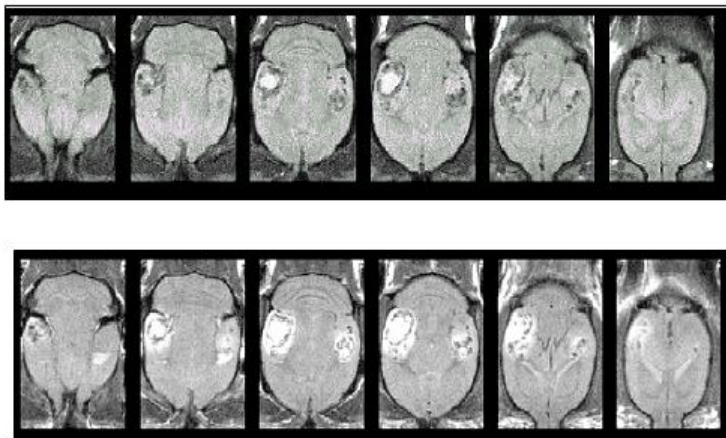


FIGURE 2-3 Effect of PEG Weight on Dynamic MRI Scanning of Nanoparticles. This figure shows Transverse multislice T1-weighted MR images acquired prior to injection of Gd: PEBBLES and Transverse multislice T1-weighted MR images acquired 60 minutes post-intravenous injection of Gd: PEBBLES revealing a significant contrast enhancement due to the presence of the nanoparticles within the tumor tissue. SOURCE: Brian Ross, University of Michigan, unpublished. Reprinted with permission.

tion Philbert's group demonstrated good cessation of growth or actual reduction in the tumor mass and increased life span of these animals by using these Sol Gel Ru DNPs.

Nanoparticles used in tumor killing experiments are larger than 100 nanometers; thus, they do not cross the blood-brain barrier (BBB), and therefore are excluded from healthy brain tissue, said Philbert. These nanoparticles penetrate into the tumor only when a tumor changes the porosity of the blood vessel. This process of BBB penetration takes approximately 5–10 minutes and once clearance through renal and other mechanisms is considered to be complete, the laser is turned on. The nanoparticles are delivered systemically and then pass through the BBB before a laser is turned on to activate the killing activity, but further research will be needed to understand what happens to these particles as they circulate through other parts of the body?

Approximately twenty different kinds of these nanoparticles have been created and researched *in vivo* in the Philbert lab alone, all of which have shown effects on the reticular endothelial system and the kidneys. These nanoparticles are discarded as the ultimate goal of this research is to create particles that are

not going to interfere with the normal biology of the organism, yet have a very high therapeutic index. Philbert suggested that many of the products that can be created will ultimately not be deployable because early safety testing will show them to be completely unfeasible from a toxicological standpoint.

3

Nanotechnology: Expanding Scientific Understanding

Today, science is at the optimal time to begin to study the impact of nanomaterials on human health, said Vicki Colvin of Rice University. Science is looking at the birth of a new industry, and beginning to address risk in a way that has not been done with any other developing technologies before (i.e. well before large-scale amounts of these materials are introduced into the environment or onto consumers). This provides public health with a unique opportunity to shape a new, emerging area with research on environmental health issues that we might encounter, while avoiding the problems that have plagued chemistry in the past.

Kenneth Olden of the National Institute of Environmental Health Sciences echoed this, and noted that very few studies have been done thus far on nanoparticles and their effect on human health and the environment. Science needs to start investing in research of these issues. Toxicity and bioavailability of engineered nanomaterials is largely unknown. He noted that it will be a daunting, costly, and time-consuming challenge to assess every single nanomaterial that is made individually, which means there will be a need to set priorities. NIH is trying to develop some effective, high output, more informative, and less costly systems. Two of its primary objectives are to maintain a comprehensive database and develop quantitative ways of measuring nanomaterials. Efforts such as this will help science develop standard materials for assessing environmental health impacts.

Unlike incidental particles, very little is known about engineered nanoparticles and how they interact with cells or human organisms. There are only about 30 papers written on the environmental and health impacts of these particles; however, there is a wealth of knowledge on incidental nanoparticles and how these particles interact with biological organisms, noted Colvin. Questions remain whether the engineered nanoparticles will act as a bulk solid or a molecular system (see Toxicology below).

SIZE ISN'T EVERYTHING

In most cases, nanoscale systems will alter in physical size upon interaction with an aqueous system. For example, it is very common for many nanostructures to adopt a different chemical form simply through relatively minor interactions; consequently, size is not a constant factor in biological interactions, noted Colvin. Furthermore, the surface area can make up a sizeable fraction of these materials, and they can be derived to make many different biomedical systems. By changing surface coatings the nanomaterial toxicity can almost be completely altered. For example, changing the surface features of the materials can change a hydrophobic particle into a hydrophilic one. Hypothetically, surface coats could, for instance, make it possible to eat nanoscale mercury if it has the right surface coating, while it may be dangerous to eat nanoscale table salt if the surface coating was not correct. For this reason, the scientists' typical view of toxicology, which is driven by the composition of an inorganic particle, may have to be modified for nanoscale materials, because the surface is going to affect different dimensions of environmental and health effects, according to Colvin.

INTERACTIONS WITH BIOLOGICAL SYSTEMS

Chemists and engineers interested in creating biocompatible nanostructures need to understand their interactions with biological systems. Colvin suggested that the challenge that nanomaterials pose to environmental health is that they are not one material. It is difficult to generalize about them because, similar to polymers, they represent a very broad class of systems. Many engineered nanomaterials have precisely controlled internal structures, which are structures of perfect solids. Over a third of the atoms in a nanoparticle are at the surface, and these are extremely reactive systems, which in some cases can generate oxygen radicals (see oxidative stress later in the chapter); however, nanoparticles can be tied up very tightly in covalent bonds and wrapped with a polymer. Because of the size of nanostructures, it is possible to manipulate the surface interface to allow for interactions with biological systems. Colvin noted that with the correct coating particles below 50 nm can translocate into cells relatively easily and are able to interact with channels, enzymes, and other cellular proteins. Those particles above 100 nm, based primarily on size of the particles, have more difficulty. Through the interactions with cellular machinery, there is potential for medical uses, such as drug delivery and cellular imaging.

ENVIRONMENTAL INFLUENCE OF TOXICOLOGY OF NANOMATERIALS

For applications such as drug delivery devices and therapeutics, there are well-established testing regimes utilizing whole animal and *in vitro* testing. How-

ever, for some of the environmental applications, scientists do not have those testing procedures in place, noted Eva Oberdörster, Southern Methodist University.

