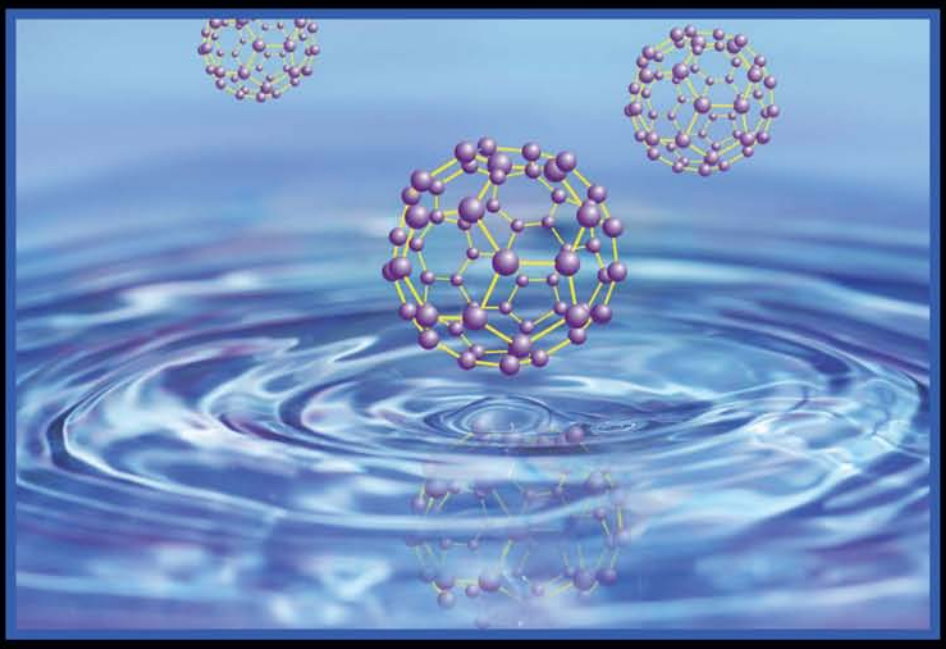
PERSPECTIVES IN NANOTECHNOLOGY

Nanotechnology

Health and Environmental Risks



Jo Anne Shatkin

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Nanotechnology
Health and Environmental Risks

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Series Foreword

Welcome to the Perspectives in Nanotechnology Series — a group of short, readable paperback books dedicated to expanding your knowledge about a new and exciting technology. The book you are about to read involves subject matter that goes beyond the laboratory and the production line. It is not about technical details—the book you have taken on board your connecting flight, commuter train, or bus or to your hotel room involves a specific aspect of nanotechnology that will have some impact on your life, the welfare of your family, and the wealth and security of this nation. The degree of this impact may be unnoticeable, slight, overwhelming, or any place in between those extremes depending on the specific application, its magnitude, and the scope of its distribution. Those of us that are able to recognize trends, conduct efficient research, plan ahead, and adapt will succeed in a new world enhanced by nanotechnology. This book in the Perspectives in Nanotechnology Series hopefully will act as the catalyst for your *fantastic journey*.

Each book in the series focuses on a selected aspect of nanotechnology. No technology exists in a vacuum. All technology is framed within the contexts of societal interactions, laws, and practices. Once a technology is introduced to a society, the society must deal with it. The impact of a technology on culture, politics, education and economics depends on many complex factors—just reflect for a moment on the consequences (good and bad) of the computer, the automobile or the atomic bomb. Nanotechnology is designated to be the "next industrial revolution." Although there is much hype associated with nanotechnology, the ability to manipulate atoms and molecules in order to fabricate new materials and devices that possess remarkable properties and functions alone should be enough of a hook to draw you in.

The impact of new technology is more relevant than ever. Consider that our world is highly integrated, communication occurs instantaneously and that powerful geopolitical and economic pressures are in the process of continually changing the global landscape. We repeat—the degree of the impact of nanotechnology may be unnoticeable, slight, overwhelming, or anyplace in between. Those of us who are able to recognize trends, conduct efficient research, plan ahead, and adapt will succeed. It is all about survival. It always has been. Darlene Geis in her book, *Dinosaurs and Other Prehistoric Animals*, states:

> …and finally even the mighty T-Rex died out, too. His size and strength and remarkable jaws were of no use to him in a world that was changing and where his food supply was slowly disappearing. In the end, the king was no greater than his subjects in a world whose rule has always been Change with Me–or Perish![1]

Although stated with a bit of drama, the quotation does bring the point across quite effectively. Your future is in your hands—perhaps holding this very book.

Societal Implications Societal aspects (implications) consist of a broad family of highly integrated components and forces that merge with technology to form our civilization. Government, business, academia, and other social institutions have evolved over millennia and are in a constant state of dynamic flux. Civilizations change for many reasons. Technology always has been one of the primary drivers of this change. The change may be beneficial, detrimental, or anywhere in between. From the first stone implement, the iron of the Hittites to the microchip, technology has always played a major role in the shaping of society. Societal implications of nanotechnology are rooted in the technology. Societal implications in turn have the capacity to alter any technology. How many times have social forces inspired a new technology? The technology developed in the space program is one example of such a relationship—the development of penicillin another.

What exactly are "societal implications"? How do they relate to nanotechnology? In this series, we intend to cover a wide variety of topics. Societal implications of nanotechnology are both numerous and diverse and encompass the legal, ethical, cultural, medical, and environmental disciplines. National security, education, workforce development, economic policy, public policy, public perception, regulation are but a few of the areas we plan to address in the near future.[2] All aspects of government, business and academia are subject to the influence of nanotechnology. All vertical industrial sectors will be impacted by nanotechnology—aerospace, health care, transportation, electronics and computing, telecommunications, biotechnology, agriculture, construction and energy. For example, all Fortune 500 companies already have staked a claim in nanotechnology-based products. Service industries that focus on intellectual property and technology transfer, health and safety, environmental management and consulting, workforce sourcing and job placement, education development and curriculum, and investment and trading already engage the challenges brought about by nanotechnology. There is no lack of subject matter. We plan to cover the most urgent, the most relevant and the most interesting topics.

Ethical implications are associated with every form of technology. Artificial intelligence, weapon systems, life-extending drugs, surveillance, altered organisms, and social justice all have built-in moral implications—ready for us to discuss. Nanotechnology is creating new ethical dilemmas while simultaneously exacerbating (or alleviating) older ones. Nanotechnology is already changing our legal system. How does one go about obtaining a patent of a process or material that is the result of an interdisciplinary collaboration, e.g., the convergence of engineering, chemistry, physics, and biology? Even more so, the environmental footprint of nanotechnology is expected to be three orders of magnitude less than that of any current technology. The health (and environmental) consequences of nanomaterials are mostly

unknown. And what of public perception? How many of you want a nanotech research center in your back yard (are you a NIMBY)? How should we update our educational system to accommodate nanotechnological topics? What should we do to make sure our workforce is current and prepared? How will your job or career be influenced by nanotechnology?

There are other relevant questions. How does one go about building a nanobusiness? What new kinds of partnerships are required to start a business and what exactly is the *barrier of entry* for such an undertaking? What are *nanoeconomic clusters*? What Fortune 500 companies and what business sectors require a book in this Series to describe its NT profile? And what of investing and funding? What is the status of nanotechnology programs on the international stage? What about nanotechnology and religion? What about the *future of nanotechnology*? The list goes on.

The Books Web resources that address societal implications of nanotechnology are plentiful but offer usually encapsulated or cursory information. On the other hand, comprehensive (but tedious) summary reports produced by research and marketing firms are suitable for the serious investor but require a major financial commitment to procure and therefore, are generally not available to the public at large. In addition, government entities, e.g., the National Nanotechnology Initiative (http://www.nano.gov), have generated comprehensive reports on the societal impact of NT.[1,2] Such documents, although excellent, are generally not well known to the public sector. A reader-friendly, affordable book with commercial appeal that targets the nanoaware (as well as the unaware) layperson or expert in the field offers a convenient alternative to the options listed above.

The intent of each book is to be informative, compelling, and relevant. The books, in general, adhere to the criteria listed below.

- **Readability**. Each book is 200 to 300 pages long, with an easy to read font and is abundant with non-technical but certainly non-ponderous language.
- **References**. Each book is well researched and provides links to more detailed sources when required.
- **Economical pricing**. Each book is priced within easy reach and designed for accelerated distribution at conferences and other venues.
- **Subject matter**. The subject of each book is relevant to nanotechnology and represents the cutting-edge in the state-of-the-art.
- **Relevance**. The books are dynamic. We must stay current if we are to abide by T-Rex's rule! Specifically, the content will stay relevant in the form of future editions as the climate of nanotechnology is expected to change dynamically over the years to come. A strong temporal component is inherent in the Perspectives in Nanotechnology Series.

It is our hope that readers delve into a book about their special interest but also to transform themselves into a state of *nano-readiness*. Are you nanoready? Do you want to be able to recognize the drivers that surround nanotechnology and its potential promise? Do you want to be able to learn about the science, technology and potential implications? Are ready at this time to plan and adapt to changes? Do you want to become an agent of change? Do you want success in that future? If your answers are, in order—NO, YES, YES, NO, YES, and YES—you are ready to begin reading this book.

Gabor L. Hornyak
Series Editor

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2. M.C. Roco and W.S. Bainbridge, Eds., *Societal Implications of Nanoscience and Nanotechnology*, National Science Foundation, Arlington, Virginia (2001).
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Preface

Technology is a powerful force of change in our world. We live longer and arguably better lives than our great-great-grandparents because of advances in medical, communication, and transportation technology. As we enter this new century there is apparently no end in sight for the transformative potential of human innovation. However, there is now ample evidence that the real legacy of invention is defined in equal parts by its benefits to society as well as its costs. There is no technology that comes without some level of risk. What this can or should mean for the process of creating and nurturing emerging technology remains a central question for all of society, one which this book explores for the emerging area of nanotechnology.

The term 'nanotechnology' encompasses a dizzying array of individual technologies, integrated into products in virtually every industry we can define. Nanotechnology can be found in humble products like antibacterial fabrics, as well as in the memory and computing elements of the latest high-end computers. What links these very different applications is their reliance on materials that are designed and shaped with nanometer scale precision. These systems can possess very special chemical, optical, and magnetic properties that motivate their use; their size—from one to one hundred nanometers—can also be a great advantage for engineering design. Some nanoparticles, for example, can mix with and penetrate both solid and liquid media normally impermeable to larger size particulates. The small size, chemical reactivity, and tunable properties together drive their use across a wide swath of products.

These same features, when considered through the lens of risk assessment, drive a different set of concerns about nanomaterial safety. Some unbound nanoparticles are often engineered for persistence, high chemical reactivity, and can be found in a wide set of products and thus a wide set of exposure conditions. It is reasonable, but not yet proven, that given the sheer number of nanoparticle types and possible exposures there exists some potential for unwanted environmental impacts. The technical data that could prove or disprove this hypothesis are still incomplete, and the best practices for generating such information are just now being clarified. Regulatory policy is still evolving but the early signs in several countries indicate a watchful, but not overly cautious stance. It is in this climate of uncertainty and optimism that nanotechnology is taking its first steps into commercial products.

Whether these steps lead to a sustainable and secure industry depends in large part on how well all stakeholders participate in defining and managing nanotechnology's risks. Researchers, policymakers, industry leaders, and consumers must make difficult decisions about the pace and direction of nanotechnology's commercialization. They must discuss, disagree, and eventually find a common path that navigates between innovation and caution.

Central to this decision making process is risk assessment. Contributions such as this one provide an updated view of risk assessment and management practices that accounts for the quirks and complexities that are unique to products of nanotechnology. Ultimately, such information can help ensure that the examination and dialog about nanotechnology's risks can occur at the highest possible technical level.

Acknowledgments

This book would not have been written without the help and support of many people. While I cannot possibly name them all, and risk omitting key people, there are several to acknowledge for their contributions. First, I wish to thank the talented and organized staff at CRC/Taylor & Francis publishing, especially my publisher Nora Konopka, for envisioning this project and inviting my participation in it. I also wish to thank series editor Gabor L. Hornyak and my series co-authors, for the valuable conversations we had in our early stages of development.

Thanks are due to my co-authors, Brenda Barry and Mike Davis, for their expertise and insights into the ideas developed in this book, for their respective contributions, and for their continuing collegiality. Thanks to Vicki Colvin for her early work that raised my awareness of these issues, and for contributing the preface.

Thanks especially to Jim Intrater, my dear cousin, for bringing the issue of nanotechnology risk to my attention. I greatly appreciate the generous support of my colleagues at the Cadmus Group, who believed in the value of developing approaches for evaluating nanotechnology risks and encouraged my pursuit of them, particularly Ian Kline, Gene Fax, G. Tracy Mehan, Jane Obbagy, and George Hallberg.

I wish to thank numerous colleagues in the fields of colloidal chemistry, nanoscience, and risk analysis, too many to name individually, who shared their perspectives and with whom I have had many insightful conversations about managing nanomaterial, nanotechnology, and other emerging environmental risks. In particular, I must acknowledge Bob Hoch, Paul Susman, Rick Canady, Andrew Maynard, Chris Cooper, Kristen Kulinowski, Clayton Teague, and Tor Arnesen, who patiently shared both knowledge and wisdom that helped me clarify my thinking. I extend appreciation to my Clark University professors who taught me to examine environmental issues critically and broadly, notably Halina Brown, Rob Goble, Dale Hattis, Sam Ratick, and Ortwin Renn. Thanks also to early career mentors Ron Levy, Katherine Hammond, Charlie Menzie, Susan Vick, and Susan Woskie.

Finally, I wish to express my gratitude to my family for wholeheartedly supporting me in this endeavor. I thank Chris, who nourished me and left me alone to write, as well as Josh and Tony—all of whom collectively took over my share of family responsibilities so I could focus. Thanks also to my loving friends who steadfastly encouraged me, especially Dori Farrar Read, an early influence on environmental issues. I thank my sister Susan Shatkin, whose skillful editing made this book readable, and my mother, Evelyn Shatkin, for her unending encouragement and enduring belief that I can do anything I set my mind to. I am also indebted to my sister Lenore, to whom I

dedicate this book, for the many gifts she gave me, in her decurtate, poignant life on earth.

Author

Dr. Jo Anne Shatkin is a recognized expert in strategic environmental initiatives, human health risk assessment, technical communications, and environmental aspects of nanotechnology. Her work focuses on approaches for evaluating new and emerging contaminants in the environment, particularly on assessments of chemical and microbial concerns that inform policy development. Her specialty is the application and communication of innovative science-informed analysis to address complex emerging issues affecting businesses and communities.

Dr. Shatkin has been an active member of the Society for Risk Analysis since 1989, and recently founded the Emerging Nanoscale Materials Specialty Group of the Society for Risk Analysis, with 130 international members from public and private organizations. She is a research fellow at the George Perkins Marsh Institute at Clark University. Her research interests include developing risk-informed management tools for environmental health and safety evaluations, community-based research, and cumulative risk assessment approaches.

She received her Ph.D. in environmental science and policy in 1994 and her master's degree in risk management and technology assessment, both from Clark University, Worcester, Massachusetts and she possesses a bachelor of science degree from Worcester Polytechnic University in biology and biotechnology. She is managing director of CLF Ventures, the non-profit affiliate of the Conservation Law Foundation.

Contributors

Dr. Brenda E. Barry is a senior toxicologist at ENSR in Westford, Massachusetts. Her areas of expertise include toxicology, environmental exposure concerns, occupational health and safety, biosafety and nanotechnology. She is a member of the ENSR Nanotechnology Initiative and the risk assessment and toxicology group in the Westford office. Dr. Barry has been a senior project manager for numerous indoor and outdoor environmental quality investigations involving exposures to air pollutants, asbestos, chemicals and microbial agents. She also previously developed and managed environmental health and safety programs for biotechnology companies in the New England area. An accomplished writer and speaker, she has provided expert testimony for environmental litigation.

Dr. Barry received her doctorate in pathology at Duke University where her research interests focused on the health effects of exposures to environmental agents, including ozone and asbestos. She received her B.S. in zoology and M.S. in biophysics from the University of Rhode Island. Dr. Barry is a member of several professional organizations, including the Society of Toxicology, the American Biological Safety Association, and the ASTM International Committee E56 on Nanotechnology. She is also certified as a registered biosafety professional.