While coating or covalently modifying the outer surfaces of nanomaterials eliminates the toxicity of most particles, questions remain about whether under environmental conditions—as opposed to laboratory conditions, the nanomaterials will still be benign. In a recent study, it was demonstrated that if surface-modified C₆₀ materials were irradiated to UVA (i.e., ultraviolet radiation of 320–400 nm in wavelength) for 11 min or UVB (i.e. ultraviolet radiation of 290–320 nm) for 22 min, cytotoxicity returns (Rancan et al., 2002). Additional research by Drefus et al. (2004) suggests that air exposure and nanoparticle dose are also important for cytotoxic effects. When cadmium selenide (CdSe) quantum dots in a liver culture model are exposed to air or ultraviolet light, hepatocyte viability decreases as assessed by mitochondrial activity of QD-treated cultures (Figure 3-1). In this study, exposure to ultraviolet light for only 4 hours significantly decreased hepatocyte viability even at very low doses of nanomaterial. So, while these nanomaterials may be safe under laboratory conditions, a more reliable or maybe environmentally relevant endpoint is to weather these compounds under environmental conditions, concluded Oberdörster.

While these nanomaterials may be safe under laboratory conditions, a more reliable or maybe environmentally relevant endpoint is to weather these compounds under environmental conditions.

—Eva Oberdörster

ROUTES OF ADMINISTRATION AND POTENTIAL HEALTH EFFECTS

Fullerenes and other nanomaterials can accumulate in the body, depending on the dosing route. For oral administration, 98 percent of fullerenes are eliminated within 48 hours via feces and urine (Yamago et al., 1995). The 2 percent that is not excreted is found throughout the rest of the body, noted Oberdörster. Intravenous dosing is rapidly transported to the liver (73–92 percent), the spleen (up to 2 percent), lung (up to 5 percent), kidney (up to 3 percent), heart (approximately 1 percent), and the brain (approximately 0.84 percent) within 3 hours. After 1 week, 90 percent of intravenously administered fullerenes are still in the body, noted Oberdörster.

Inhalation of nanoparticles may also be problematic because the particles are often small enough that alveolar macrophages cannot detect or scavenge the particles for elimination. By evading alveolar macrophages, nanoparticles can enter the lymphatic and circulatory systems to be distributed throughout the body within 24 hours, noted Oberdörster. This has been studied with a number of

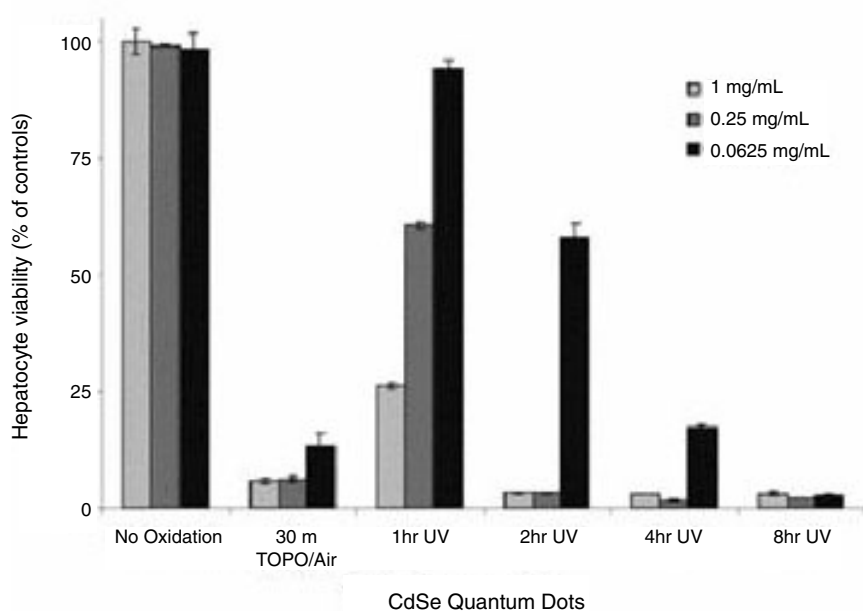


FIGURE 3-1 Toxicity of cadmium selenide (CdSe) quantum dots in liver culture model is dependent on processing conditions and nanoparticle dose. Hepatocyte viability as assessed by mitochondrial activity of QD-treated cultures relative to untreated controls. Thirty minutes of exposure to air while TOPO-capped renders QDs highly toxic at all concentrations tested. Ultraviolet light exposure also induces toxicity that increases with exposure time and is QD-concentration dependent. Biochemical assays of viability were confirmed via phase contrast microscopy where control hepatocyte cultures exhibited distinct intercellular boundaries, well-defined nuclei, and polygonal morphology. SOURCE: Drefus et al., 2004. Reprinted with permission from *Nano Letters* 4:11–18. ©2004 American Chemistry Council.

particles, including titanium dioxide. It should be noted that not all nanomaterials evade phagocytosis, and in studies using nano- vs. bulk TiO_2 , ~20% of nano-sized TiO_2 can be recovered by repeated lung lavages to obtain alveolar macrophages, as compared to ~80% of bulk-sized TiO_2 . Depending on the quantity of inhaled materials, it is also possible to overload macrophages. Inhaled particles can also be transported to the brain via the olfactory or trigeminal nerves. This process was first noted in studies from the 1940s, and the current hypothesis is that these nano-sized particles move in a similar mechanism as viruses. This is one mechanism to bypass the blood–brain barrier, Oberdörster suggested, and could be exploited for drug delivery.

OXIDATIVE STRESS

Nanoparticles, including C_{60} , metal Qdots, and TiO_2 can be redox active, which may lead to DNA cleavage, oxidative stress, and/or an inflammatory response. For example, C_{60} fullerenes, if exposed to light, can either make singlet oxygen or be electron donors to make super oxide radicals. The potential dilemma is that not only does the immune system use super oxide radicals to kill foreign toxicants; the super oxide radicals can cause hydroxyl radicals, which can lead to DNA cleavage. The good news is that the body has some ability to prevent the undesired DNA cleavage through super oxide dismutase, part of the antioxidant defense system, noted Oberdörster.

Oxidative stress is potentially a larger issue. A number of ambient or laboratory-produced ultra-fine particles cause oxidative stress, a mechanism that leads to cell damage or cell death. The severity of damage is dependent on the chemistry, as some particles result in more oxidative stress than others. In a recent study in her laboratory, Oberdörster looked at oxidative damage, brain translocation, and gene expression changes in large mouth bass exposed to fullerene C_{60} .

Glutathione (GSH), a molecule involved with antioxidant activity, can be used as a marker of redox activity. The gill region, where fullerenes would probably be present, showed decreased levels of GSH, which was unchanged in the liver and brain. Protein oxidation, another marker of oxidative stress, was unchanged in the liver, brain, and gills. What was interesting, noted Oberdörster, was the increase in lipid peroxidation in the brain, an increase not seen in the gills or the liver. She hypothesized that lower lipid peroxidation in the gills and liver of fullerenes-exposed animals suggests that some tissues are more capable of responding to and repairing fullerene-induced cellular damage.

Complementing this data, she found that in the liver the expression of some inflammation-related genes was modulated. Genes associated with hormone regulation, immune cell response, and clotting and anti-clotting pathways were found to alter their expression after exposure to fullerenes. Expression of repair enzymes was increased, suggesting that the fish were starting to repair damage incurred by the response to fullerene molecules. As this was a preliminary study, the fish were euthanized for experimental study before further response to the fullerene molecules could be studied.

Genes associated with hormone regulation, immune cell response, and clotting and anti-clotting pathways were found to alter their expression after exposure to fullerenes.

—Eva Oberdörster

NANOTECHNOLOGY, INHALATION, AND CYTOTOXICITY

Particle size determines whether particles are respirable or inhalable. This difference can be critical, as inhaled particles can be trapped and cleared, whereas respirable particles are often more likely to be retained. In rats, particle sizes less than 3 μm are considered to be respirable. For humans less than 5–10 μm is respirable, while 10–50 μm is inhalable, noted David Warheit of the DuPont Company. These particles tend to be deposited at the junctions of the terminal bronchioles and alveolar ducts in rats and the level of respiratory bronchioles in humans. The alveolar regions of the lung, which are primarily used for exchange of oxygen and carbon dioxide comprise 95 percent of the lung surface area and are the pulmonary compartment where diseases such as asbestosis and silicosis are manifested.

Particle size and aggregation is an important consideration for deposition in the alveolar region. Particles such as fine-sized iron (i.e., 1 μm) are primarily deposited as discrete particles though they have some limited potential to aggregate. Conversely, although there is a potential for some types of particles to disaggregate, ultra-fine or nanoparticles generally tend to deposit as aggregates due to high Van Der Waals forces, rather than discrete particles. This means that if an inhaled particle with a diameter of 50–100 nm forms an aggregate of 5–10 particle types, in

Whether particles aggregate and then disaggregate once they reach the lung fluids and the process for generation of nanoparticles will become increasingly important.

—*David Warheit*

terms of deposition it may have the properties of a 200–500 nm particle, suggested Warheit.

In addition to concern about deposition, particle clearance from the lungs may also be important for assessing nanoparticles. Normal clearance in the lung is performed by phagocytosis of particles by alveolar macrophages. These cells exit the lungs via the mucociliary escalator to be coughed up or swallowed. This process is effective for the fine-sized (100 nm to 3 μm), low toxicity particles if the clearance system is not overloaded; however, it is unknown if this happens with ultra-fine particles or nanoparticles.

Some current hypotheses suggest that nanoparticles are more toxic (inflammatory, tumorigenic) than fine-sized particles of identical composition, noted Warheit. This concept is based on a systematic evaluation of only three particle types: titanium dioxide, carbon black, and diesel particles. Thus, he noted that the current hypotheses are based on a paucity of data.

Determining toxicity can be complicated because not all nanoparticles are more toxic than fine-sized particles of the same chemical composition. The surface coatings of particles, exposure to UV radiation, and dispersion properties

can change the behavior of the particles. Whether particles aggregate and then disaggregate once they reach the lung fluids as well as the process for generation of nanoparticles—for example, gas phase versus liquid phase synthesis—will become increasingly important. He suggested that developing a working hypothesis for determination of particle toxicity will depend on the capacity of the particles to cause cell and lung injury, promote inflammation, inhibit macrophage function, and persist in the lung. Finally, Warheit observed that species' differences complicate research because some species, such as rats are particularly sensitive to particles, sometimes making it difficult to extrapolate the results to humans.

Toxicity of Carbon Nanotubes

In a recent study, Warheit investigated the toxicity of intratracheally instilled carbon nanotubes, which are approximately 1 nm by 1–5 μm as a singular particle. However, due to strong electrostatic potential, they rarely exist as individual discrete particles and agglomerate into nanoropes.

Following instillation of the carbon nanotubes into the lung, the tissue was analyzed by looking at cell proliferation, histopathology, lung weights, etc. at 24 hours, 1 week, 1 month, and 3 months post instillation. Through this paradigm, the researchers would be able to determine the initial, transient reaction, but also ask whether the toxicity was sustained or progressive.

Fifteen percent of the animals died within the first 12 hours due to high agglomeration from electrostatic attraction, which essentially coated the airways of these animals. This was not because of the toxicity of the material, but rather because the material coated their airways. Thus, these animals died from suffocation because of the unique properties of carbon nanotubes, said Warheit.

The animals that survived the first 24 hours post instillation survived through the 3 months. Exposure to carbon nanotubes produced only a transient inflammatory response at 24 hours, but this was acute, with no inflammatory effects seen at 3 months. Interestingly, Warheit reported that they did see multifocal granulomatous lesions in the lung tissue studies. These lesions are not commonly seen in dust-exposed rats. In the center of the lesions were the agglomerated carbon nanoropes walled off by foamy multi-nucleated macrophages cells. The distributions of the lesions were not consistent, nor were they dose dependent or progressive from 1 to 3 months.

Warheit put these results into the context of possible exposure in the workplace. Since carbon nanotubes are used in the electronics field for diode, transistors, cellular-phone signal amplifier, and ion storage for batteries, his DuPont colleagues, as well as NIOSH

Particles need to be thought of as having inherent toxicity, and being carriers for organic molecules and metals.

—John Froines

researchers, performed exposure assessments in the workplace. The results suggested that the dust was less than $53 \mu\text{g}/\text{m}^3$, which was extremely low. Most of the nanotubes were aggregated into nanopopes, which may not be respirable. Warheit concluded by stating that scientists cannot assume that all nanomaterials are the same as their bulk counterparts, which suggests that materials will need to be tested on a case-by-case basis, a process that may be infeasible because of resource constraint. He suggested that priorities for studying particles based on surface coating, surface charge, and particle aggregation will need to be made.

WHAT CAN WE LEARN FROM DIESEL PARTICLES?