J. Michael Davis is senior science advisor with the National Center for Environmental Assessment in the U. S. Environmental Protection Agency's Office of Research and Development at Research Triangle Park, North Carolina. He received his Ph.D. degree from Duke University in 1973, held postdoctoral fellowships at the University of Oxford, England and the University of North Carolina at Chapel Hill and has been with the EPA since 1979. He has played a major role in the United States and internationally in assessing the health risks of lead, manganese, MTBE, methanol, and other chemicals used as fuels or fuel additives, and has led in the formulation of multi-disciplinary research programs in these areas. His current activities include the development of a research strategy for the comprehensive environmental assessment of nanomaterials. Among his recent publications is "How to assess the risks of nanotechnology: Learning from past experience" in the *Journal of Nanoscience and Nanotechnology* (2007).

1

Introduction: Assessing Nanotechnology Health and Environmental Risks

Jo Anne Shatkin

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> Exposure to free engineered nanomaterials (as opposed to fine particles that are naturally occurring or that are the incidental byproducts of human activities such as combustion or welding) is for the most part still low. So we are well positioned to assess possible risks before nanoparticles become widely used or make their way into the environment in large quantities.
>
> **E. Clayton Teague, Director**
> **U.S. National Nanotechnology Coordination Office**

Throughout my career, I have been amazed at the tiny risks that people are really afraid of, and equally amazed at the large risks taken daily — sometimes by the same people — that are so well known and so dangerous. Risk analysis is a way to put different hazards in perspective, to ensure focus on the most significant concerns, which are not necessarily the ones people are

most vocal about. According to some projections for nanotechnology, everyone may be affected one way or another as nanomaterials and nanotechnology increasingly enter more sectors of the economy. If the projections are correct, then it is important to gain perspective on potential risks of nanotechnology to inform your decision making — whether you are a developer, user, investor, consumer, or regulator. This book explores the respective fields of risk analysis and nanotechnology, and proposes an adaptive framework for taking on the challenge of risk assessment of this rapidly developing field of technology.

Many of the current applications of nanotechnology are in consumer products. Maybe your MP3 player or the coating on your cell phone uses nanotechnology. Your laptop screen may use nanotechnology for a stronger, scratch-resistant coating, or a more energy efficient and higher resolution display. You could be wearing antimicrobial socks or static-free pants. Your home may have a self-cleaning toilet (or perhaps you wish it did). You may be working with nanomaterials in a laboratory.

This book explores questions about the introduction and uses of nanotechnology for energy, industry, medicine, technology, and consumer applications. And how to determine whether there is — and ways to manage the risk — even if there is no current evidence. Why is there so much attention to the risks associated with nanotechnology? Why write a book—or read one—about tiny, tiny risks that may or may not be more than theoretical? Considered in the context of global environmental and public health concerns such as global warming, bird flu, war, AIDS, malaria, antibiotic resistance, or nuclear threats, how significant are the potential risks from nanoscale materials and nanotechnology? What are the risks from nanotechnology and why is there seemingly international consensus that significant resources are necessary to understand and address them?

The unique behavior of substances engineered to sizes 100 nanometers and smaller (a nanometer is one billionth of a meter) is what makes them attractive to nanoscientists and engineers for developing new materials and applications in almost every sector of the world's economy. The size raises questions, however, about whether their unique behavior also affects biological systems (people and the environment) differently than other materials.

Deoxyribonucleic acid (DNA), the basic building block of life, is made of molecules that are only a few nanometers in width. Because it is not engineered, DNA may not fall into everyone's definition of nanoscale materials; however, a key point is that other nanoparticles and nanoscale materials are in the same size range as DNA, and perhaps these can react with one another in ways that larger particles cannot. Simply, it is important to address the questions of health and environmental risks now, so that nanotechnology can fulfill its promise to improve medical diagnoses and treatment, help address our energy needs and mitigate global warming, help reduce existing pollution, and perhaps even provide tools to stem global pandemics. Answering the questions about health and environmental risks from nanotechnology raises broader societal implications about managing technology, and whether

we are up to the task of addressing more complex and integrated changes to our economy and quality of life.

Evaluating the potential risks early in product development creates an opportunity to safely manage them. The main reason to address the health and environmental aspects of nanotechnology is uncertainty. Even while the behavior of nanomaterials in biological systems is poorly understood, there are hundreds of products containing nanomaterials on the market today and many more in the pipeline, including more sophisticated applications that include active nanostructures that change in response to an external stimulus. Some people are concerned that the uncertainties associated with the introduction of nanotechnology may create new and unmanageable hazards to health and to the environment.

There is no reason for technology to develop in an unsustainable manner. In the past, lack of foresight has yielded staggering costs in terms of lives and lost use of land — costs to corporations, governments, and individuals — that could have been avoided by proactive efforts. The tools to develop safer technologies and less harmful products exist. There exists plenty of experience that demonstrates how *not* to proceed. The chemical industry has learned this, and now participates in voluntary and regulatory efforts to create safer products (e.g., HPV Challenge, Responsible Care). As discussed in Chapter 9, the electronics industry is also seeking to provide leadership and voluntary initiatives to develop nanotechnology safely. Those developing nanoscale materials and using them in technologies have a responsibility to ensure they do not harm people's health or the environment. Governments and many industries recognize this and have initiated efforts to do so, but the complexities raised by some of the unique properties of nanomaterials studied to date raise concerns about whether existing risk management approaches make sense, and there is still uncertainty regarding how to proceed.

The field of risk analysis has grown enormously in the past four decades and provides a systematic, coherent, and tested foundation for managing the uncertain health and environmental aspects of nanotechnology. Years of managing hazardous substances has led to development of sophisticated tools for evaluating the behavior of materials, and by identifying the needs early, industry and governments can conduct the necessary research and make better decisions about how to manage nanomaterials, to ensure a safer path forward. Risk analysis offers the tools to identify and manage risks under uncertainty; however, the challenge is to adapt it to the rapid stream of developments in nanotechnology that may affect environmental and health hazards.

Nanotechnology is rapidly becoming the technological future, and there is an exciting opportunity to design that future. Nanotechnology presents an opportunity to redesign and to engineer technologies to specification. This offers the chance to minimize the risks and maximize the benefits of technological innovation. So if it seems a material or technology may be more hazardous than we are willing to accept, this is an opportunity for innovation — to engineer out the hazard. New materials can be (and increasingly are) designed to be safer (so-called "green manufacturing") and more

environmentally friendly. Risk analysis is a tool to help achieve a sustainable future with nanotechnology.

Many people within and outside of government are working to ensure the safety of nanomaterials, to avoid the unintended effects that occurred from other substances: asbestos, polychlorinated biphenyls (PCBs), DDT, and lead, for example. These substances were widely used because they offered solutions to many industrial and societal needs, but over decades of use their impacts on health and the environment began to emerge. While the health and environmental effects of these substances are among the most studied, they are still poorly understood, suggesting a different path is needed for identifying and managing substances going forward.

This book seeks to give the reader some tools and information to help improve understanding of the health and environmental dimensions of nanotechnology. As with other books in the series, this volume is intended to be accessible to the non-specialist, and explores a breadth of technical and societal topics relevant to the discussion. This book cannot answer most questions about the health and environmental risks of nanotechnology; the answers simply are not known today. But it does provide perspectives about what types of risks could exist, and what can be done to address them.

1.1 What is Nanotechnology?

Nanotechnology is a *scale* of technology, not a type, and it has applications in every economic sector: medicine, energy, industrial applications, materials science, engineering, electronics, communications, cosmetics, additives, coatings, food science, water purification, and agriculture. Ever Google "nano"? Today there are 61 million hits — many of which have nothing to do with nanotechnology, but one finds "nano" everywhere — some of the discussion is hype about the promise or the perils (for example, an advertisement for a "nano" Hummer H3), and it is important to consider the source of information. But there are also numerous applications in development that suggest a brave new technological world — self-assembling materials that act on demand — not the world of *Prey*, a science fiction novel in which intelligent nanoscale robots take over (Creighton 2002), but of smart technology that combines information technology with nanotechnology in novel applications. An example might be a targeted pesticide, released only when a specific pest appears, triggered by detecting a key protein, rather than routine spraying of crops.

Nanomaterials have been in commerce for decades, including carbon nanotubes, first patented in the 1990s, but the pace seems to be accelerating now. A database of consumer products containing nanomaterials or using nanotechnology lists nearly 500 entries of products on the market today (WWCS 2007), and there are numerous industrial applications that

use nanotechnology or incorporate nanomaterials into products. Funding for research and development of nanotechnology is also rapidly accelerating. In the U.S. in 2007, there were over 12,000 patents containing the term "nano." The number of nanotechnology patents worldwide doubled between 1998 and 2003 (Hullman 2006). Most major universities now offer programs in nanoscience, or at least have researchers working in it. In 2003, over 1000 university and research institutions and nearly 1200 private companies were actively working in nanotechnology. In 2005, over 1500 organizations were registered in the European database *Nanoforum* (www.nanoforum.org) (Hullman 2006).

Simply, the opportunities for nanotechnology development are vast and represent enormous potential for technological innovation to devise smarter, more precise solutions to meet a breadth of human needs. The ability to engineer at the nanoscale means technology can be designed and developed to specifically address societal needs, and this specificity presents an opportunity for sustainable technology development, but only if the goals are established and widely agreed upon. Mikhail Roco, who envisioned and worked extensively to create the U.S. National Nanotechnology Initiative, sees further implications. "Besides products, tools and healthcare, nanotechnology also implies learning, imagination, infrastructure, inventions, public acceptance, culture, anticipatory laws, and architecture of other factors" (Roco 2004).

As you can begin to appreciate, nanotechnology is a vast, complex field that is rapidly developing in all directions. My aim is to make this discussion accessible and understandable to an audience that includes those unfamiliar with nanotechnology or risk analysis. I especially want to avoid a lot of dense scientific terminology. However, it is necessary to offer some definitions to clarify the discussion. This is particularly important because, with discussions about nanotechnology occurring in so many fields, an interdisciplinary conversation has begun. As scientists explore behavior at the nanoscale, phenomena never seen before may complicate learning about the behavior of nanotechnology. That is to say, the tools and instruments that allow observation at the nanoscale will lead to discoveries unrelated to nanotechnology per se, that simply relate to the ability to see things not previously observable. As it turns out, how nanotechnology is defined affects how the risks from nanotechnology are addressed.

1.1.1 What, Then, is Nanotechnology?

"Nano" is a prefix used in the metric scale to represent one billionth. A nanometer (or nm) is one billionth of a meter (~39 inches). Nano comes from the Greek word for "dwarf," so in combination with technology, it becomes dwarf technology. Technology applies science and materials for human uses, and nanotechnology applies science and materials at the nanoscale. People refer to nanotechnology as "tiny tech" or "nanotech": it represents the scaling down of technology to a new scale, generally agreed to be between 1 and 100 nm.

A nanometer is so small, it is hard to conceptualize. The head of a pin is one million nanometers wide. A piece of hair is 100,000 nm wide, the size of most bacteria is roughly 1000 to 5000 nm, viruses are about 100 to 500 nm in width. DNA, the genetic foundation for life, is about 1 to 2 nm wide. Nanotechnology is on the scale of our DNA. However, not everything at the nanoscale is nanotechnology. Natural and human-generated nanoparticles occur in the environment. Air pollution, for example, includes nanoscale particles, but these are not technology. They are not manufactured or specifically designed to use nanoscale properties. Fires and volcanic eruptions release nanoparticles to the atmosphere, but these occur naturally, not the result of human activities, and are nanoscale particles, not nano*technology*.

According to the U.S. National Nanotechnology Initiative (NNI), *"nanotechnology is the understanding and control of matter at dimensions of roughly one to one hundred nanometers where unique phenomena enable novel applications"* (NNI 2007). An alternative definition from the American Society for Testing and Materials (ASTM) International is, *"nanotechnology is a term referring to a wide range of technologies that measure, manipulate and incorporate materials and/or features with at least one dimension between approximately 1 and 100 nanometers (nm)"* (ASTM 2007). Such applications exploit the properties distinct from bulk/macroscopic systems of nanoscale components. In the discussions on nanotechnology in which I have participated, dozens of different definitions of nanotechnology have been offered, but they all share two basic tenets: size and unique properties.

One of the main reasons for the explosion of interest in nanotechnology is the unique properties and behavior of matter at the nanoscale. When particles are synthesized at the nanoscale, their properties change. For one thing, *nanoparticles have much more surface area compared to their weight than larger particles*. This single property means that much less material can be used for an application, allowing us to save natural resources, energy, and money providing it does not cost more to produce. Using less material can offer both economic and environmental benefits.

The greater surface area relative to mass also means that nanoscale materials are more reactive than larger particles, so less goes further. In addition, because of the size, and/or structure some basic chemical and physical properties change. Titanium dioxide, a white pigment widely used in coating materials and consumer products such as paint and toothpaste, becomes transparent when manufactured at the nanoscale. Nanoscale titanium dioxide is used, among other purposes, to make sunscreen and other ultraviolet ray-resistant coatings transparent. Gold changes color at the nanoscale — depending on the size of the particles, it can be orange or red — so it is being used in sensing technology, the color being an indicator of a particular reaction. It is not shiny or conductive, as macro-gold is. At the nanoscale it behaves as a semiconductor.

Imagine a surface so smooth that water cannot stick to it, and instead rolls off. Imagine a sensor so sensitive that it can detect a single molecule of a

contaminant in your drinking water. A few other current and proposed applications that use nanotechnology include:

Self-cleaning and air purifying surface coatings — incorporating nanoscale titanium dioxide into surface coatings for toilets, window glass, and building exterior and interior walls. Surfaces are smooth and, when exposed to light, cause chemical reactions, killing bacteria and sweeping away dirt; creating a more sanitary environment, safer windshields, and walls that become graffiti-proof. This saves water and cleaning chemicals, and surfaces remain intact longer.

Reducing pollution — applications range from removing nitrogen oxide from air pollution on the walls of buildings (by nanoparticles reacting with the air pollutants, breaking them down), to breaking down chlorinated solvents in ground water.

Self-healing coatings — surfaces of automobiles and other equipment that can repair themselves after being scratched.

Stronger, more flexible sporting equipment — golf clubs, bicycle frames, tennis balls, and baseball bats made from lighter composite materials, improving performance.

Static and wrinkle-free fabrics — fabric fibers are very small and thus do not wrinkle, preventing charge build-up.

Antibacterial applications — wound covers, kitchen equipment, socks, underwear, camping gear, door knobs, bus seats, waiting room furniture, and medical devices that kill bacteria on contact.

Water filtration — devices that regenerate and continually remove bacteria and chemicals from drinking water.

And, coming soon:

Smart food packaging — a food container that tells you if the food inside has gone bad. (Some have suggested packages that release substances to treat and purify contaminated foods.)

Electrically conducting thin films — an electronic surface made so thin that it becomes more like fabric, but can be used for electronic displays of video, cell phones, and computer screens. Imagine your clothing being a video display, your mobile phone wrapped around your wrist, your MP3 built into your jacket, or your computer screen folding up in your pocket.

Solar paint — solar cells so small they can be incorporated into paints and applied directly onto buildings.

Doctor on a chip — a medical diagnostic test that finds a problem, diagnoses it, and automatically treats it. For example, a cancer cell detector that selectively kills cancer cells.

Fuel cells — powered by viruses.

Light emitting diodes — a breadth of materials improves resolution and lowers energy usage.

Lighter, stronger composite materials for automotive and aerospace applications, increasing safety and fuel efficiency.

Smart dust — tiny sensors, smaller than dust particles, that monitor the environment, ensuring the air is pure, conducting surveillance, measuring pollen, checking for chemical weapons, air pollution, or wind speeds in real time.

Looking ahead, as with the advent of automation in the 20th century, many of the proposed applications of nanotechnology could even further streamline the way people live. Some features might alleviate the need for manual surface cleaning. Titanium dioxide has been called "the environmental white knight" because it is not considered toxic, is very functional, and can be used for numerous coatings (Frazier 2001). This could be used in the creation of a nanoscale coating so fine and smooth that nothing would stick to it that can be used for self-cleaning surfaces and could limit the need to dust, mop, sweep, wash windows, power-spray, clean toilets, and wash dishes. These examples focus on consumer applications, but there are many industrial benefits, including better energy transmission, improved water treatment technology, more effective food contact surface cleaning, and many others.

1.2 The Roots of Nanotechnology and the Next Industrial Revolution

A brief look back at the historical evolution of nanotechnology gives a deeper understanding of its only currently imagined future potential. Richard Feynman, the legendary Caltech physicist, gave a seminal talk at the American Physical Society in 1959 entitled, "There's plenty of room at the bottom." Feynman described how technology can miniaturize and continue to miniaturize. He conceptualized shrinking technology from its current scale to a scale one sixteenth its size, repeatedly, until achieving technology at the scale of matter. At that point, he theorized about the ability to manipulate matter at the atomic scale (Feynman 1959).