John Froines of UCLA raised the question, does the research that scientists are doing on airborne particulate matter related health effects have relevance to understanding potential issues with respect to nanotechnology? He suggested that there are areas where there are significant differences, but there are also places with commonalities. For example, most of the ultra-fine particles from diesel emissions are in the 10 nm range, classifying them as nanoparticles. He suggested that a number of biochemical processes may be similar between the air pollution particles and the engineered particles.

Redox Cycling

Nanoparticles from diesel exhaust may contain pro-oxidative chemicals. Quinones, one such chemical, can undergo redox cycling to semiquinones, subsequently generating reactive oxygen species (ROS) such as superoxide radical anions. This cycling can lead to a build-up of ROS that result in oxidative stress. Oxidative stress then produces pro-inflammatory effects, such as allergic airway disease, adjuvant effects in asthma, and propagation of cardiovascular disease.

Airborne particulate matter has a coarse, a fine, and an ultra-fine or nanoparticle mode. These particle modes differ in the carbon, organic carbon, metals, inorganics and polycyclic aromatic hydrocarbon (PAH) content. Ultra-fine particles have a greater organic carbon and PAH content than the coarse or fine particles. More interestingly, noted Froines, is that the redox activity is greater in the ultra-fine particles, which leads to an increase in glutathione depletion and mitochondrial damage in cells exposed to these particles.

The redox activity in nanoparticles was confirmed in a recent study by Li et al. (2003). Redox activity was examined in the coarse, fine, and ultra-fine particles at 50 or 150 meters from a freeway. At both distances, the redox activity per microgram was greatest in the nanoparticle region. At a distance of fifty miles from downtown Los Angeles, Froines collected particles with the same size distribution, and once again, the ultra-fine particles had the greatest redox activity.

Persistent Redox Activity

Diesel particles need to be thought of as having inherent toxicity, because of their being carriers for organic molecules and metals, noted Froines.

Organic extraction of the particulate matter only removes 10–30 percent of the redox activity from the particles. The remaining redox activity cannot be extracted from the particles, noted Froines. Mucociliary fluid is even less effective in extracting capability. Thus, the active chemical species remain on the particles themselves, which means that the particles retain their toxicity.

Particles need to be thought of as having inherent toxicity, because of their being carriers for organic molecules and metals.

—John Froines

Health Endpoints

There have been a number of health endpoints associated with ultra-fine particles. Animals exposed to ultra-fine particles from freeways show enhanced allergic airway responses and CNS inflammation. In human clinical studies with particles from freeways, particles have also been associated with a statistically significant decrease in heart rate variability and other cardiovascular parameters in normal subjects. Further, exposure to mobile sources has been associated with increased risk to preterm birth and low birth weight. Froines concluded by suggesting that as nanotechnology continues to evolve there is accumulating evidence in the area of air pollution from ultra-fine particle work that there are health endpoints that need further research.

NANOTECHNOLOGY AND STRATEGIES TO ENSURE OCCUPATIONAL HEALTH

The people currently most affected by nanomaterials, nanoparticles, and their potential impact on the environment and health are the groups that generate and handle the materials, that is the people in the workforce and the laboratories, noted Andrew Maynard, National Institute for Occupational Safety and Health (NIOSH). NIOSH has established a very active research agenda to reduce the potential health impact in these groups. Yet as they begin to look at the research agenda, he noted that there are a number of pressing issues.

Since the 1950s, industrial hygienists have mostly concentrated on inhalation exposure related to mass of the material, because this has been the most useful information for relating exposure to health effects. The use of mass as a paradigm marginalizes nanoparticles and nanostructured materials, because even if there are many of these particles there is very little mass associated with them. A 1 nanometer particle has only 1 billionth of the mass of a 1 micron-sized

Under the mass paradigm nanometer-sized particles are not looked upon as dangerous; however, we cannot ignore the chemistry of nanoscale materials that have other unique and unusual structures and properties which may cause health problems.

—Andrew Maynard

particle. Therefore, under the mass paradigm nanometer-sized particles are not looked upon as dangerous, noted Maynard. However, scientists cannot ignore the chemistry of nanoscale materials that have other unique and unusual structures and properties, which may cause health problems. As noted above, most nanomaterials are insoluble and the surfaces of these materials are very different from the core properties. Nanomaterials have very specific hetero-

ogeneous structures, and they are exclusively engineered to specification.

Mass, particle size, and surface structure are all important properties for determining where these particles deposit in the respiratory system upon inhalation and how the body will react, as discussed previously. This is where occupational health faces its first challenge. Health scientists need to understand how these materials may impact health in the workplace or the laboratory, and they may need to undergo a philosophical change in the way these materials are viewed, said Maynard.

NIOSH is concerned with identifying the risks from nanoparticle exposure and considering how to control the risks, whether through reducing risk or reducing the impact. However, to be in a position to assess risk, additional information is needed regarding toxicity of the materials including: how they interact biologically in the body and what the health effects are resulting from toxicity, environmental exposure, and potential exposure routes (i.e., whether the material is inhaled, ingested or absorbed cutaneously), noted Maynard.

He noted that the toxicity of nanomaterials needs to be understood in a framework of the materials' characterization. If scientists do not understand the materials from a physical and chemical perspective, they cannot interpret exposure or toxicity measurements. Scientists already know how some of the small structure materials behave, but they have a long way to go before understanding the risks posed by these materials, said Maynard.

There are a number of steps that need to be taken in order to understand the occupational health impacts of the nanomaterials, according to Maynard. These include the need to:

- Understand the problem from different perspectives (e.g., industry, public, workers, and regulatory).
- Perform gap analyses to determine a course of action.
- Create a strategic plan for achieving short-, medium-, and long-term goals.

In order to achieve these goals, there is a need to coordinate activities between stakeholders (i.e., the people who are directly impacted by the processes), the materials, and the service providers (i.e., the people who have the knowledge that allows us to take action to impact health effects at the workplace). He concluded by suggesting that nanotechnology is a multidisciplinary area that covers a large range of disciplines and that a multidisciplinary approach to the problem is necessary in order to be effective.

Unless we have a multidisciplinary approach to the problem we are not going to make any significant impact.

—Andrew Maynard

AN OPEN PROCESS

There is a need for increased levels of cooperation between the industries involved, public interest groups, and government parties to find solutions that are economically viable, but still protect the environment and health, asserted John Balbus, Environmental Defense. This is not a small goal, because it is important that nanotechnology development is done right the first time. Modern history has produced a number of technological advances that held such great promise for revolutionizing society; that they were accompanied by safety short-cuts. Not all technological advances proved to be health concerns, but DDT, polychlorinated biphenyls, tetra-ethyl lead, and chlorofluorocarbons are just a few examples where wide-scale release had a number of unintended side-effects.

Potential Problems

These past problems have implications for nanotechnology. The federal government, through various agencies in the National Nanotechnology Initiative, has increased nanotechnology research funding in the last 5 years from \$200 million to \$850 million. During the same time period, the investment in environmental health and safety implications research funding had only a slight increase from 0.2 percent to less than 1 percent of total investment in nanotechnology. Balbus noted that the public expects the federal government to anticipate and to be proactive about the risks of any future commercial products and he questioned whether the funding levels were adequate for environment and health research.

Balbus noted there are a number of reasons why the public and public interests groups have reason for concern about nanotechnology. Currently, there is a lack of knowledge about these products that will need to be addressed before scientists can adequately address environmental health concerns. Nanomaterials are:

- Deliberately manufactured so that they have novel physical-chemical properties, and many times unpredicted physical-chemical properties.
- Heterogeneous, and this is not only in terms of the different kinds of nanomaterials that are deliberately engineered, but it is very likely that different nanomaterials will be heterogeneous in terms of fate, transport, and degradation. Should these materials be distributed in the environment, they will be in different stages of transformation.
- Poorly soluble in water, at least for the carbon-based nanomaterials. These nanoparticles have to have surface coatings or surface modifications in order to make them biocompatible.

These properties have a number of implications for environmental health. Nanomaterials are the size of viruses, and as such are able to be transported through the body along nerves and through the lymphatic system, providing an

opportunity for these materials to cross the blood–brain barrier, which may result in a number of unintended consequences. Poor water solubility may lead to similar problems—seen with other poorly water soluble chemicals such as PCBs—with increased potential for bioaccumulation through repeated cycle absorption, evaporation, and transpiration. These are only two examples,

The current observations are not “doom and gloom,” but they haven’t been reassuring from a health and safety standpoint.

—*John Balbus*

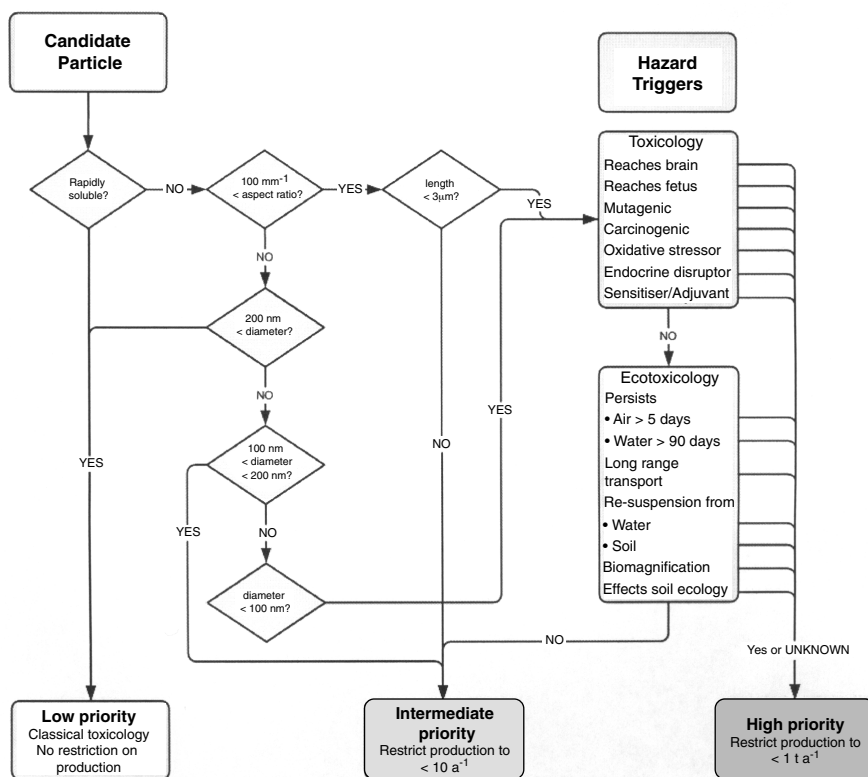
but Balbus questioned whether science is in a position to answer to these questions, since there is a paucity of data presently. The current observations are not “doom and gloom,” but they haven’t been reassuring from a health and safety standpoint, he concluded.

Regulatory Framework

The regulatory framework for bringing these products to market also needs to be discussed. The statute that covers new chemicals, other than pesticides, cosmetics, and pharmaceuticals, including nanotechnology, is the Toxic Substances Control Act (TSCA), but Balbus questioned whether TSCA could meet the challenges for nanotechnology. For example, pre-manufacture notices require the company to provide only information on the process, likely uses, and physical-chemical properties of the substance, but not to generate new data on the toxicity of the substance. Furthermore, he noted that there is no requirement for post-marketing surveillance, which means that once the compounds are in commerce, there is no requirement to assess whether they are causing any kind of damage. The EPA does have the capacity to generate a test rule, and insist on

toxicity data, but the burden for findings is high for the agency and these provisions only very rarely have been invoked.

Balbus noted that one model that has been put forward is the European Commission's decision algorithm for bringing nanomaterials to market. This decision algorithm considers solubility, ability to be transported within the body, and probability of ecotoxicity. The products are assigned low, intermediate, and high priority (see Figure 3-2), and level of priority is then used to drive the research agenda. It remains to be seen if the actual implementation and enforcement of the algorithm will be reached, concluded Balbus.



NOTE: At decision points, UNKNOWN values should be taken to equal YES

FIGURE 3-2 Flow chart utilized by the European Commission on Community Health and Consumer Protection to assess solubility, ability to be transported within the body, ecotoxic probability, and other hazard probability and priorities and is assigned low, intermediate, and high priority. SOURCE: European Commission, Community Health and Consumer Protection, 2004. Reprinted with permission.

Moving Forward

Balbus noted that it is not a question of whether we develop nanotechnology, or we move forward. Rather, it is a question of how does the science move forward in a way that best protects the public, and gets the health and safety right the first time. While assuring health and safety, scientists need to be reminded that lack of toxicity evidence is not the same as lack of toxicity. We also need to recognize that industry moves faster than government. Scientists know that it is going to take several years to get the nomenclature in place. This will complicate the application of TSCA¹ for these compounds. The government will need to develop strategies that harness some of the nimbleness and speed of industry.