Eric Drexler, an early pioneer in molecular manufacturing, began his famous 1986 book, *Engines of Creation*, with **"**Coal and diamonds**,** sand and computer chips, cancer and healthy tissue: throughout history, variations in the arrangement of atoms have distinguished the cheap from the cherished, the diseased from the healthy. Arranged one way, atoms make up soil, air, and water; arranged another, they make up ripe strawberries. Arranged one way,

they make up homes and fresh air; arranged another, they make up ash and smoke. Our ability to arrange atoms lies at the foundation of technology."

Of course, in 1959, at the time of Feynman's lecture, materials at the nanoscale were already in use in the chemical industry, among others, but it was not called nanotechnology. These applications were not manipulating matter or engineering to specification at the nanoscale — and that is the difference between chemistry and nanotechnology. The ability to design and manipulate matter at the nanoscale is what is unique about nanotechnology. Drexler (1986) explains: "Just as ordinary tools can build ordinary machines from parts, so molecular tools will bond molecules together to make tiny gears, motors, levers, and casings, and assemble them to make complex machines."

This is Drexler's vision for the future of nanotechnology. The manipulation of matter at the nanoscale and manufacturing on a molecule-by-molecule basis is called *molecular manufacturing.* At this point in time it has not yet occurred. Many argue it is impossible, but the possibility of molecular manufacturing holds enormous potential benefits, safer products, manufacturing air and water purification technology, and other environmental advantages such as making new materials and products without waste — no need for big stacks to treat, capture, or release air pollutants, storm water permits for releases to our water systems, or trash and hazardous waste to go to our landfills or incinerators. And no need to waste the inputs to industrial processes. Drexler and many others who envision this future have paved the way for much creative work to come.

This is the promise of nanotechnology — to transform the way energy is generated, diseases are identified and treated, food is grown, and fabrics, building materials, and consumer goods are manufactured — a promise based on current research, as well as on applications that exist already in our economy, suggesting dramatic changes ahead. Many call nanotechnology "disruptive" — it will disrupt our current way of operating — radically changing our infrastructure, commerce, industry, trade, education, and manufacturing. It seems nanotechnology represents the beginning of the next industrial revolution. Other books in this series consider the societal dimensions of this disruption; this discussion considers how nanotechnology may impact health and the environment.

1.3 Nanomaterials: The Current State of Nanotechnology Application

Drexler's vision of the future of nanotechnology through molecular manufacturing, though as yet largely unrealized, has been borne out thus far in the development of many new materials — "nanomaterials" — a prime

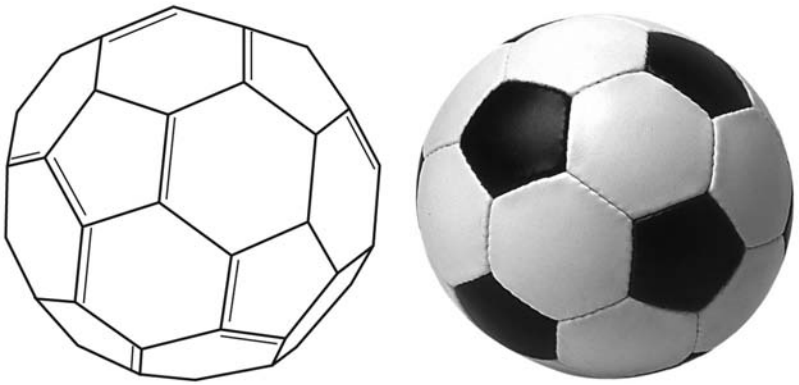

FIGURE 1.1
Schematic of a C60 Buckyball compared to a soccer ball.

example of which are those made from carbon. Carbon, the basic building block of life, can be formed into novel structures at the nanoscale, including nanotubes, nanowires, nanohorns, and the buckyball. Richard E. Smalley, with Robert Curl, Jr. and Sir Harold Kroto, won the Nobel Prize in Chemistry in 1996 for their discovery of the C_{60} molecule they called buckminsterfullerenes, after Buckminster Fuller, who developed the geodesic dome.

Buckminsterfullerenes are also called buckyballs or fullerenes, and most commonly contain 60 atoms of carbon in a spherical, soccer ball formation, with a diameter of about 1 to 2 nm (Figure 1.1 shows a C_{60} fullerene). Each of the intersections is a carbon atom, five or six atoms connect to form a ring, and the rings are interconnected, fused together in a cyclic molecule. Fullerenes can have more than 60 atoms of carbon (C_{60}), C_{70} is also commonly fabricated, and smaller molecules are possible, as are larger ones. There is a growing field of fullerene chemistry.

Fullerenes have been reported to behave as antioxidants, scavenging radical oxygen molecules. Hydroxyl radicals have been associated with aging and stress, and antioxidants are hot market items for skin creams and nutraceuticals. The Woodrow Wilson International Center for Scholars Project on Emerging Technologies lists six cosmetics containing fullerenes in their Nanotechnology Consumer Products Inventory (WWCS 2007). C_{60} also appears to disrupt cell membranes, reducing cell viability, and is being investigated as an antibacterial additive for disinfectants. Other potential uses for fullerenes include: industrial catalysts, drug-delivery systems, lubricants, coatings, catalysts, electro-optical devices, and medical applications (e.g., antibiotics and targeted cancer therapy). However, the antioxidant properties of fullerenes could lead to their inclusion in other consumer products. C_{60} may also be used in lithium ion batteries, for fuel batteries, ultra-conducting material, highly functional paints, and industrial grinding material.

In 2004, the first year of commercial scale C_{60} manufacturing, production was estimated at 1500 metric tons, but as uses develop, production costs are

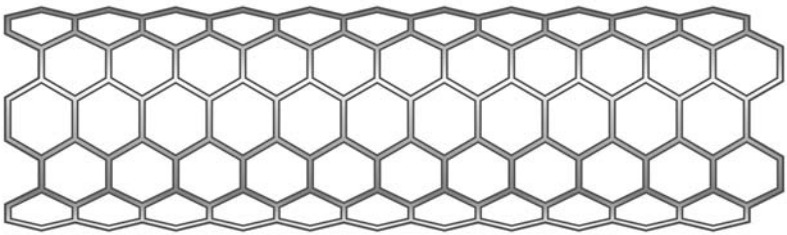

FIGURE 1.2
Side view of a carbon nanotube.

likely to decrease, and production volumes could increase. Near future uses of fullerenes may be relevant to water, waste, air, energy, transportation, and pesticide applications. Its catalytic and antimicrobial properties may warrant use of C_{60} for water treatment and disinfection (Boyd et al., 2005) or as additions to products. Fullerenes could also have environmental applications in sensor technology, being able to measure other substances accurately and at low levels. C_{60} has also been measured in ambient air pollution from combustion sources such as vehicle exhaust (Utsunomiya et al., 2002), so even before it could be manufactured, C_{60} was part of our environment. However, the ability to manufacture C_{60} allows for new applications.

Carbon structures can become quite complex. One of the more common structures is the carbon nanotube. The formation of carbon nanotubes is like creating a roll of chicken wire. Laid flat, sheets of graphite (used in pencil lead) resemble chicken wire made of carbon. Rolled up into a tube, these become carbon nanotubes (see Figure 1.2). Nanotubes can be of variable length and width, and can be single-walled or multi-walled (multiple concentric tubes encasing one another). Each variation in structure brings new properties that at the time of this writing do not even have a standard nomenclature. That is, there is no universal classification for describing the length, width, and characteristic properties of carbon nanomaterials and nanostructures. Any substitution of these molecules, or embedding a different molecule in them, also changes their structure and function. How many potential combinations are there? According to estimates by Vicki Colvin of Rice University, there are upwards of 50,000 combinations (Colvin 2006).

What's so great about carbon nanotubes? They possess a breadth of electrical, optical, thermal, and physical properties that are being investigated for numerous applications. Some nanotubes conduct electricity better than copper, and depending on their charge properties, they can form an electrostatic coating for easier painting of surfaces. Nanotubes are stronger than steel, and are also lighter and more flexible, and they conduct electricity at low temperatures. Many current applications include adding nanotubes to composite structures to make them both stronger and more flexible. Examples include auto body parts and sporting gear such as baseball bats, bicycle frames, golf clubs, and tennis balls. Carbon nanotubes also have applications

in computing and electronics, for flexible displays, circuits, semiconductors, and conducting films with potential fuel cell and solar technology applications. Some carbon nanotubes possess catalytic properties, that is, they are reactive with certain other substances. They can be used to decontaminate air and water, and also potentially for desalinization (removing salt from sea water to make it drinkable). In other words, nanotubes possess unique properties with advantages in most industrial sectors, and could widely enter the economy in numerous applications.

Nanotubes and other nanostructures do not need to be made from carbon. Titania, silica, and copper have all been used to make nanotubes. Many materials take on new properties at the nanoscale, and new structural configurations are likely. These materials, while novel by today's standards and currently in development in laboratories for numerous applications, are in actuality simple materials — compared to the full-scale molecular manufacturing envisioned by Drexler (1986), who wrote, "…our spacecraft are still crude, our computers are still stupid, and the molecules in our tissues still slide into disorder, first destroying health, then life itself." Drexler envisions biologically based technology, suggesting a level of complexity for the next generation of nanotechnology that few can currently envision. Nanotubes represent the future — engineered structures with specific properties used in a variety of applications.

1.4 Nanotechnology Risks Now

The commercialization of nanotechnology is literally under the microscope. Numerous non-governmental organizations that focus on environmental health and consumer issues currently are calling for a moratorium on all products containing nanotechnology until their safety and risks are known (e.g., ETC Group, CFTA). Regulatory agencies are being asked to develop standards, yet the data are not currently available to ascertain safe levels of many new materials. Many of the international organizations discussed in Chapter 9 are working toward voluntary standards for environmental health and safety of nanotechnology.

Demands to understand and address risks in real time, that is, during development, add a difficult dimension to nanotechnology development. As will be discussed, the understanding of behavior at the nanoscale is in very early stages, and it is premature to make long-lasting decisions about nanotechnology without this understanding. However, now is the time to begin the analysis, while the actual risks from nanomaterials are small because they are produced in low levels and very few people are exposed in very small amounts, to guide decision making for when they are in widespread use. Addressing potential exposures now is the best way to mitigate

the long-term risks of nanomaterials and nanotechnology that are currently unknown.

1.5 Environmental Aspects of Nanotechnology

Many applications of nanotechnology benefit the environment, for example, treating drinking water, eliminating toxic chemicals, reducing water and energy consumptions, and harnessing cleaner energy technologies. How can the applications of nanoscience affect the environment? It is not clear today what the potential impacts are from nanoscale materials in the air, water, and soil. It is not understood whether nanomaterials might enter the food supply and become part of the human diet, or whether and how they can affect forests, coral reefs, or air quality for example.

Will there be a nano-environmental legacy? Are nanomaterials already entering the environment in ways that will allow them to persist and enter or upset the food chain? Will nanomaterials follow the path of other legacy pollutants, such as lead? How will this be determined if data are not being collected? One could argue that the amounts will be small, and in the near future, it is true that there are few applications of nanotechnology likely to allow free nanoparticles to enter the environment in significant amounts. However, as more and more applications adopt nanotechnology, the production, uses, and releases of nanoparticles will dramatically increase.

By way of example, in a hospital environment, it is very important to keep surfaces sanitary free from contamination, and many cleaning and disinfection chemicals are used for cleaning equipment for washing floors and surfaces to help prevent the spread of germs. Using a product containing a nanomaterial as a disinfectant might mean it would be sprayed, wiped, poured into buckets and on floors, and washed down drains. An obvious question arises: where could the nanomaterial end up? Any time chemicals are washed away with water or flushed down the drain, they are released into the environment. From drain pipes, these materials enter the ground water and eventually can move to the nearest rivers and streams. Of course, this may affect drinking water sources and oceans.

Researchers now are detecting chemicals such as triclosan, commonly found in antimicrobial soaps and cleaning products, in rivers and drinking water sources. Some populations of bacteria routinely exposed to substances designed to eradicate them (e.g., pesticides and medical antibiotics) are now found in the environment and have become resistant to antibiotics used in agriculture and for human diseases. Antimicrobial resistance is a big problem because bacteria are no longer susceptible to the treatments developed to kill them, and outbreaks can occur that cannot be managed. Currently, a number of hospitals are battling antibiotic-resistant *Staphylococcus* infections in patients. More questions arise: if a nanomaterial is used in an antimicrobial

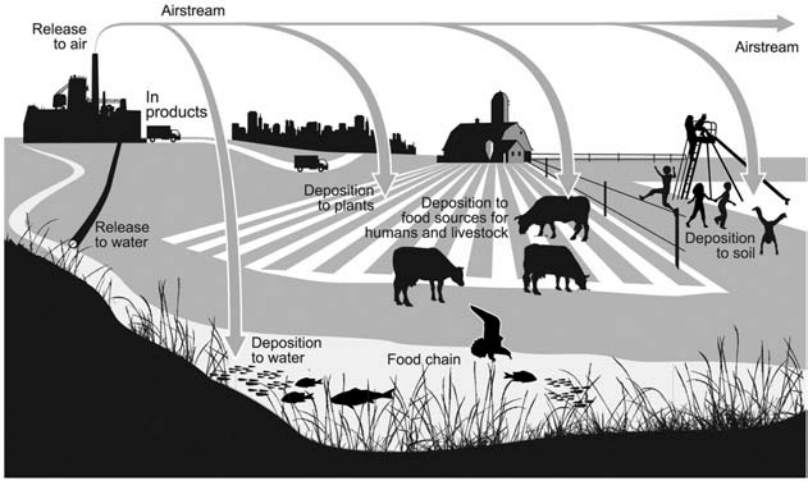

FIGURE 1.3
Potential exposure pathways for nanomaterials. (See color insert following page 76.)

treatment, can it cause antimicrobial resistance in the environment? What other unintended effects could a substance that is released in water cause?

One of many pathways that nanomaterials can enter the environment is through the drain pipes from the hospital that may lead to a treatment plant where the water gets treated, and then released to the environment. (Figure 1.3 shows other pathways for nanomaterials to move in the environment.) What types of effects can occur from these environmental exposures? Nanomaterials could contaminate the water that is home to many plants and animals. Fish might absorb them from the water, or they could be taken up by bacteria and transformed to something else that is more toxic, more mobile, or more persistent. Nanomaterials could enter the food web. It is not always easy to predict what will happen when introducing materials into an ecosystem. Since all organisms require water to survive, this discussion focuses on the aquatic ecosystem, but there are many other environments to consider including forests, deserts, mountains, tundra, savannahs, and broader marine systems, not to mention the ecosystem of the built environment, buildings and cities. By way of beginning the discussion, let us consider an example from the past that has structured much of the current framework of risk assessment and its application to nanotechnology.

1.6 DDT, Learning from the Past

Over 40 years ago, a scientist named Rachel Carson motivated much of society's current environmental management by writing a book about chemicals

in the environment and how the pesticide Dichloro-Diphenyl-Trichloroethane (DDT) was harming birds and other wildlife. In *Silent Spring*, Dr. Carson explained how DDT and other chemicals were entering the environment and affecting birds and their reproduction (by thinning eggshells), notably the bald eagle (Carson 1962). Arguably, Carson's careful research led to many international developments, including the introduction of the U.S. Endangered Species Act and the formation of the U.S. Environmental Protection Agency (EPA).

Much has changed since the 1960s. In 1967, the bald eagle was one of the first endangered species to be listed on the Endangered Species List, and on June 30, 2007, was removed from the list. In the United States, DDT was among a dozen "persistent organic pollutants," or POPs, banned between the 1970s and mid-1980s (Stockholm Convention 2001). The U.S. EPA is currently undergoing re-registration of all approved pesticides as required by the Food Quality Protection Act of 1996, conducting risk assessments that consider both human and environmental impacts (FQPA 1996). Today's pesticides are less toxic, and much less persistent. After they are applied to crops, most break down quickly into less toxic compounds, and less of their residue ends up on fruits and vegetables. More and more pesticides are designed to target specific pests by interfering with their biochemistry. They are designed to act only on those species that affect crops and thus are less harmful to people.