One way to accomplish this is to create a road map that draws from the strengths of government, academia, and non-governmental organizations. There are at least four steps to accomplish this goal, noted Balbus. First, science needs to define the categories based on potential for environmental health effects. Second, there is a need to develop a testing strategy to answer the basic questions. A component of this may require developing new techniques or methods. Third, industry and government need to commit to pre-manufacture testing that examines ecological and human health. There should be some consensus about what testing needs to be done and when. Fourth, industry should consider voluntary use restrictions in the absence of data, especially for those uses that are likely to be highly dispersive.

Risk Communication for Emerging Technologies

During the course of the day's discussion, roundtable members, speakers and participants centered their discussions on public trust and risk communication. Continuing on the examples discussed by John Balbus early in his presentation, participants also raised the examples of the times when nuclear energy was introduced in the United States and there was a lot of positive publicity about the peaceful atom which later on produced a large backlash when the public realized that there were also hazards in the new technology. Another example was when biotechnology was advertised as being absolutely safe and, again, later the public realized about the negative sides of biotechnology. Nanotechnology also holds promises but on the other hand there is a lot of uncertainty from the scientific and technology development communities about the downsides of the new technology being communicated to the public. Vicki Colvin said that the scientific

¹While it is true that changing the particle size does not necessarily trigger TSCA reporting, EPA does have jurisdiction through significant new use of TSCA to review industrial uses of nanomaterials. EPA could require reporting of new uses of certain nanomaterials by issuing a significant new use rule. The lack of CAS numbers will not impede the need for regulatory reporting, nor will a new CAS number necessarily require reporting.

community maintains communication with the public about both positive and negative sides of the new technology but she argued that it is better to articulate the positive benefits of nanotechnology. However, she agreed that in order to build public trust, the scientific community needs to assess and determine the risks of nanotechnology as well.

Finally, trust takes more than just good risk communication skills. The best way to get the public to perceive things correctly is by right action, and by a clear demonstration that everything in the power of government and industry is being done to insure protection of consumers and the environment, concluded Balbus.

4

Nanotechnology: Government Involvement

Current developments in nanotechnology are increasing at such a rapid pace that it is a challenge for any government to stay up-to-date with progress. Nanotechnology has received considerable attention from scientific communities and governments worldwide. The United States, France, Japan, and Canada have centers and government agencies where they make assessments of the potential risks and benefits to human health posed by nanotechnology. During the workshop, there were presentations on work by the United States and Canadian governments in the area of nanotechnology.

APPROACHES FROM THE CANADIAN GOVERNMENT

The Canadian government sees its responsibility in terms of ensuring that their society will be able to interact with new technologies, contribute to them, and manage them as they develop. In order to do so, the Canadian government conducts discussions with more than 11 departments and agencies and holds workshops that bring people together and allow them to take leads on different issues. The Canadian government plans to continue this interdepartmental, interdisciplinary approach.

Nanotechnology is one of the priorities for the Canadian government, said Paul Glover, Health Canada. Canada wants to be a world leader in developing and applying twenty-first century technologies such as biotechnology, environmental technology, information and communication technologies, health technologies, and nanotechnology. In order to achieve these goals, the Canadian government invests about \$45–50 million a year in nanotechnology. The Canadian government also has realized that it is time to break down barriers between research disciplines and to foster multidisciplinary approach. In this spirit, the government in Canada no longer funds one lab working on one item in isolation and favors a multi-faculty approach, where people with different backgrounds (physicists, biologists, and chemists) can work together on nanotechnology issues.

This approach encourages progress, and Canada is making big steps forward, said Glover.

Nanotechnology has tremendous potential, and the role of Canadian government is to produce a lasting social change and economic benefits to the country, said Glover. However, new technologies pose risks to the environment and human health and are not well understood, noted Glover. Because Canadian consumers are very proactive in the management of their own health and health-related information, the government needs to know the downsides of the new technologies and also how to manage the risks. Informing people about nanotechnology is critical and challenging, said Glover. Nanomaterials involve multiple chemicals and mixtures used over varying periods of time with varying levels of intensity. Therefore, a chemical-by-chemical risk assessment approach will not be effective. Thus, there is a need for government to update risk assessment methodologies via multidisciplinary approach with industry, different levels of government, and broad scientific input.

TECHNOLOGIES FOR IMPROVED RISK STRATIFICATION AND DISEASE PREVENTION: U.S. GOVERNMENTAL INVOLVEMENT

The U.S. government coordinates work on nanotechnology by 19 government agencies through the National Nanotechnology Initiative (NNI). The goal of the NNI, which was enacted into legislation in 2003, is to use government funding and coordinate funding across all government agencies in order to enrich our nation's economy, security, and quality of life by advancing the technology while protecting public health and the environment, said Clayton Teague of National Science Foundation and head of NNI. The NNI is coordinating the effort through a number of strategies and working groups. Some basic strategies are:

- Encouraging basic research to achieve fundamental knowledge and understanding of nanoscale phenomena and processes.
- Promoting applied research in specific "grand challenge" areas to accelerate transition of scientific discovery into innovative technologies.
- Providing mechanisms to facilitate transfer of technology into commercial applications and to support basic and applied research.
- Establishing research programs to understand the social, ethical, health, and environmental implications of the technology.
- To accomplish these goals, the NNI is encouraging inter- and multidisciplinary research through 16 centers of excellence located across the United States. These centers, either in university or governmental laboratories, provide best-in-the-world instrumentation and facilities available to researchers. In conjunction with the broad support of academic research, the NNI is also achieving the applied research goals through

Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs.

Nanotechnology at NIH

The budget for the Initiative for 2004 is \$961 million and the government agencies are involved in all phases of research of nanomaterials. Included in the NNI, NIH spends \$80 million a year on nanotechnology, and NIEHS contributes about \$2.5 million per year, said William Suk of NIEHS. Approximately \$1.1 million of the amount is funded by the Superfund Basic Research Program (SBRP). At Michigan State University, SBRP-funded research is developing biomarkers and the use of functional nanostructures for groundwater remediation; at the University of California, San Diego, sensors for toxicity in genomics are being studied.

All the technologies that are being developed will produce large amounts of data; thus, scientists will need to develop new computational tools that can be used to refine the data collection, storage, analysis, and dissemination. They will also need to start focusing on real-time risk assessment to be able to make real-time decisions that will better prepare ourselves and the public for any potential exposure, noted Suk.

Biosensors, nanoprobes, and quantum dots have the potential to detect individual exposures and tissue distributions of toxins. The development of smart sensors would allow their use in population-based epidemiology studies aimed at developing better prevention tools. Two functions of nanoprobes are chelation and catalysis. Chelation should be used primarily for metals and radioactivity. It would bind to the hazardous agents with a high affinity immobilizing and concentrating them and allow the agents to be removed. Catalysis would convert the agents to a non-toxic form either through reduction or oxidation.

NIEHS also is attempting to look inside the cell quantitatively in real time, as well as in a special and temporal manner and is developing nanotechnology tools that can be used in systems biology. Today, we have the potential to possess tools that will enable us to understand how cells communicate with each other within the cell. It is very important to toxicology, because if we understand how cells network together we can understand how they can be perturbed, said Suk.

NIH is also working on developing the tools that can be engineered to detect physiological responses to exposures and to determine whether these tools can be used to intervene or intercede in the course of disease processes and interrupt the sequence of biochemical events involved in disease development, for example, tumor progression. Another tool that is being developed by NIH is remediation as a way of reducing the amount and toxicity of hazardous substances and as a way of preventing risk.

The potential ramifications of nanotechnology are important; however, their entry into the food chain and their bioavailability, accumulation, potential bio-

magnification, and toxicity are largely unknown. Thus, scientific results will have a very important impact on our future actions. Nanotechnology is a highly interdisciplinary field, and it will present a substantial number of challenges, concluded Suk.

Technology and U.S. Regulation

According to Teague, the government has active efforts under way, involving all the regulatory agencies as well as research agencies, examining the degree to which the existing statutes cover the risk that we might be having from nanoscale materials.

Furthermore, federal laboratories, academia, and industry are conducting research into how the new nanoscale materials—especially nanoengineered materials—may or may not differ from the ones that have already been researched, such as ultrafine particles and other materials that have been in our environment for a long time.

The government is keeping an eye on the nanomaterials used in commerce and is trying to understand risk characteristics and risk assessment of the products used in the marketplace from each category of nanoscale materials. Since nanotechnology engages many different disciplines, different agencies are involved in risk assessment and regulation. They communicate with each other and try to ensure that the nanoscale materials are covered by the existing regulations, noted Teague. Some of the new nanoscale materials can be incorporated into existing statutes and regulations; others require new evaluation because their properties are different from those of the existing regulated materials and they need to be assigned new Chemical Abstracts Service (CAS) numbers. The government is working closely with industry, academia, and researchers to evaluate the new chemicals and ensure that new CAS numbers are issued to all the new nanomaterials.

The NNI strategy is to ensure the long-term results of nanotechnology, both in terms of preserving the environment and providing means that will prevent further damage. If the promise of nanotechnology holds true, there are many opportunities for remediating and improving the existing environment and, in turn, improving health through its environmental interactions, concluded Teague.

5

Next Steps

*Lynn Goldman**

The new technologies discussed throughout the workshop have a tremendous potential across a number of areas in the economy and promise to improve our lives in different ways. Due to advancements in nanotechnology, its application in areas such as pollution reduction, new methods of energy production, and medical innovation is likely to have a positive effect on our lives in the near future. However, because the technologies are so new, they may have a hazardous impact on our health as well.

During the workshop, the Roundtable heard from the speakers and participants that this technology is very complicated and that there are potentially thousands of new substances that can be developed which, like chemicals, can have numerous different attributes. While we can quantify the potential for economic benefit and other benefits to society, presently science does not have the information necessary to quantify the potential for hazards or to develop a method for assessing those hazards. The research is hampered by a lack of nomenclature, which is necessary in order to discuss these substances, a lack of risk-benefit analysis, and a lack of both a research framework and strong leadership.

NOMENCLATURE

Today, there is no precise nomenclature developed for the field of nanotechnology which causes confusion to the public, policy makers, and researchers as it cannot receive clear messages about the benefits and risks of the new technology. The issue of nomenclature is critical for the field of nanotechnology and it must be addressed by all groups involved, including scientists, regulators, media, industry, and others.

*This is an edited version of the transcript of Lynn Goldman's final summation at the meeting.

Because of the lack of knowledge the media often interprets scientific findings related to toxicity of one nanomaterial and paints everything in one color—implying that one result can be extrapolated to the entire array of nanomaterials regardless of size or other important properties specific to a particular nanomaterial. It is challenging to communicate the risk effectively without a precise nomenclature; therefore, the scientific community needs to establish a nomenclature in which the language is clear and specific so that journalists and the public can understand the benefits and risks of various materials.

Researchers are also dependent on nomenclature. A scientist who publishes his or her research or reviews the literature about a substance with which they are working needs to know that the particle in their experiment is equivalent to the particles in other research papers. Another group that is reliant on nomenclature is regulators. To write a regulation, a chemical abstract service registry number is useful but it is not sufficient because a regulator needs to be specific about what they are trying to regulate. Otherwise, it is very difficult to analyze the impact of the regulation and to enforce the regulation. It will take a joint effort of different agencies and groups to work on the issue of naming and to establish a precise and clear nomenclature in the field of nanotechnology.

RISK–BENEFIT ANALYSIS

There are multiple agencies in the United States and other countries of the world that are concerned with nanotechnology and risk assessment. Many countries are committed to assessment of risks but the means to do so have not been developed yet. The risk–benefit equation in nanotechnology is likely to be very complicated. At one end of the spectrum, there are potentially life-saving drugs and medical devices where the only risk might be to the person whose life is being saved; at the other end of the spectrum, there are materials that are being used in cosmetics and other relatively insignificant applications. The government needs to examine closely the benefits and risks of nanotechnology and agencies involved in decision making need to find out if nanomaterials with little societal benefit and some risk to environmental health should be allowed to be introduced into the environment.

During the workshop, the participants suggested that the train has not left the station yet, i.e., that technology is newly emerging and opportunities exist to address environmental health concerns before there is a wide-scale release. While it is true that some of these trains have not left the station, other trains appear to have already left, and the problem is that we do not know enough about what kind of freight these trains are carrying and the risks associated with unloading them. Some of the nanomaterials such as semiconductors are already in the commercial marketplace and some of them are going to go into waste, water, and the environment. To identify the environmental and health hazards of these

materials we need to understand how they interact with the environment once they are released.

NEED FOR FRAMEWORK AND LEADERSHIP

A number of times during the workshop, the need for a risk assessment framework was discussed. The discussion highlighted the need for bold leadership in this area, such as the effort made by the federal government when it established the National Nanotechnology Initiative.

Nanotechnology needs to have a regulatory framework similar to the one that was developed in the early days of biotechnology in the United States—where regulatory agencies got together to determine how existing laws and authorities could be used to fill the regulatory gaps for these new technologies. There is a need for the federal government to establish such a framework. Since biotechnology went on the market, many organizations have assessed hazards after the fact. With nanotechnology, the process of external scientific advice could occur earlier and provide an opportunity to steer the process more wisely before the fact. Other creative approaches, such as stakeholder dialogues convened by mutual parties, can also be helpful.