Ironically, the World Health Organization (WHO) recommends indoor residential spraying of DDT for control of mosquitoes that carry malaria in Africa. When used in the 1950s and 1960s, DDT successfully eradicated malaria in many parts of the world. One of the impacts of banning DDT included the spread of malaria in parts of the world such as Africa and India, where prevalence of this devastating disease today can be as high as 50% or more. WHO promotes the use of DDT for malaria because they feel the evidence shows that the benefits outweigh the risks. Weighing the risks of malaria against those of DDT led WHO to advocate that used under well-managed conditions, DDT poses no harm to wildlife or humans (WHO 2006). From this point of view, the alternative to DDT spraying is widespread malaria outbreaks and millions of people dying, because of a preventable and treatable disease spread by mosquitoes. WHO feels that the potential cancer risks associated with exposure to DDT are low, and these must be balanced against the millions of people who would suffer and die if malaria-spreading mosquitoes are not eradicated.

Scientists have been studying the effects of DDT since the 1950s. While much is known about its effects on people and animals, uncertainty remains regarding specific effects, for example, the association of DDT with cancer. Several studies suggest that DDT exposure does not increase the risk of cancer, but a few studies indicate it does (JMPR 2000). Looking back at DDT as a case study in chemical management that led to current environmental management generally, and for pesticides specifically, shows that much is learned from looking at the evidence and weighing the risks and benefits. The concern about DDT, and its thinning of bird eggshells, motivated decades of research on pesticide

behavior effects in mammals, people, the environment, drinking water, and foods. On the one hand, the risks associated with pesticides need to be managed, and are, by current legislation. On the other hand, the risks of limiting pesticide use have implications for public health, not only in the case of DDT and malaria, but for farmers, farm workers, and their families who may use greater quantities of less effective substances because of their regulatory status (Gray and Graham 1995). DDT may not be highly toxic and, in comparison to death from malaria, demonstrates that benefits of using substances sometimes outweigh the risks, in this case weighing young children dying versus low-level cancer risks. The larger issue in the 1960s may have been the indiscriminate use of DDT, not its use for mosquito control. It is easier to see in hindsight, of course, than to predict the future. There are many variables to consider. One important lesson from looking at DDT is that in over 50 years of study, there is still uncertainty about the associated health effects.

Society benefits from new technologies. But we must ensure that we do not replace our existing problems with new ones that we do not understand and cannot manage. *Nanotechnology development presents an opportunity to transform our society to a more sustainable technological future, but requires a ground swell of activity to steer in this direction, or it will not.*

1.7 What is Risk?

Much of this book focuses on risk analysis and its potential applications for nanotechnology and nanomaterials. But first — what is risk? Defining risk is not as straightforward as one might expect. Understanding risk is a complex, multi-disciplinary endeavor. There are many dimensions: technical, economic, social, and political, and these dimensions are not universal and are often divergent. This book adopts the view that while risks are shaped by the societal and political context in which they occur, there are discernable physical and biological impacts associated with exposure to substances that can be defined and assessed. This view is born from years of working in the field of risk analysis seeking practical approaches to assessing risks associated with emerging potential threats in the environment as a first, essential step. Thus, as may already be apparent, the complex societal dimensions of risk are often noted, but not broadly considered as part of this discussion.

Early definitions of risk simply focused on the number of deaths associated with a particular hazard (Starr 1969). Over the years the understanding of risk has evolved to encompass a much broader and more precisely defined range of meanings. Risk may be defined differently depending on the context. For example, the U.S. Nuclear Regulatory Commission defines risk as"the combined answers to 1) what can go wrong? 2) How likely is it? And 3) What are the consequences?" (NRC 2007). The U.S. EPA defines risk in the context of human health as: "The probability of adverse effects

resulting from exposure to an environmental agent or mixture of agents" (USEPA 2007). WHO currently defines risk as "the probability of an adverse effect in an organism, system, or (sub)population caused under specified circumstances by exposure to an agent" (WHO 2004).

At Clark University in 1985, the founders of one of the earliest Science Technology and Society programs, Chris Hohenemser and Bob Kates, with others, broadened the scope of understanding risk beyond its early definitions. They defined risk as the "quantitative measure of hazard consequences expressed as conditional probabilities of experiencing harm" (Kates et al. 1985). Social scientist experts in risk perception adhere to a broader definition of risk. According to Paul Slovic (2000), Ortwin Renn, and other experts, risk is a construct (IRGC 2006). That is, risks are judged in the context of individual and cultural views of the world. The International Risk Governance Council (IRGC), based in Switzerland, defines risk as "an uncertain consequence of an event or an activity with respect to something that humans value (definition originally in Kates et al. 1985). Such consequences can be positive or negative, depending on the values that people associate with them." This brings out a highly significant point: risk has a societal dimension, a context for individuals and for groups with specific points of view. As a construct, there are many dimensions of risk that are not universal, rather, these are personal, developed in response to a number of factors, including whether people feel they have control over a hazard or feel it is imposed on them, and how scary a hazard is perceived to be based on an individual's level of experience with it. An example is traveling by air versus on the road. Statistically, fatalities are higher per mile driven on a road than flying in an airplane. But many people are more concerned about their safety on airplanes than when driving because of the familiarity and feeling of control over the potential risk associated with driving versus flying.

People's perceptions of risk are also influenced by their peers and by the media. Concern levels about risks decrease when the risks are more familiar, especially if they are associated with valuable benefits. For example, exposure to radiation as a cancer treatment is a more acceptable hazard than exposure to radiation from spent nuclear fuel. Ragnar Löfstedt describes the role of trust in perceptions of risk. If institutions are trusted, there is less concern about managing risks than in cases where there is little trust in decision makers (Löfstedt 2005). Societies continually manage many hazards, some better than others (e.g., food safety, water quality, terrorism, and air traffic). As a result, societies have defined acceptable levels of risk for many substances and technologies that people are willing to bear (Kates et al. 1985). Because of the role of perception though, the levels of acceptability can vary for different concerns. In this context, it is clear that early views of risk analysis simplified the societal dimensions. "If we understood quantitatively the causal relationships between specific technological developments and societal values, both positive and negative, we might deliberately guide and regulate technological developments so as to achieve maximum social benefit at minimum social cost" (Starr 1969).

1.8 Risk Analysis

Having introduced the concept of risk, now we can consider risk analysis and its role in nanotechnology and nanomaterials. Risk analysis is a multidisciplinary approach to understanding how substances behave and to judge whether that behavior is acceptable. Risk analysis involves both science and judgment, and this is part of the reason for its controversial nature. The science of characterizing materials, their toxicity, and their exposure characteristics is weighed against other materials and standards established as acceptable in a society. In the view of the WHO, risk analysis is "a process for controlling situations where an organism, system, or (sub)population could be exposed to a hazard. The risk analysis process consists of three components: risk assessment, risk management, and risk communication" (WHO 2004). Risk assessment is thus a key part of risk analysis.

This book explores risk analysis and risk assessment in much greater depth in subsequent chapters. Suffice it to say, risk analysis is a way of evaluating and weighing benefits and environmental concerns in a consistent and transparent way. It helps to balance perception with scientific analysis, and to consider substances and technologies through a framework that allows clearer decision making about their potential to cause harm to health and the environment. In the chapters that follow, the premise and mechanics of risk analysis are developed, along with examples of past, current, and future technologies that demonstrate the need for, and benefits of, evaluating the health and environmental risks of nanotechnology.

1.9 Overview of the Book

This book discusses nanotechnology and risk analysis, and how through their marriage a sustainable future can be built by design. We consider why we *must* proceed this way, the risks of not addressing health and environmental concerns, and ideas on how to go forward from here.

Chapter 2 explores the use of risk analysis in decision making, and its development as a field of analysis and a policy tool. The chapter describes the steps of risk analysis, what types of information are developed and used, and how uncertainty is addressed. Chapter 3 looks at the "opportunity costs" inherent in current nanotechnology development, and explores in depth the possibilities for using nanotechnology to create a sustainable future. Chapter 3 also discusses life cycle analysis, an assessment approach that takes a broader look at the behavior of substances from their generation to ultimate disposal or reuse. Chapter 4, contributed by Dr. Brenda Barry, introduces the topic of toxicology of nanoscale materials, what is known about impacts of specific nanoscale materials on people, and key questions for further research.

Chapter 5 addresses environmental impacts and exposure — a crucial component that distinguishes *hazard analysis* from *risk analysis*. Exposure assessment looks in detail at the behavior of substances in the environment, including in occupational and ambient systems. There is somewhat of a convergence of thinking across sectors about evaluating nanomaterials and nanotechnology throughout the life cycle, from manufacture to disposal. Chapters 6 and 7 explore tools adapting life cycle thinking into risk analysis for nanotechnology. These approaches represent the state of the art for assessing the risks of nanotechnology, but also require corollary risk management responses. Chapter 6 introduces NANO LCRA, the author's proposed framework for nanotechnology that incorporates adaptive management and life cycle thinking into a streamlined screening-level risk assessment process. Chapter 7 describes alternative methods for evaluating risks of nanoscale materials and nanotechnologies, including a discussion of Comprehensive Environmental Assessment contributed by J. Michael Davis, Senior Science Advisor in the U.S. Environmental Protection Agency's National Center for Environmental Assessment. Dr. Barry contributed Chapter 8, which describes current practices for managing hazards and risks of nanoscale materials — who is doing what in this arena, and the state of the art. Finally, in Chapter 9, we survey the current state of numerous efforts internationally to address risks and develop science and policy for nanotechnology.

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2

Defining Risk Assessment and How It Is Used for Environmental Protection, and Its Potential Role for Managing Nanotechnology Risks

Jo Anne Shatkin

CONTENTS

> "We should be guided by the probability and extent of harm, not by its mere possibility."
>
> **Aaron Wildavsky**

There are two main dimensions of risk — the probability of an event occurring, and the magnitude of the consequences. However, as discussed earlier, the analysis of risk also includes judgments about the severity of risk as

part of the assessment. This chapter walks through the basics of risk analysis, how risks are analyzed, and how scientists and regulators make decisions about how to manage them. Adopting the World Health Organization (WHO) definition, the risk analysis process consists of three components: "risk assessment, risk management, and risk communication" (WHO 2004). Risk assessment is a key feature of risk analysis. Several alternative frameworks are introduced for assessing and managing risks from substances and technologies.

One of the key features of risk assessment is that while there is always potential for hazards to occur, there is a difference between hazard and risk, and that difference is *exposure*. If there is no exposure to a hazard, then there is no risk from it. The level of risk associated with a hazard is dependent on the extent of exposure. Explicitly considering exposure is the main difference between assessing hazards and assessing risks. For example, people with infectious diseases are encouraged to stay home from work. By showing up, they would expose co-workers to the disease, increasing the risk that they too would contract it. Without exposure, the co-workers are not at risk.

The ways in which different hazards are managed depends in part on where they occur (in the environment and in the world) and what kinds of hazards are being managed. There are numerous inconsistencies in society's level of concern, and the safety standards applied for different hazards. Governmental programs and even individual actions can be inconsistent about the level of protection from different hazards. Some regulations require risks to be, "as low as reasonably achievable" for example, while others set standards based on a quantitative measure of risk.

Some of the inconsistency is determined by regulation. If you live in California, the standard for exposure to products containing cancer-causing chemicals — one in a million at risk — is determined to be an acceptable risk level (the scientific notation for this is 10^{-6}). Note that this does not mean one person in a population of one million people *will* get cancer, it means one person of one million exposed is *at risk* of getting cancer from exposure. In the same way that being exposed to someone with an infectious disease does not mean with certainty that you would be infected, being exposed to a carcinogen does not mean you will get cancer. An exposure increases the risk of getting cancer.

In occupational environments in the U.S., OSHA (the federal government's Occupational Safety and Health Administration) generally regulates carcinogens in the workplace to a risk level of one in one thousand (10^{-3}), which is one hundred times higher risk than environmental standards in California. The U.S. Environmental Protection Agency (EPA) sets clean-up levels for hazardous waste sites to cancer risk levels between one in one million (10^{-6}) and one in ten thousand (10^{-4}). A 10^{-4} risk level might also be expressed as a 99.99% chance of not getting cancer from the exposure (10^{-6} is a level of protection of 99.9999%). These risk levels are on par with the risk of dying in an automobile crash in the U.S. (10^{-4} in the year 2000, before everyone talked on cell phones), a bicycle crash (10^{-4}), or the odds of being struck by

lightning (10^{-5}). Contrast these (low) risk levels with the lifetime risk of getting cancer in the U.S. of one in 3.5, which is less than 1% per year (10^{-2}), or the annual incidence of malaria worldwide (less than one in 10, under 10%; 10^{-1}). In parts of Zambia, the risk of contracting malaria exceeds 100% for children under five, meaning many may be infected more than once. The probability of infection in some provinces is observable, a far cry from the theoretically calculated extrapolations to the risks from low levels of environmental contaminants (Finkd, 2007).

Clearly, these threats are not evenly distributed across time, space, or the type of hazard. However, one commonality from each of these hazards to health is that exposure is required to be at risk. There are hazards in daily life, and these differ depending on specific life circumstances. But, if you are not exposed to a hazard, then you are not at risk from it.

It is a key point so let us reiterate: there are hazards everywhere, all the time. Risk is distinct from hazard because risk also considers the potential for *exposure*. Hazards alone do not constitute risk: there must be both hazards and exposure potential for there to be a health risk. That is why many of our current products and processes use very toxic materials without harm to people or the environment, because there is no exposure. The risk assessment paradigm includes the two dimensions of hazard and exposure. Risk analysis offers more opportunities to manage hazards safely. One option is to eliminate the hazard, but another is preventing exposure to it.

Some argue that it is preferable to remove hazards rather than prevent exposure to them. This approach has appeal, and I agree that ultimately it is safer to not have hazardous materials in products. However, looking at hazard and exposure can tell a different story than one judged on the basis of hazard alone. Adopting a broader view of potential impacts, considering both hazard and exposure, can lead to more informed decisions about the potential impacts of choosing one material, or technology, over another.

2.1 Context for Technological Risk

A 2006 survey to assess people's perceptions of the risks of a range of technologies found that U.S. respondents thought nanotechnology was scarier than bicycles (Nanotechweb 2006; Curall et al. 2006). What is the relationship between bicycles and nanotechnology? Both nano and bicycles may be considered enabling technologies; that is, their use enables other applications. A bicycle is a technology, but it is not a new one. Even though components, frames, and accessories are often made with state-of-the-art materials, bicycles are a way of life in societies around the globe. Certainly, while nanotechnology is used for stronger, more flexible and lighter frames for bicycles, cycling is not new, bicycles are not new, and to many, they are simple machines.

The modern bicycle was invented in the late 19th century. While continuously evolving in the materials, components, and aerodynamic design, bicycles are common enough that each of us likely conjures up an image that includes two wheels, a frame, seat, and handlebars. Some applications of the bicycle are for transportation, while others are for exercise, and for others, professional employment (racers). When someone says, "bicycle," it is easy to conjure up an image of what they are describing. These might be canals in the Netherlands, crowded city streets in China, the hilly roads near my home devoid of cars most hours of the day, the sleek bodies of racers climbing the mountainous roads in the Alps. What does the word bicycle conjure up in your mind?

Now, let us try nanotechnology. Does the word nanotechnology conjure up a specific image for you? Do you think of coated fabrics, tiny sensors, bacteriostatic medical devices like catheters, or self-cleaning toilets? Do you think of molecular machines? Bacteria in a fuel cell churning out energy? Does nanotechnology conjure up spybots, like *Prey* (Creighton 2002)? Nanotechnology involves creating molecules that enable applications in medicine, energy, coatings, sensors, electronics, fabrics, and industrial uses. Although diverse in terms of composition, structure, and physical properties, nanotechnology can be defined by the size and through its application. But, it is not as easy to conjure up an image of "nanotechnology" as it is to envision a bicycle. One can have a different image every time a report of a new application appears.

These represent images of the technologies, but what about the risks? The 2006 survey compared people's perceptions of nanotechnology to a host of others, and found people to be fairly neutral about nanotechnology risks. In fact, survey respondents were less concerned about nanotechnology than DDT (Curall et al. 2006). The perception of technological risk has a lot of influence on individual and collective decisions about whether or not to adopt new technology. Perceptions of technological risk can also influence how extensively risk assessments are conducted. The assessment approaches used also influence the decisions about management approaches adopted to make them safer. The level of threat to something valued (e.g., health, loved ones) is a key driver in an individual's assessments of technological risk.