Additionally, the government needs a process to steer research and development, taking into account uses, life cycle issues (manufacture through disposal), and environmental fate and transport of these materials. One model for research coordination is the Global Climate Research Initiative. In the 1980s, a budget was established for competitive use by agencies if they were willing to come to the table with projects that would meet the goals of a comprehensively assessing climate change. It makes a difference to have that kind of leadership coming from the top.

It is important for government to make the right decisions so there is honest and straightforward communication. Bad decisions lead to bad risk communication. No matter how hard one tries, there is nothing that substitutes for making the right decisions and preventing the adverse events.

There is a need for international leadership as well. Any adverse event happening with nanotechnology anywhere in the world is going to reflect negatively on it everywhere in the world. Thus, early engagement of the global community and having leadership on all issues, including establishing a common language for identifying these substances is critical.

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Appendix A

Workshop Agenda

TECHNOLOGY AND ENVIRONMENTAL HEALTH: IMPLICATION OF NANOTECHNOLOGY

Sponsored by
The Roundtable on Environmental Health Sciences, Research, and Medicine
National Academy of Sciences Keck Building
500 5th Street, N.W., Washington, D.C.

MAY 27, 2004

Moderator: Paul G. Rogers, J.D., Roundtable Chair

- 8:30 a.m. Opening Remarks
The Honorable Paul G. Rogers, J.D.
Chair, Roundtable on Environmental Health Sciences, Research, and
Medicine
- 8:40 a.m. Nanotechnology: Issues Involving Environmental Health and Safety
Kenneth Olden, Ph.D.
Director, National Institute of Environmental Health Sciences
- 9:00 a.m. What is Nanotechnology?: Overview and Relevance to Environmental
Health
Vicki L. Colvin, Ph.D.
Associate Professor, Rice University
Executive Director, Center for Biological and Environmental
Nanotechnology

- 9:25 a.m. Preparing for Nanotechnology: Health, Policy, and Emerging Issues
David Rejeski, M.P.A., M.E.D., B.F.A.
Director, Foresight and Governance Project, Woodrow Wilson
International Center for Scholars
- 9:50 a.m. Societal Implications of Nanotechnology Products
Douglas Mulhall
Author: *Our Molecular Future*
- 10:10 a.m. General Discussion
- 10:25 a.m. Break

The Promise of Nanotechnology

Moderator: Myron Harrison, M.D., M.P.H., Roundtable Member

- 10:40 a.m. Nanotechnology and Environment: The New Future in Remediation
Barbara Karn, Ph.D.
National Center for Environmental Research
U.S. Environmental Protection Agency
- 11:00 a.m. Nanotechnology and Health: A Promise for Better Medicine?
Martin Philbert, Ph.D.
Associate Dean, School of Public Health, University of Michigan
- 11:20 a.m. General Discussion
- 11:45 a.m. Lunch

Nanotechnology: A Tale of Precaution?

Moderator: James Melius, M.D., Dr.P.H., Roundtable Member

- 12:30 p.m. The Central Nervous System as a Target: The Good and the Bad
Eva Oberdörster, Ph.D.
Lecturer, Department of Biological Sciences, Southern Methodist
University
- 12:50 p.m. Potential for Bio-Uptake and Bioaccumulation of Nanotechnology
Particles
David Warheit, Ph.D.
Toxicologist, Haskell Laboratory, DuPont, Inc.

- 1:10 p.m. Ultrafine Particles and Health Risks
John Froines, Ph.D.
Professor, School of Public Health, University of California, Los Angeles
Director, Center for Occupational and Environmental Health, Southern
California Particle Center and Supersite
- 1:25 p.m. Moving Technology Research Forward: Public Perception and Concern
John Balbus, M.D., M.P.H.
Director, Environmental Health Program, Environmental Defense
- 1:45 p.m. General Discussion
- 2:05 p.m. Break

Nanotechnology: Governmental Involvement

Moderator: Lynn Goldman, M.D., M.P.H., Roundtable Vice-Chair

- 2:20 p.m. Nanotechnology and Strategies to Ensure Occupational Health
Andrew Maynard, Ph.D.
Senior Service Fellow (Acting Team Leader), National Institute for
Occupational Safety and Health
- 2:35 p.m. Technologies for Improved Risk Stratification and Disease Prevention:
Future Direction for NIEHS
William Suk, Ph.D., M.P.H.
Director, Center for Risk and Integrated Sciences
Director, Superfund Basic Research Program
National Institute of Environmental Health Sciences
- 2:55 p.m. Approaches from the Canadian Government
Paul Glover, M.B.A.
Director General, Safe Environments Programme, Health Canada
- 3:15 p.m. Technology and Regulation: Encouraging Research While Protect-
ing Health and the Environment
Clayton Teague, Ph.D.
Director, National Nanotechnology Coordination Office, National
Science Foundation
- 3:35 p.m. General Discussion
- 4:25 p.m. Adjourn

Appendix B

Speakers and Panelists

John Balbus, M.D., M.P.H.

Director
Environmental Health Program
Environmental Defense

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Safe Environments Programme
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Johns Hopkins University

Myron Harrison, M.D., M.P.H.

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William Suk, Ph.D., M.P.H.

National Institute of Environmental
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Clayton Teague, Ph.D.

Director
National Nanotechnology
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David Warheit, Ph.D.

Toxicologist
Haskell Laboratory
DuPont, Inc.

Appendix C

Workshop Participants

Norris Alderson

U.S. Federal Drug Administration

James Alwood

U.S. Environmental Protection Agency

Martin Apple

Council of Scientific Society Presidents

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Office of Management and Budget

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DuPont Co.

David Brown

National Institutes of Environmental
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John Bukowski

ExxonMobil Biomedical Sciences, Inc.

John Carberry

DuPont Co.

Soma Chengalur

Margaret Chu

U.S. Environmental Protection Agency

Eileen Collins

Rutgers University

Maryann D'Alessandro

National Personal Protective
Technology Laboratory

John DiLoreto

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Brenda Ecken

Booz Allen Hamilton

Thomas Elwood

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Peter Fehrs

The Gray Sheet

Steven Fleischer

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Mary Gant

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Turkan Gardenier

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Alex Genetos

Woodrow Wilson International Center
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Ken Gertz

Rensselaer Polytechnic Institute

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U.S. Consumer Product Safety
Commission

Bethany Halford

American Chemical Society

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James Votaw

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Kevin Wright

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Responsible Conduct of Research