As we discuss later in this chapter, there may be differences between the level of concern consumers and others have about a substance or a technology, and the views of those with a lot of expertise in it, including the developers. Those involved in regulating or managing risks from a technology will be influenced by both public opinion and industry views. Often, the level of public concern is the key determinant in how extensively the risks from one technology versus another are managed. Like it or not, public concern is a driver of governmental efforts in democratic society. This is important to our discussion because focusing on risks that do not really affect public health, safety, and the environment can come at the expense of those that do.

The current U.S. EPA regulatory process is driven by the concerns of the American public that prevailed in the 1970s and 1980s. The Comprehensive

Environmental Response, Compensation, and Liability Act (CERCLA) or Superfund program, for example, requires that hazardous waste sites be remediated when they pose risks above an acceptable range of one in one million (10^{-6}) risk to one in ten thousand (10^{-4}) risk of getting cancer from exposure to contaminants in soils and/or ground water (in some cases also from rivers and lakes, and air pollution) on the site for a lifetime. Compared to the risk of harm from riding a bicycle, those are pretty long odds. Over one million people *in a year* are injured on bicycles (Petty 1991). Yet many people fear the effects of hazardous waste, and the EPA oversees the clean-up to ensure Superfund sites pose residual risks that are extremely low. From a utilitarian view, it would make more sense to regulate bicycle safety than hazardous waste site clean-up. In a democracy though, institutions reflect public will, or at least the will of those influencing politics at the time of their establishment. Understanding the role of public concern in the assessment of risk is a key dimension.

Returning back to the comparison of risks from bicycles verus nanotechnology, the Centers for Disease Control estimates 67 million Americans ride bicycles. In the year 2005, 784 people were reported to have died in bicycle crashes. Therefore, the risk of dying in a bicycle crash is about one in 10,000 (10^{-4}). Are people afraid of dying on a bicycle? Apparently not, since only about 19 percent of adults and 13 percent of children who ride bicycles wear helmets consistently (CDC 2000). How many people are dying from nanotechnology in a year? Currently, none. Is it likely that hundreds of people each year will die from nanotechnology? If not, then what causes people to fear nanotechnology? And, why are we not more afraid of bicycles?

Is it fair to compare the risks from nanotechnology to bicycles? The risks of bicycles are very well-known as are the benefits of bicycle riding. The risks and the benefits of nanotechnology are yet to be determined. It is fairly obvious that people generally have a lower level of concern about familiar technologies versus ones not well known with little experience. In a survey of 16 technologies, Morgan et al. (1985) found bicycles were among the lowest of the dreaded risks, and also among the most known. When the risks from bicycles are among the least dreaded and the best known, how surprising is it to learn that nanotechnology risks are perceived as greater? The finding does not suggest concern about nanotechnology as much as it indicates a lack of familiarity. It does suggest that as people learn more about nanotechnology, perceptions may change.

As you continue reading and form your own opinions about nanotechnology risks, here is a point to keep in mind. The modern bicycle became popular in the late 1890s, including among women. The famous suffragist, Susan B. Anthony, said, "Let me tell you what I think of bicycling. I think it has done more to emancipate women than anything else in the world. It gives women a feeling of freedom and self-reliance."

In the 19th century, few could envision that a technology like the bicycle could change American culture (Anonymous 2007). Women gave up corsets and long gowns in favor of more practical clothing so they could ride

bicycles. My point is, as with risks, the benefits of new technology are also uncertain and may not be predictable. When there is little knowledge, it is important to keep an open mind, and readjust thinking as new information is obtained, to be adaptive in our thinking.

2.2 Why Risk Assessment for Nanotechnology?

Each of us conducts risk assessments based on our own judgments. A successful venture capitalist told me he has two very simple decision tools regarding whether a new product he may invest in has the potential for health and environmental risk: (1) is the product free in the air, are there free particles? And (2) his gut reaction to the question, is it too risky? This is indeed conducting risk assessment. However, without formal tools, he is unable to document the decision process, and perhaps has less confidence in his decision than if a formal analysis had been conducted that considers not only the available data, which are sparse, but the characteristics of the material. In answering the question about free particle exposure, one type of risk assessment is conducted, will the material present an inhalation hazard in the workplace? This is an important question, but as explored in later chapters, determining that a nanomaterial does not pose an inhalation hazard is not the same as concluding a lack of health or environmental risk. Other pathways, as well as the potential for exposure outside the research and development environment, are also key factors that must be addressed.

As discussed in Chapters 6 and 7, an alternative is to adopt a new risk analysis process for nanoscale materials, to conduct a more comprehensive assessment of their potential for harm to health, safety, and the environment, and to make the assessment iterative, improving analysis as more data become available. The current regulatory framework for substances and technologies is a patchwork of levels of protection. Substances in drinking water are allowed at much higher levels than in soils on a hazardous waste site. Occupational risk standards can be much less protective than permitted releases to the environment, where exposures are more diffuse. To address these inequities, risk assessment is increasingly the basis of standard setting.

Risk assessment helps to identify potential concerns, and evaluate how they compare with other types of materials and technologies that have been adopted. This achieves a better level of protection for people and the environment, with a rational basis to compare one risk to another, and an even playing field for newcomers compared to existing substances and technologies.

One benefit of using risk assessment to set standards is that it allows decision making under uncertainty. That is, often decisions need to be made before all information is known. If the details were known, the discussion would not be about risks, it would be about safety. But there is not always time or other information resources to allow complete understanding. Risk

analysts have dealt with this problem by making reasonably conservative assumptions that tend to overestimate risk, but yet allow decisions to be made in the absence of a complete database of information.

Nanotechnology is not specifically regulated today, except Berkeley, California, which requires companies to disclose the current toxicology associated with their products. One reason for the lack of regulation is that it is so early in the development and use of nanomaterials in technology that there is not enough experience to discern which aspects of nanotechnology need to be regulated, or how to regulate them. As discussed in Chapter 3, lack of information (in this case on toxicology) has created concerns with the Berkeley law which could relate to nanotechnology regulation in general. As discussed in Chapter 4, many studies have measured the effects of nanoparticle exposure on health, but they often suffer from methodological concerns and raise more questions than they answer. It is likely that nanotechnology will be regulated, but developing rules takes time. Even without regulatory requirements, risk assessment provides a transparent process to frame and characterize risk.

Throughout the book we examine the consequences of not identifying potential problems early. Nanotechnology eventually may affect everyone. Instead of pretending there will not be any problems, it is time to look, to begin to identify concerns early, in time to take steps to address them. Unless we are looking, we will not know whether the products are safe, even if the necessary tools to see all of the details are not yet available.

Risk assessment allows prioritization of data collection. Stepping through the assessment process identifies where the missing pieces of information are and how important they are to overall decision making. If the key question relates to what happens to a material when it is released in water, then experiments can be designed to ask and answer this question. Before beginning lengthy toxicology studies, it is important to first consider the real world conditions for nanoscale substances and nanotechnology. How will these materials be used? By whom? How much contact would there be? Characterizing the potential for exposure is necessary to answer in terms of conducting good toxicology studies, and can be identified easily in screening-level risk assessment frameworks.

One reason for early assessments is to distinguish perception from reality. As discussed, what people worry about is an artifact of who they are, their social network, and where they get their information. People's perception of what is harmful may not match reality in terms of probability of harm. Risk assessment provides a sound basis to clarify what is harmful and what is not even when there are data-groups.

Choosing to use risk assessment yields many benefits, including early identification and prioritization of health, safety, and environmental concerns.

Risk assessment allows examination of the balance of risk/benefit tradeoffs. Not necessarily economic benefits, but rather, that introducing new technology means replacing existing technologies, and there can be health and environmental benefits of doing so. A new substance that can reduce

dependence on a very toxic chemical reduces risk; even if it not completely benign, there is still a benefit.

There are other reasons to conduct risk assessments, even if they are not required for the approval of a nanoscale material or technology. One is to demonstrate commitment to regulators and the surrounding community. Even if a producer is not required to look at the risks from products, it might make sense to do so, in order to inform "stakeholders" — people who are concerned about or responsible for effects from products — of the state of knowledge. If you own a manufacturing plant, neighbors could be concerned about what is released into the air and water, what is stored on-site, and what would happen in the case of a fire or explosion. Conducting a risk assessment and communicating the findings allows you to communicate about these concerns and promote healthy relationships with the community.

Another reason for risk assessment is to allow comparison of alternative management strategies. There is always more than one way to solve a problem, and it is best to be informed by the available data when making decisions. A technology may require working with a material of unknown toxicity, and how best to handle it can be informed by examing the potential for exposure and risk. Knowing what the concerns are creates an opportunity to address them in a proactive manner. Even if the available data do not allow quantitation, risk assessment informs effective risk management, and addressing risks earlier is cost efficient and responsible.

2.2.1 Adaptive Risk Assessment for Nanomaterials

Here is where I believe risk assessment makes sense, to inform the decisions about how to manage nanomaterials and nanotechnology amid uncertainty. As you might imagine, it is not a simple question of whether nanotechnology is safe or toxic; there is a whole spectrum of more likely possibilities in between the two extremes. Even with significant uncertainty, a risk-informed evaluation makes sense.

There are many ways to conduct risk assessments. One important first step, especially for nanotechnology and nanoscale materials, is to conduct a *screening-level assessment* (described in Chapter 6). The ease of modifying nanoscale materials through engineering makes it overwhelming to consider detailed quantitative risk assessments for every type of material. However, it would be very useful to conduct screening-level risk assessments for new nanoscale materials, since this would allow the assessments to keep pace with the rapid developments in nanotechnology.

The real value of conducting early screening-level risk assessments is that understanding risks allows more efficient management of them. Looking for potential problems early reduces the potential for unforeseen impacts. Customers, regulators, manufacturers, and activists will have increased confidence about the safety of new products if the concerns about them are assessed and addressed early. It is also important to *consider the entire life cycle of a material* to understand the potential for impacts to the environment.

What is the life cycle? Some refer to it as "cradle-to-gate" or "cradle-to-cradle." Considering the potential for effects throughout the life cycle is an important step in generating assessments for new materials. Life cycle analysis is discussed in Chapter 3.

2.3 Origins and Development of Risk Assessment, and the Societal Dimensions of Risk

For decades engineers have been making calculations about the strength of support beams for buildings, stability of bridges, and the crash resistance of automobiles, among others. The U.S. Food and Drug Administration (FDA) reviews studies of the safety of drugs, food additives, and medical devices, among others. The Food and Agriculture Organization (FAO) devises international protocols for identifying and managing a range of threats to the food supply. Public health officials study the outbreak of diseases associated with various exposures. These efforts inherently involve the assessment of risk.

However, many people conduct risk assessments all the time. Will the stock market go up or down? Is it safe to cross the street? How long has that leftover been in the refrigerator, and will it make me sick if I eat it? Is it safe to drink the water from the tap? Will I need an umbrella today? Are people adequately protected from exposure to materials in the lab? Individually, each of us might answer some of these questions differently. You might be unconcerned about the safety of your drinking water, but your best friend may insist on bottled water for drinking (which may or may not actually be safer to drink because it is not regulated). Regardless of whether the assessments calculate probabilities, we judge the likelihood and the consequences of our actions and the actions of others, and use that judgment to make decisions. That, in a nutshell, is risk assessment.

Chauncey Starr, founder of the Electric Power Research Institute, is considered the godfather, or grandfather, of quantitative risk analysis. His seminal 1969 paper, published in the journal *Science*, described what is still recognized as the key principles of risk analysis. Starr describes a quantitative analysis of the probability of dying from an industrial accident, and relates it to the exposure, and the length of time someone works. This approach formed the foundation for the current approaches to risk analysis.

Interestingly, Starr conducted this analysis to evaluate the social acceptance of risk — an integral, but less explicitly discussed concept that as a society, people are willing to accept some level of risk when the benefits of the risk source are valued. Starr was indeed exploring the nature of the technology/society interface, yet the main result of his work was the use of quantitative measures of exposure and effects to estimate risk. The basic principles of risk

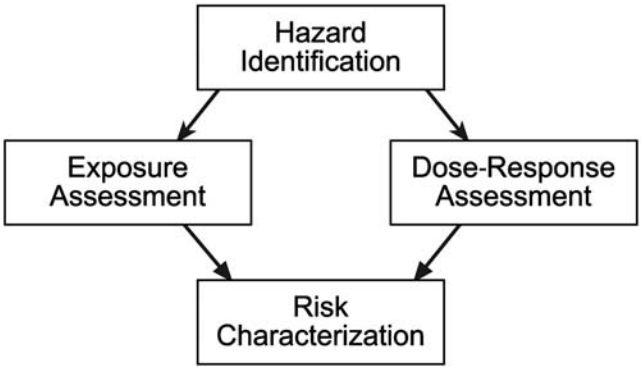

FIGURE 2.1
The four steps of the National Academy of Science risk assessment framework. (See color insert following page 76.)

are key concepts that are revisited later in this chapter. Starr noted that the perception of risk is different when the risks are voluntary or chosen versus those that are imposed. This, in part, explains why some people are afraid of low probability risks, such as a nuclear power plant failure, but not of higher probability risks such as developing lung cancer from smoking cigarettes (Starr 1969).

In 1983, the National Academy of Sciences convened experts to look at how risk assessments were being done by the U.S. government. The report, *Risk Assessment in the Federal Government: Managing the Process* (NRC 1983) is also commonly called the Red Book. A key theme of the Red Book was the distinction between the process of risk assessment and that of risk management. Risk assessment should be done by people different than those responsible for making decisions based on the assessments and those managing the risks. Thus, the assumptions and conclusions that constitute risk assessment must be independent of the broader management and policy. The reason is to keep the analysis independent of external concerns, such as economics or political pressure that can factor into decision making about risks. The Red Book laid out four main steps for risk assessment: hazard identification, dose-response assessment, exposure assessment, and risk characterization. This process of risk assessment has become the foundation of both voluntary and regulatory policies for analyzing risks and developing quantitative estimates of risk that inform decision making.

Figure 2.1 shows the basic four-step process of risk assessment. In the 25 years since the Red Book was published, much work has been done to refine the processes and approaches for these steps, which are described in more detail later in this chapter. Some frameworks use different terminology, and others outline steps for including stakeholders (people affected by decisions, or those with responsibility to manage or bear the results) or revising assumptions, but this basic model remains the current approach for using risk assessment for decision making.

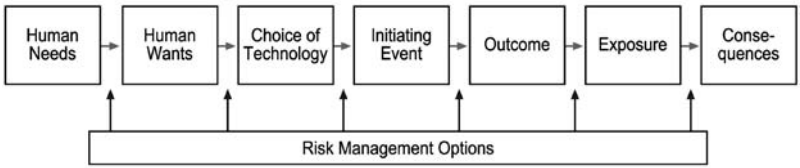

FIGURE 2.2
Technology assessment using causal chain analysis. (See color insert following page 76.)

2.4 Frameworks Addressing the Social Dimensions of Risk

One early contribution to the issues of society and technological risk was *Perilous Progress: Managing the Hazards of Technology* (Kates et al. 1985). *Perilous Progress* laid out an approach for assessing technology, and addressing the societal components of risk, using causal chain analysis. *Causal chain analysis* focuses on how to assess and manage technological risks. It identifies the alternative risk management options in terms of mitigation measures at different steps in the technology development and implementation process. As shown in Figure 2.2, technologies are developed in response to human wants and needs. Some hazards can be managed by choosing alternative technologies. In other words, there may be more than one technological solution to addressing a particular need. Often, however, a technology is developed, and no effort is made to address the attendant hazard occurring until some *initiating event* occurs. In this situation, risks are managed by mitigating the consequences of that event. Evaluating technologies using causal chain analysis allows the opportunity to compare alternative management strategies for technological risks.

Perilous Progress also develops an approach for evaluating technological hazards in a societal context. It includes the work of Paul Slovic, Baruch Fischhoff, and Sarah Lichtenstein (Kates et al., 1985), which addressed the social factors that contribute to the perception of technological risks. In surveys of lay persons and experts, they found that people with a limited understanding of the technical aspects of risk perceived some hazards such as nuclear power to be riskier than experts did. The hazards that people associate with risk factors, such as dread and unknown risk, were perceived at a higher level of risk than those based on the probability and magnitude of those hazards. This means that while experts tend to judge risks by the statistical probability of adverse events happening, other people may judge risks not by how likely they are, but by the type of risk — for example, how much is known about a hazard and its impacts; how much it is dreaded; the nature of the consequences, including the severity of effect; and the potential for catastrophic effects.

The significant body of work on the societal dimensions of risk is beyond the scope of this text. The topic is introduced to raise awareness for the

discussion of using risk analysis for environmental decisions. Risk analysis only informs better environmental decisions if it addresses the key concerns in the assessment. Having experienced developing sound, scientific assessments of environmental concerns to inform governmental decision making, and then seeing them disregarded because of public pressure (generally leading to overly conservative measures to eradicate risk) has humbled my view of the role of science in environmental decision making. Yet, I have participated in decision making processes that involve educating people about risk and risk analysis, and have seen that process lead to more informed decisions about managing environmental risks. People need to be informed about risks and risk analysis so they can make educated decisions. Even so, the power of people to influence decision making should never be underestimated.

Researchers in the field of risk perception continue to survey attitudes toward technological and societal risks and refine the understanding of the factors that contribute to public perception of risk. While it may seem irrational to some scientists and engineers, public reactions are predictable by the nature of the risk, in terms of whether hazards are reversible, dreaded, the level of media attention to them, and the association to other types of hazards. The often cited concern that the fate of nanotechnology will be like genetically modified organisms (GMO) relates to the framing of the GMO debate by Greenpeace, who termed GMOs, "Frankenfood" (Asian Economic News 2001). There are signs that some groups are already trying to take a similar approach with nanotechnology. For example, the ETC Group, an advocacy group in Canada focused on issues of "erosion, technology and concentration," held a contest for a hazard symbol for labeling nanotechnology, presumably to label all things nano as hazardous, regardless of whether data suggest a concern (ETC 2007). The few surveys to date on public attitudes toward nanotechnology reflect a low level of understanding, but also a perception of the benefits of nanotechnology. However, in the information age, this can change rapidly.

As Kahan stated, "Not much more is known about public perceptions of the risks of nanotechnology than is known about nanotechnology risks themselves" (Kahan et al. 2007). In their survey of 1800 people in the U.S., they found strong opinions about nanotechnology risks, despite more than half of survey respondents never having heard of nanotechnology. Interestingly, while those with more knowledge were more favorable toward the benefits of nanotechnology over the risks, the authors conclude the real finding is that people's opinions about nanotechnology align with their cultural values, not with knowledge, meaning that whether nanotechnology is likely to become as controversial as nuclear power did is as yet to be determined. One challenge for nanotechnology development is the need to evaluate risks at the same time as they are being developed, in real time. In the information age, where a video can be viewed by millions of people within hours of posting on the Internet, social networking allows unstructured communications

not limited by geography, and the flow of information, whether it is true or not, is nearly instantaneous.

The case of the recall of a product called "Magic Nano" is instructive. In 2006, the German government recalled Magic Nano©, a bathroom cleaning product, after 80 people were hospitalized with respiratory symptoms resulting from using it (Weiss 2006). Within days, the ETC Group called for a moratorium on nanotechnology. A month later, the German government declared that the product did not contain nanotechnology, that it was a flaw in the manufacturing of the aerosol propellant that caused adverse reactions. Scientific and government responses cannot match the speed of electronic communication.

One theme revisited in this book is the considerable uncertainty associated with the impacts of nanotechnology on health and the environment. When there are missing data, risk assessments apply professional judgment and other tools to extrapolate risks. The judgments reflect values. For example, defining the significance of the risk presented by a nanoparticle measured in air is a question of its acceptability. Because of the importance of societal dimensions of risk assessment, several risk frameworks incorporate public participation.

The NRC also addressed the issue of uncertainty in the 1996 report (known informally as the Orange Book), *Understanding Risk: Informing Decisions in a Democratic Society* (NRC 1996). This effort addressed the nature of risk assessment as an analytic-deliberative process — that is, it involves both analysis of the problem and discussion to reach agreement among people about interpreting the analysis. The decision-making process needs to focus both on the technical issues and on improving understanding and participation. According to the NRC panel, "Appropriately structured deliberation contributes to sound analysis by adding knowledge and perspectives that improve understanding and contributes to the exact ability of risk characterization by addressing potentially sensitive procedural concerns." In *Understanding Risk,* NRC lays out elements of an analytic-deliberative process: getting the science right; getting the right science; getting the right participation; getting the participation right; and developing an accurate, balanced, and informative synthesis. All of this is to say, be clear what problem you are solving, and ensure it is the one that people care about, and that people agree with how you are doing the assessment, what data are used, and how they are interpreted.

The societal dimensions of risk were addressed by the 1997 U.S. Presidential Commission on Risk Assessment and Risk Management report, *Framework for Environmental Health Risk Management.* Figure 2.3 shows a schematic of the proposed framework for risk management that puts stakeholders in the middle of the decision process, engaging their participation at each step of the process. This risk management framework is intended to be broad, to address a range of types of hazards, and to implement an iterative process that revisits the problem and the risk management options.

The Presidential Commission framework recognized the role of uncertainty in risk assessment. "Risk assessors have to use a combination of scientific information and best judgment" (1997). Uncertainty is a key attribute of risk. If there

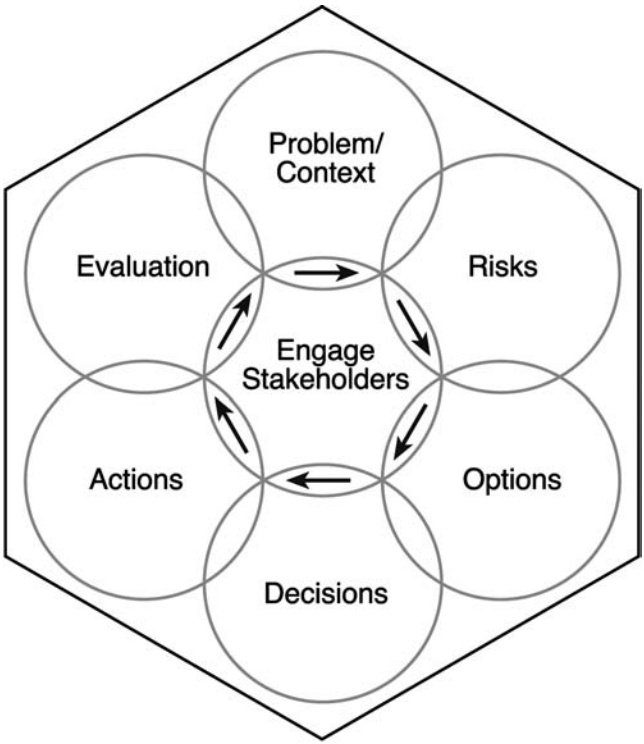

FIGURE 2.3
President's commission framework for environmental helath risk management. (See color insert following page 76.)

were certainty about the impacts of a particular substance, or technology, one would conduct a safety assessment level of and establish a definitive safe level. But with new materials, there is rarely that level of certainty that all of the relationships between exposure and effect are understood, and assumptions are made to address the inherent uncertainty. That is a main reason to involve stakeholders in decisions about managing risks. Stakeholder values and preferences must be considered in deciding how to manage risks under uncertainty.

The EPA acknowledges that environmental decision making can be controversial, involving not only science, but also social and economic factors, political considerations, technological feasibility, and statutory requirements that may often be conflicting. The EPA "conducts risk assessments to provide the best possible scientific characterization of risks based on a rigorous analysis of available information and knowledge (USEPA 2004)."

The International Risk Governance Council (IRGC 2005) considered these and many other models in the development of their framework. The main contribution of the IRGC framework is the inclusion of the societal context in risk assessment and risk management. In their governance framework, IRGC gives equal weight to the societal dimension of risk management,

recognizing that some societal risks are more complex, and of greater concern, than others in a governance model. A major innovation of the IRGC framework is categorizing risk-related knowledge. Categorization addresses complexity, uncertainty, and ambiguity of risks. The IRGC framework also considers risk/risk and risk/benefit tradeoffs. An example of a risk/risk tradeoff is the risk of complications from surgery (the risks of complications may or may not outweigh the benefits of the surgery).

The IRGC has applied this framework to nanotechnology. In *Nanotechnology and Risk Governance*, Mikhail Roco and Ortwin Renn, pioneers in nanotechnology and societal dimensions of risk analysis, respectively, describe four generations of nanotechnology and their differences in terms of complexity, uncertainty and ambiguity (IRGC 2006). The first generation, passive nanostructures, represents those materials that exist or are in development today. The second generation involves active nanostructures, such as smart packaging or targeted drug delivery. Third generation (self assembling structures) and fourth generation (molecular manufacturing) are viewed as forthcoming. Moving beyond the first generation of types of materials currently applied in nanotechnology (generally passive nanoscale particles, or substances and structures created at the nanoscale such as silver or gold that are smaller than larger particles, but pretty much remain as they were manufactured), complexity, uncertainty, and ambiguity increase and risk governance models must adapt (IRGC 2006).

The common themes in these various frameworks and approaches to risk assessment are (1) the delineation of an analysis, generally the stepwise process relating hazards to exposure to assess risk; and (2) transparency in the process for making decisions about how to manage risks — including acknowledging the societal dimensions of risk — through a process that includes some level of participation by stakeholders.

2.5 How Risk Assessment Is Used in Environmental Decision Making

With some grounding in the broader societal dimensions, now the discussion hones in on how environmental risk assessment becomes a decision making tool used to analyze and help make decisions about substances and technologies. Simply stated, risk assessment allows the estimation of health and environmental impacts from exposure to a substance.

Governmental and private organizations all over the world use risk assessment in environmental and public health decision making for risk management. In the U.S., the EPA uses risk assessment to understand risks and make management decisions regarding cleaning up hazardous waste sites, closing municipal solid waste landfills, setting standards and managing substances

in drinking water, evaluating air quality, establishing tolerances for pesticides and other chemicals, and for setting policy on specific substances. Risk assessment is also used in the U.S. for regulating food safety and allowing additives in food and food packaging.

The European Commission passed chemicals legislation in December 2006 that requires registration of, and risk assessments for, all chemicals used in commerce in the European Union. The program, called REACH (Registration, Evaluation and Authorization of Chemicals), is viewed as a precautionary approach to chemical management, and envisioned as a way to identify, prioritize, and manage chemical hazards. Depending on how much of the chemical is produced, different levels of testing and reporting are required. The assessments also depend on specific properties of chemicals, known either from testing or predicted by models (European Commission 2006). REACH is also an integrated framework that considers occupational exposure, consumer exposure, and environmental exposure. One key feature of REACH is that it includes a screening framework. Based on the results of the screening determination for a substance, a more detailed assessment is made (screening aspects of risk assessments are described later in Chapter 6) (European Commission 2006).

Risk assessments are also increasingly the basis for occupational exposure standards. In the U.S., OSHA conducts risk assessments for substances to establish a standard for U.S. workplace environments. Occupational risk assessments typically involve studies of large groups of workers in specific industries, using epidemiology studies to relate workplace exposure to effects, as was done recently for hexavalent chromium. The U.S. National Institute for Occupational Safety and Health (NIOSH), a non-regulatory governmental organization, recently conducted a risk assessment for titanium dioxide in the workplace, specifically considering the evidence for nanoscale titanium dioxide and establishing a workplace exposure limit (NIOSH 2005), discussed further in Chapter 5.

Risk analysis is also used for food safety. Decision making governmental organizations deal with safety by conducting risk analyses of food ingredients and products. CODEX Alimentarius develops international standards under FAO and WHO, which are internationally adopted and generally focused on biological safety of food (FAO 2005). The Organization for Economic Cooperation and Development (OECD) is an international organization that conducts many activities in its member countries to assess and evaluate chemicals, biocides, and other materials. OECD develops databases and tools, and also harmonizes approaches to risk analysis (OECD 2007).

The American Society for Testing and Materials, ASTM International, has several committees that develop voluntary standards. One standard developed by committee E50 applies a tiered approach to risk analysis, called Risk-Based Corrective Action, for oil-impacted or hazardous waste sites. This approach applies a screening-level risk assessment first, which then leads to decision making and more detailed analysis where warranted (ASTM 2004). The U.S. FDA uses an approach called HACCP for food safety

hazard analysis, combining assessment and management processes to determine the most effective way to manage risks in food safety (FDA 2001). Risk-based approaches are also used for managing medical devices and pharmaceuticals.

The U.S. EPA has published a process on how to conduct ecological risk assessments that has a somewhat different focus, because the assessments may evaluate risks to a population (e.g., a species of fish in a particular location) or an entire ecosystem made-up of several levels of organisms within a food web. Ecological risk assessment has an additional layer of complexity over the assessment of risks to human health. It follows the same general process, but instead of defining a particular hazard, it begins by formulating a problem. The next step is to identify the assessment endpoints — in other words, what measures will be evaluated in the assessment? The measurement endpoints are the actual tests conducted to evaluate the endpoints that might include models, and also field evaluations (EPA 1998).

2.6 The Four Steps of Risk Assessment

As we've discussed, if there were an absolute answer to what is safe and what is not, there would be no need to conduct an assessment of risk. However, where there is uncertainty in the information needed for making decisions, the information is interpreted, using judgments from prior experience. This uncertainty and individual attitudes toward risk affect how the data are judged and the conclusions reached about the significance of risk. It is the combination of scientific data and judgment about the data that constitutes the assessment of risk. Conducting formal risk assessments allows us to apply a process to determine the relative level of risk, and on that basis judge whether the risk is acceptable or not.

As shown in Figure 2.1, there are four basic steps in a risk assessment:

- Hazard Identification
- Exposure Assessment
- Dose-Response Assessment
- Risk Characterization

First, the problem or the hazard is defined. The various international frameworks use different terminology for this step, referring to it as problem formulation, hazard characterization, or **hazard identification**. The step of hazard identification defines how to conduct the remainder of the assessment. It defines which questions the risk assessment will ask and answer. It provides a characterization of the hazard that describes its key attributes. First, define the nature of the hazard: Where is the contaminant? Is it in the

air, in a product, or in the water? How much is present? Where is the contamination likely to go? What is the nature of the source material?

The second step is to develop an **exposure assessment**. Exposure assessment involves identifying the potential for an exposure to a hazard—a substance, a pathogen, or a technology—by considering all of the potential circumstances of exposure. Key steps include identifying receptors who may be impacted, pathways of exposure (where is the material released and how could one come in contact with it?), media of concern (soil, air, water, food, or injection), and routes of exposure (can the hazard be inhaled, ingested, or absorbed through the skin?). Exposure assessment also considers the magnitude of potential exposure (how much exposure occurs), its likelihood of occurring, how frequently, and for what length of time. Exposure assessment can be very complex, and often involves models and other estimation methods and assumptions.

In human health risk assessment, *receptors* are those who may be exposed to an agent under different scenarios, such as workers in an occupational environment who manufacture a chemical, users of a product, and others who may have incidental exposure occurring as a result of manufacturing, use, or disposal of a product. If a substance is in drinking water, the person who drinks the water is the receptor. In ecological risk assessment, the receptors may be specific species, populations, or entire ecosystems.

Substances have physical and chemical characteristics that govern behavior in the environment, and will impact their behavior in the environment, so it is important to understand whether exposure is likely to occur by a particular pathway (e.g., inhaled, ingested, or absorbed through the skin). For example, a solid substance would have to somehow be released in the air that is breathed; otherwise, one would not evaluate an inhalation pathway for that substance. Generally, one of the key contributions to risk is the extent of exposure, or potential exposure, so defining the magnitude of exposure and how likely it is to occur is another very important step in characterizing risk. Even substances required in the diet, such as Vitamin A, can be toxic if over-consumed (this would amount to over-exposure).

It is important to determine whether any exposure occurs at all. For example, if your neighbor uses an MP3 player with nanotechnology-enabled components inside his home, does this create an exposure for you? You would have to somehow come in contact with the nanotechnology parts in the MP3 electronic components, say by visiting your neighbor and destroying the MP3 player, to have an exposure. Again, without exposure, there is no risk. If, for example, your neighbor burns the MP3 player, then it might be possible to have exposure to a very small dose; otherwise, there would not be an exposure.

The next step in a risk assessment is to evaluate how or whether a substance may cause harm. The toxicity or **dose-response assessment** asks how effects might occur following exposure. It identifies the nature of a substance's toxicity via different exposure routes. These may vary depending on whether the exposure occurs because of inhalation, or by ingestion, and also by how

much of a substance is absorbed in the body, as well as the effects on cells and on whole organisms from these doses. The dose-response assessment asks what is known about the mechanisms of action of substances; how they behave when absorbed — are they metabolized or excreted; and what are the kinetics, or time-associated parameters, of those reactions in the body. Sometimes substances themselves are not toxic, but they are metabolized to toxic compounds in specific organs in the body. Thus, a detailed understanding of those behaviors is required for dose-response assessments.

The dose-response assessment relies on data from toxicology studies in laboratory animals and studies in test tubes, or from in exposed populations. The dose-response assessment identifies the health effects observed at different doses of substances, and determines the lowest levels where effects, or no effects, have been observed. These effect levels become the basis for comparing the exposure levels to effects levels.

Things work differently for substances that are shown to cause cancer in studies, or are toxic to DNA (genotoxic), the basic building block of life. The cancer model currently used assumes that if tumors are observed in test animals at high doses, that the risk to people from low doses in the environment can be extrapolated by drawing a straight line from the high dose to the low dose, adjusting for differences in physiology between laboratory animals and humans. As knowledge of cancer mechanisms improves, other approaches to dose-response assessments are identified, but for most genotoxic substances, this linear low dose extrapolation method is currently used. The U.S. EPA and others recognize that some substances have different mechanisms of toxicity that may result in different dose-response relationships, but few of these assessments have been carried out to date.

Linear low dose extrapolation assumes there is always a probability that cancer might occur, the risk is never zero, it just gets smaller and smaller as exposure levels decrease. For example, a toxicology study might identify the percentage of tumors observed in 20 out of 50 animals (40%) at a high dose, which when extrapolated to environmental levels people could be exposed to might correspond to a cancer risk of 0.00001% for the people exposed! With this methodology, the assumption is that the probability that cancer can occur from exposure is never zero, it continues to lower levels of risk, so low that people generally agree they are acceptable, or *de minimus*.

The fourth step of risk assessment is **risk characterization**. This step brings together the exposure and dose-response assessments, comparing the exposure levels to the levels associated with health effects, to evaluate whether there is potential for significant risk. Different models and frameworks use different approaches for this step, but generally one can consider the ratio of exposure levels to effects levels. There is often a lot of uncertainty associated with this comparison; the risk characterization step identifies and evaluates these uncertainties.

In the absence of adequate data for comparing exposure levels to toxicity levels, the risk characterization may be qualitative — that is, no numbers are assigned, and the risk level is descriptive rather than quantitative. Also, most

of the time, studies are not directly applicable; for example, a dose-response assessment may be based on animal toxicology and this must be related to human exposure. And, people differ in their susceptibility to certain substances, by age, genetic variation, or because of other factors such as immune status, and these are accounted for when characterizing risk.

Another example of uncertainty is that often exposure cannot be measured exactly, so estimates are made that rely on assumptions and extrapolation, i.e., assuming a person drinks two liters (about half a gallon) of water every day. Not everyone drinks exactly two liters of water per day: some drink one liter, some three liters, and others drink little, if any, water. Children may drink a lot more. This and other sources of population variability add uncertainty to risk estimates because assuming some exposure occurs when a person ingests two liters of water per day simplifies reality. There is a distribution of risk levels that gets simplified to a "most likely" number.

Risk characterization also evaluates the risks in context of regulations that define how much exposure is allowed under different circumstances, and makes comparisons with other types of risks that help to inform how the risks are managed. Despite these and other sources of uncertainty, risk assessment is a valuable technique for estimating the potential health and environmental impacts of nanoscale materials used in nanoscience and technology. Even when all of the necessary information is not available, risk assessment can still be helpful to make estimates of potential risk to set research agendas, or make safety decisions about working with or using specific materials.

2.7 Issues in Applying the Four Steps of Risk Assessment to Nanotechnology

Because of the unique properties of nanomaterials, particular issues arise in applying the steps of risk assessment specifically to them.

2.7.1 Hazard Assessment

Hazard identification questions for nanomaterials may not differ from other substances; however, the measurements are not necessarily widely available. When considering the novel properties of nanomaterials and nanotechnology, significant issues arise in terms of defining them: for example, if nanoscale particles are aggregated to micron size, are they nanoparticles? Typically, substances are reported in terms of their concentration (mass of a substance per unit of volume in air, food, water, or blood, for example). But for nanomaterials, the surface characteristics are also important, and at the moment, the key parameters are poorly understood. The mass may not

be the best measure for characterizing risk. Other properties that have not traditionally been measured, such as the number and type of particles or surface properties (surface area, charge, and level of contamination) may be key parameters, but these are not definitively known. In fact, a risk screening strategy proposed by the International Life Sciences Institute (ILSI) described in Chapter 5 has defined over a dozen potential measures to characterize nanoscale materials (Oberdörster et al. 2005). As Powers et al. (2006) pointed out, even these measures may oversimplify reality.

2.7.2 Exposure Assessment

For nanotechnology, some additional issues are raised for characterizing exposure. New metrics must be developed for characterizing how people are exposed to nanoscale materials. The current techniques available for analysis may not be sensitive or specific enough to understand exposure. Historically, risk assessment has considered the mass or a concentration of a substance. However, with nanoparticles, far more salient features may be the number of particles, the total surface area, and the reactivity of the surface area. New analytical techniques with low detection limits are required; because exposures may be very low, background exposures to nanoparticles may become a major interference. For nanoparticles, there is a need to develop measures to assess and characterize background exposure to nanoscale materials and particles.

With nanoscale materials, it is also not clear how to measure exposure as it relates to toxicity (as a concentration, by surface area, or reactive surface area), and there are few analytical techniques currently available that quantitatively measure substances at the nanoscale. Information is lacking about the transport, fate, and transformation of nanoscale materials in the environment. There is limited understanding of what happens when these particles are released to the environment or even if they are. For example, when water used for processing nanomaterials is sent out from a factory to a waste treatment facility, does the current waste treatment capture the nanoparticles, or are they released to the environment? When in the environment, are nanoparticles still at the nanoscale? This is an issue in exposure assessment for which there is a need to develop and test models to improve the current understanding.

There is also a need to understand nanoparticle exposure in the body. If you touch them, can nanoparticles penetrate the skin? There is some evidence that because they are so small, some particles can enter the skin. But, can they get across the outer barrier layer, the stratum corneum, and enter the body? Similarly, if particles are inhaled, can they cross from the lungs into the blood? If they enter the nasal cavity by nose breathing, can they travel into the nervous system? These issues are explored in greater depth in Chapter 4, but are important areas of exposure assessment that need to be addressed for evaluating exposure to nanoschele materials.

Today, it is likely that any exposures to engineered nanoparticles are very low. For most, production levels are below reporting thresholds, indicating

a low potential for widespread consumer and environmental exposure. It is timely to develop exposure characterization methods now, before large scale production occurs.

2.7.3 Dose-Response Evaluation

As discussed in Chapter 4, one widely observed effect from exposure to nanoparticles is inflammation, an immune system response. Inflammation is associated with the development of many diseases such as asthma, heart disease, cancer, and autoimmune diseases. Inflammation has been observed following exposure to nanomaterials in whole animal studies (*in vivo*) and in cellular assays (*in vitro*). It is presently unclear whether or in what ways the chemical composition, size, shape, or surface characteristics affect the toxicity of nanoscale materials.

Classical models of toxicity look at a range of non-cancer endpoints including whole system toxicity, reproductive endpoints, neurological effects, and effects on the immune system. Carcinogenic effects (the ability of the substance to cause cancer) are also commonly evaluated for substances. Again, there is uncertainty in defining the dose. Dose-response studies have demonstrated that nanoparticles behave differently than larger particles, and this may create difficulties in measuring responses. Also, studies have demonstrated that small changes such as the crystalline structure and the surface charge of a nanoparticle can greatly affect its behavior in the body. The outcome of the dose-response assessment is to identify the lowest levels at which an effect occurs (the lowest observed adverse effects level, LOAEL) or the level at which no effects occur (no observed adverse effects level, NOAEL).

A number of researchers are trying to develop predictive approaches to toxicity studies that do not involve testing in whole animals. These test tube or *in vitro* (literally, in glass) assays to date have not been shown to be relatable to *in vivo* studies for nanoparticles. This may be due to the difficulties of getting nanoparticles to separate from one another. Most nanoparticles are very sticky, and tend to agglomerate, or aggregate. When they do, it is difficult to measure the toxic effects, or to be certain about the exposures that have occurred. Some researchers have addressed this by using techniques to separate the particles, so it then becomes a question of whether the findings can be related to real world exposures. One recent study showed that some nanoparticles interfere with the reactive agents in the *in vitro* assay, producing a false positive (the assay would say there was an effect when there was not). Many hurdles remain for assessing the toxicity of nanomaterials. These are explored in more depth in Chapter 4.

2.7.4 Risk Characterization

What does the assessment infer about health, safety, and the environment? Considering risks from nanomaterials and nanotechnology in context may mean comparison to existing standards for risks posed by other substances

for which there has been greater investigation. There are few available risk assessments for nanomaterials. Those currently available are comparative — that is, compare risks for nanotechnology to risks from other things. For example, Robichaud and colleagues used an insurance risk model to compare the risks of production of carbon nanotubes to the production of wine, petroleum, silicon wafers, and aspirin (Robichaud et al. 2005). While this assessment was limited because of the lack of information on nanomaterials, it is instructive to characterize risk in a particular context. Although the assessment did not consider nanoparticle risks, it did demonstrate that otherwise, production of some nanomaterials is not all that different from other types of manufacturing.

An additional challenge is that most people will come closest to exposure with nanomaterials from using them in products, as opposed to those who generate the raw materials and may be exposed to nanoparticles themselves. In the workplace, exposure to substances can be managed if there is determination to do so — it is a fairly controlled environment. But in the broader environment, it may be the products that need to be managed, not the substances, because their uses will vary greatly. This is an added challenge for risk management and risk assessment, to determine the potential risks associated with the use of nanomaterials in products. In Chapter 3 and beyond, we consider how risk assessment can help accomplish this task, and help to achieve the many benefits of nanotechnology without incurring so many of the risks.

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3

Sustainable Nanotechnology Development Using Risk Assessment and Applying Life Cycle Thinking

Jo Anne Shatkin

CONTENTS

> "For a successful technology, reality must take precedence over public relations, for nature cannot be fooled."
>
> **Richard P. Feynman**

We do not need to look far to find examples of how past approaches to substance management were inadequate. Perfluorinated organic compounds, lead, PCBs, and asbestos are examples of substances that have an environmental legacy that proved costly. Engineers and materials scientists found they possessed unique and brilliant properties, and identified more and

more applications for them. These materials were developed or used widely, while their toxic properties were not identified until later, in part because they offered benefits as well.

Non-stick polymer coatings are frequently used to coat cookware, packaging materials, fabrics, and medical equipment; they reduce friction, increase water resistance, retard flammability, and limit staining potential. As a polymer, these coatings have little to no toxicity when the compounds used to make them are tightly bound in the matrix. But when heated to high temperature, the building blocks of the polymer can release into the air. Some of these building blocks, perfluorinated organic compounds, have been found to be very persistent in the environment. Persistent compounds are of environmental concern because they bioaccumulate; that is, low levels in the environment tend to increase in concentration as they move up the food chain, for example from water to small fish to bigger fish to fish-eating birds and wildlife. Perfluorinated compounds have been measured in people's blood in countries all over the globe, and in drinking water, fish, birds, and marine mammals, including polar bears off the coast of Greenland (Bossi et al. 2005; WWF 2004). Some of these compounds (e.g., PFOS) are no longer manufactured, and U.S. EPA is conducting a risk assessment of several of the perfluorinated compounds.

Lead was used in antiquity in glazes, paints, beads, currency, and cosmetics, and is mentioned in the Bible. Lead poisoning occurred in Roman times, including the effects from lead in pipes. Lead poisoning was widespread during the Industrial Revolution. In 1925, lead was the first chemical contaminant to be regulated in drinking water in the U.S., long before the establishment of the EPA. Yet lead possesses unique properties that found wide application in fuel stabilizers, pesticides, pigments, soldering pipes, automotive batteries, bullets, insulation, and glass (Winder 2004; ATSDR 2005).

The U.S. EPA still spends millions of dollars of its shrinking annual budget on lead abatement. Lead is a metal; it cannot be broken down. Putting lead into gasoline, paints, and plumbing means that, even though it is now banned from these uses, people are still exposed to lead, directly or indirectly as a result of its prior use. Children still suffer from lead poisoning. From years of exhaust emissions from automobiles that spread lead, first into the air, then to soils mean that those now living near major roadways may have lead in the food they grow. When the wind blows, lead in the soil can be entrained in the air, and enter people's nearby homes or workplaces. The lead and other pollutants become part of the dust, which people inhale, and young children can ingest while playing on the floor.

There is an *opportunity cost* associated with lead abatement, the missed opportunity of investing in something else, such as research to prevent the next legacy of pollutants. But the existing environmental and health burdens from past activities require at least the current level of effort to reduce lead levels in the environment, and to find ways to prevent children and others from exposure to lead in their homes, drinking water, toys, and play areas.

With the numerous lead abatement measures in the U.S. that have been enacted since the 1970s, lead levels have decreased significantly. Lead levels in air have decreased to 5% of 1980 levels, following the banning of lead from gasoline. The number of children in the U.S. with elevated blood lead levels is 97% fewer than in 1978. But because lead is an element and does not break down, regulatory action is required to prevent exposure to painted building materials, plumbing, and soils that contain it (U.S. EPA 2007).

When lead was banned from fuels, its main replacement was an additive called MTBE or methyl *tert* butyl ether, another relevant and interesting example of the unsuspected environmental impacts created by our lack of foresight. MTBE is an oxygenate, a fuel additive that promotes cleaner burning of gasoline, increases octane, and reduces automobile emissions; it was developed to reduce air pollution from carbon monoxide and ozone (Davis and Farland 2001; CalEPA 1999; U.S. EPA 2006b). The 1990 Clean Air Act amendments mandated oxygenates (not MTBE specifically) be added to gasoline, to improve air quality in areas of high air pollution in the United States. MTBE was not considered very toxic when its use was approved for reformulated gasoline. Problems soon arose, however. The first reports of adverse health effects were complaints of headaches and nausea following exposures at filling stations.

At least 25 states have now banned MTBE. The main reason was its widespread release to the environment. While intended to improve air quality, MTBE emerged as highly mobile and very soluble in water, often at the leading edge of other petroleum constituents that leak into ground water (water that flows underground). When gasoline leaks — from an underground storage tank or from an accidental spill during fuel transfer — it runs underground until it reaches ground water; and once in this medium, MTBE can move very quickly and contaminate drinking water supplies.

When MTBE was banned in California in 1998, the state had already set a public health goal for drinking water based on its cancer-causing potential, although it remains controversial whether MTBE is a human carcinogen (cancer-causing substance) (NRC 1996; Stern and Tardiff 1997; Mennear and McConnell 1997; Mehlmann 2002). Some researchers claim that studies of carcinogenicity in rats and mice are not relevant to humans because of (1) differences in biology, and (2) the very high dose levels associated with the effects in the studies, which humans would never tolerate because of taste and odor issues. Others claim rodent carcinogenicity models are inadequate predictors for low-dose human exposure (Ames and Gold 2000). As of 2007, the U.S. EPA has not completed a determination of the carcinogenic potential of MTBE, and has not regulated MTBE in drinking water, although the EPA has prioritized MTBE for consideration, listing it on the contaminant candidate list, the EPA's list of priorities for regulatory determination for drinking water standards.

As discussed in more detail by J. Michael Davis of the U.S. EPA in Chapter 7, in their alternative fuel strategy over a decade ago, EPA called for "research to assess the impact of reformulated gasoline on the potential for

groundwater contamination and result in pollutant exposure" and to "characterize the impacts of oxygenates on the fate and transport of fuel components" (U.S. EPA 1992). However, the early warning signs of toxicity and environmental mobility were not heeded soon enough and now MTBE has a legacy that many property owners, oil companies, and drinking water suppliers must address. MTBE, the safer alternative to lead, has arguably become a significant environmental issue.

Davis and Farland (2001) point out that the MTBE experience should teach us to look comprehensively at the behavior of any additives that we might introduce into fuels or broadly into the environment. There were early signs that MTBE was not a good candidate for widespread introduction in the environment. The chronology of MTBE's rise and fall is also instructive: Oxygenates were mandated for use in gasoline in 1990, and in reformulated gasoline in 1995. In 1997, MTBE was the second most produced chemical in the U.S., but was banned first in California in 1998. Half of all U.S. states have now banned it, and its use may be phased out by 2008. Among other things, the MTBE example demonstrates that collectively society is learning to act and react relatively more quickly to substances that pose risks. However, this experience teaches that there are benefits to being more proactive in managing and more broadly considering the risks as materials are developed and before they are commercialized.

3.1 Opportunity Costs

These examples demonstrate that there is a cost to introducing materials into the environment without considering their long-term impacts. These *opportunity costs* are also "risk-risk tradeoffs," and it makes sense to consider them early in technology development. Research for lower impact materials could be funded if less were spent on managing legacy pollutants. There is a nano connection here: a British company is pilot testing a chemical called cerium oxide as a fuel additive. Adding cerium oxide nanoparticles to diesel fuel has been demonstrated to improve fuel efficiency, and reduce soot formation (lowering air pollution) and volatile emissions (Oxonica 2007). The Health Effects Institute (HEI) has conducted a risk assessment of cerium oxide in fuels, concluding that:

> Based on the limited data available, toxicity of cerium oxide appears to be small, and cerium oxide might not be of concern when inhaled or ingested at the low levels that would be encountered in the environment... The absence of more complete information precludes fully assessing the possible health effects of using cerium as a fuel additive...considerations are the additive's ability to reduce harmful emissions, its persistence in the environment, and the feasibility and cost effectiveness of

this technology in comparison with other technologies that can achieve these reductions (HEI 2001).

There are clear health and environmental benefits from adding cerium oxide to diesel fuel, and the risks appear to be low, based on the available information. However, the release of cerium oxide in vehicle exhaust will result in an increase in environmental concentrations, and the pathways to other types of environmental exposure require consideration. The broader issues raised by HEI about cerium oxide can be addressed in a broader, risk-informed framework.

3.2 Risk Assessment for Nanotechnology Is Urgently Needed

We noted in Chapter 1 several factors that make it imperative to begin the assessment of risk for nanotechnology now even without available data — including its rapidly accelerating pace of development, lack of adequate information about nanomaterials, their potential for wide dispersion in the environment, and the lack of standards or guidelines regulating them. These are explored in more depth in the following.

3.2.1 The Pace of Nanotechnology Development and the Paucity of Information

The accelerating pace of development described in Chapter 1 poses a challenge for health and safety research and the characterization of risks. With thousands of patents in nanotechnology, over 500 specifically for nanomaterials, more research on health risks is needed. Each formulation and manufacturing process creates slight differences in size, surface area, aggregation state, and contamination level. Understanding the impacts of these differences is an important factor in understanding risks.

At first glance, a lot of information seems to be available: hundreds of studies evaluating toxicology, behavior in cell systems, and behavior in the environment for select nanomaterials. It is clear from examining these papers, however, that there is a lot of uncertainty about the key parameters affecting toxicity. Generally, the key parameters seem to relate to surface characteristics. As discussed in Chapter 5, some studies suggest particle surface area is a key factor in toxicity (Bermudez et al. 2004; Warheit et al. 2007; Oberdörster et al. 1994). Others point to the electrical charge of the particles as a determinant of toxicity. Most studies investigate a relatively small set of materials, and some suggest that the test system may also affect the findings, particularly for *in vitro* studies. For example, recent studies at Rice University, birthplace of the buckyball, have demonstrated that the behavior of fullerenes in the environment is variable. C60 is neither toxic nor soluble under one set of

conditions, but with different test conditions forms a nano-aggregate that is soluble and toxic to small aquatic organisms (Lyon et al. 2006).

In other words, there are no standardized tests for nanoscale materials, and the same materials can produce different results in different tests. While there are many reports, they do not point to a clear understanding about the toxicity of nanomaterials, such that as of this writing, it is not possible to conclude that nanomaterials are safe or toxic. There are many studies underway that may provide some answers soon. Answers, however, are needed now to guide decision making about occupational and environmental protection.

3.2.2 Potential for Wide Dispersion in the Environment Amid Uncertainty

Products that consumers use are, by definition, widely dispersed. They go wherever people that use them go. If a product is sold in Wal-Mart, for example, it will travel to the 14 countries in which Wal-Mart operates (walmart.com). With nanotechnology applications in lotions, creams, cosmetics, sporting goods, food packaging, paints, fabrics, electronics, and automobiles, nanomaterials are and will be widely dispersed geographically. Some applications have greater potential than others for actual release into the environment (as we have seen, this is a factor of exposure), but all have the potential for global distribution, even with variances in local markets.

3.2.3 Few Standards or Guidelines

Perhaps by the time this book is published, there will be more than the one existing regulation specifically for nanotechnology in Berkeley, California. The regulation requires reporting the known toxicology of any manufactured nanomaterial that a company manufactures or uses within the city, and their plans to manage the materials safely. It does not set thresholds for reporting, say, to distinguish research level uses from manufacturers. It also does not specify the level of reporting. Although now required in Europe, companies generally do not conduct toxicity tests on the materials they make or use, unless the application has a regulatory requirement to do so; for example, pharmaceuticals, food additives, or pesticides. Some companies do, voluntarily, test their products but it is not clear from the language of Berkeley's law whether companies must conduct their own tests, or simply report from the available literature (Monica et al., 2007).

Another aspect of the Berkeley nanotechnology law is that essentially it is a "right-to-know" regulation, so that officials and citizens of Berkeley know what materials are being used in their community. If no information on toxicology is available, then under the law, the materials are assumed to be toxic. This clause has some people worried — if nanomaterials are labeled toxic, what process is needed to label them non-toxic? What level of proof will be

required to demonstrate the materials are safe? It comes back to Starr and the question of "how safe is safe enough?"

The city of Cambridge, Massachusetts, first in the nation to regulate biotechnology, is planning to regulate organizations working in nanotechnology. Like Berkeley, Cambridge is home to many nanotechnology companies and is seeking to build on the existing biotech regulation so that it can be applied to companies working in nanotechnology. The city is organizing an advisory panel to participate in developing the regulation. One reason these cities are developing nanotechnology regulations is that there are none at the federal level. The U.S. federal regulatory process is slow. Even if efforts began today to regulate nanotechnology, it could be decades before they were enacted (Brown et al. 1997).

Some existing regulations at the federal level do apply to nanotechnology. For example, the General Duty Clause under OSHA requires that, "Each employer shall furnish to each of his employees employment and a place of employment which are free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employees" (OSH Act 1970).

The U.S. EPA has determined that a product claiming to be antibacterial must provide data on its health and environmental effects. Let us imagine the product is a washing machine that reportedly releases nanoscale silver ions into the laundry to kill odors and bacteria. While the determination relates to a device using nanotechnology, it is not viewed as specific to nanotechnology; the focus is more on the claim that the product is an antibacterial. The decision (EPA 2006a) is interpreted by some as being about EPA regulating *devices* under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) versus *substances,* rather than as a nanotechnology regulation.

Some non-regulatory organizations in the U.S. are proposing guidelines for occupational handling of nanomaterials. As described in Chapter 8 the National Institute for Occupational Safety and Health (NIOSH) *Approaches to Safe Nanotechnology* (NIOSH 2006) describes "what is known about nanomaterial hazard and measures that can be taken to minimize workplace exposures." A group started by researchers at Rice University, the International Council on Nanotechnology (ICON), commissioned a best practices survey (ICON 2006). There are efforts to develop voluntary standards for occupational environments, such as at ASTM International and ISO. These are discussed in more detail in Chapter 9.

3.3 Environmental Risk Issues

In the examples above, problems arose when materials that posed risks were released into the environment and caused exposures to people that resulted in toxicity, eventually resulting in action to mitigate those concerns. Perfluorinated compounds, lead, and MTBE will be in the environment for

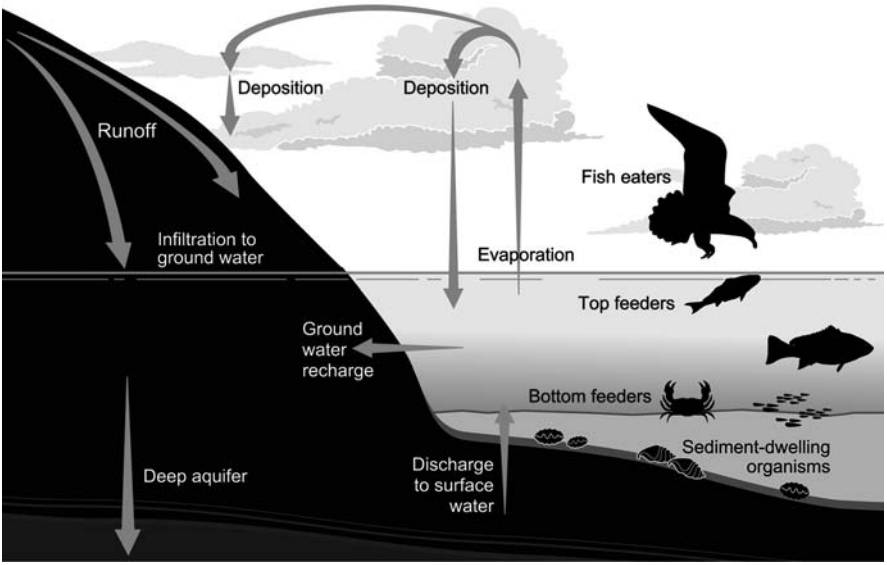

FIGURE 3.1
Environmental pathways affecting water resources. (See color insert following page 76.)

some time to come, and will require continued attention. As discussed, the opportunity costs associated with managing and removing lead from the environment consume resources that could be used elsewhere. The costs of environmental remediation also do not create future economic opportunities. These contaminants are mostly of concern because they affect people. What about effects on the rest of the ecosystem?

Figure 3.1 shows how contaminants can move into a water body. Ecosystems are usually very complex, and the dynamics are generally poorly understood. Risk models generally assume that each environmental contaminant behaves individually, regardless of what else is present. There are so many combinations, it could consume all of the public health resources of the world to understand the complex inter-relationships, so assessments generally assume there is no relationship. The risk from one exposure is simply added to the next in terms of impact. But in reality, exposures are to a multitude of combinations of substances in the environment.

Presumably, the behavior of nanomaterials is going to vary depending on the material and the type of ecosystem. Is there a need to worry about affecting the ecosystem by releasing poorly characterized materials into it? Some newly emerging concerns include the release of hormones into the environment. Every time a toilet is flushed, hormones, whether naturally occurring or synthetic, are sent out into the environment. Many people now take prescription drugs, including female and male hormones, such as steroids, estrogen, and progesterone. The U.S. Geologic Survey conducted a national study of the occurrence of hormones and other waste water contaminants and

measured low levels downstream of waste water treatment plant effluents (Kolpin et al. 2002). In urban rivers and streams, fish and other organisms are experiencing the effects of these hormone exposures, with a shocking prevalence of hermaphroditic fish containing both male and female characteristics (Jobling et al. 2006). Because the levels are low (water dilutes the concentration), many people do not feel it is important to address this concern. This cycle of life returns to humans, as people consume plants, animals, and fish. Humans are a part of the ecosystem, so even from a resource perspective it is critical to protect the environment. It is important to human survival that we do not pollute our own backyard.

3.3.1 Carbon Nanotubes — the Next Asbestos?

Carbon nanotubes (CNTs) are the next big thing! They are stronger than steel, lighter than a feather, conducting or insulating, catalytic (depending on surface charge), and easy to generate. The cost of manufacturing CNTs is coming down, as more and more applications drive manufacturing. There are dozens of potential applications — in fabrics, as drug carriers, to strengthen polymers in plastics, conduct energy, for building materials, sporting goods, water treatment, and in aerospace. CNTs are already used in automobile bodies. Thus, CNTs could be on a path to widespread use in a variety of products and economic sectors, in the same way that asbestos was used for insulation of pipes, in brake linings, and in dozens of applications.

People who have studied health effects from asbestos want to compare nanotubes to asbestos. Why? Some nanotubes are shaped like asbestos fibers, they are long and narrow. In the wrong dimensions, fibers can get stuck in lung tissue when inhaled, instead of being cleared as other particles might. Also, they are not soluble in water, are persistent, and they do not break down in the environment. These are traits of materials that can create an environmental legacy. This comparison can be made based on their other properties as well.

Because there are so many varieties of CNTs it is hard to say much definitively about their toxicity. Some studies, described in the following and in Chapter 4 demonstrate toxicity, but the mechanisms and doses are poorly understood. The surface properties appear to be very important. If the surface area is a key determinant of toxicity, then the doses of current studies may have been too high to reliably interpret the results from animal studies.

3.3.3.1 How to Define the Toxic Dose

A study by the NIOSH found the lungs of mice exposed to single walled carbon nanotubes (SWNT) formed "unusual fibrotic responses" compared to mice exposed to other types of carbon particles, specifically, an amorphous particle called carbon black. This response was seen in mice exposed to a dose of 10 to 40 μg SWNT/mouse aspirated into the lungs. The authors conclude that SWNT are more toxic than carbon black. However, if compared on

the basis of surface area instead of mass, 40 μg/mouse of SWNT is estimated to have a surface area of 1040 m^2/g while the surface area of the equivalent dose of carbon black is 254 m^2/g (Shvedova et al. 2005). In the study, the surface area was determined by Brunauer, Emmett, and Teller (BET) analysis, and diameter was measured by transmission electron microscopy (TEM).

On the basis of surface area, the mice exposed to SWNT received four times as much exposure to carbon particles in their lungs. So, on the basis of surface area the results showing three to five times more toxicity to lungs were actually found at doses four times higher! While this is not definitive evidence that nanotubes are not more toxic to the lungs than other carbon nanoparticles, on the basis of surface area, it is possible that SWNT may not be more toxic than carbon black when inhaled in the lungs.

Another complicating factor in this study is that the SWNT were found to contain about 0.23% iron, which some have suggested may have contributed to the toxic responses in the lung. Thus, it is not clear whether CNTs are more toxic than other shapes or sizes of carbon particles, and toxicology research now has to consider new factors in the assessment of toxicity.

3.3.2 Environmentally Friendly Nanotechnology

Inventors, chemical engineers, and materials scientists identify and create materials as means to achieve specific properties. Some call them nanoscientists and nanotechnologists. The discovery and exploitation of specific behavior is behind the development of novel materials with increased reactivity, conductivity, optical properties, flexibility, strength, and thermal properties — a host of desirable properties.

However, materials science is far removed from environmental science. No part of a chemical engineer's curriculum trains students on how materials behave in the environment — no discussion of the types of materials that become water pollutants or are persistent in the air, potentially contributing to smog, global warming, or asthma attacks. Simply, inventors are not trained to think about the downstream or long-term effects of the materials and new technologies they create. Rarely are new materials sought because they are less toxic, less persistent, or less biologically available.

There is a growing movement toward so called "green nano" that seeks to reduce the toxicity and environmental burden associated with substances and technologies, including a series of meetings on the topic. Generally, certain material properties are tested, which are indicators of potential for persistence, potential to accumulate in the food chain (bioaccumulation), or toxicity. Several organizations (e.g., U.S. EPA and EU) fund research into models that evaluate the behavior of materials across their life cycle, from their creation or extraction from the earth to their post-use fate in the environment, whether by recycling or disposal. EPA also has programs such as Design for the Environment, that seek out chemicals of lower toxicity to replace toxic chemicals currently used in manufacturing. Life cycle analysis is also popular in Germany, Denmark, and many other nations, as well as

private corporations. There are many initiatives addressing green technology development.

3.4 Risk Assessment for Nanotechnology

It is clear that risk assessment is an important tool for understanding and managing the potential risks from nanotechnologies and nanomaterials. Despite existing data gaps and the many questions that still need to be answered, risk assessments can be used as a screening tool that can be applied now to help identify and prioritize the information needed, and to help understand what is not known, but needs to be, before making decisions about new technologies. Even with current uncertainties, the risk analysis framework can help to make better decisions today.

Assessments can address both risks and benefits, weighing them against each other. For example, using cerium oxide in fuel improves air quality, a benefit of reducing particulate emissions from diesel exhaust, but this needs to be weighed against the risk of releasing cerium oxide nanoparticles into the air. Risk analysis allows this type of comparative analysis. It is useful to also compare the risks and the benefits of cerium oxide additives to those of other clean burning alternatives such as ethanol.

3.5 Life Cycle Analysis for Sustainable Nanotechnology

Sustainable development was defined by the Brundtland Commission as "…not a fixed state of harmony, but rather a process of change in which the exploitation of resources, the direction of investments, the orientation of technology development, and institutional changes are made consistent with future as well as present needs" (United Nations 1987). More recently, sustainability was defined as a recognition, "that the biosphere, or natural capital, sustains the economy, which in turn supports quality of life" (Koehler and Hecht 2006). Other definitions are less encompassing. Hess (2007), in an analysis of U.S. decisions to switch to cleaner buses, finds that "'sustainability' is not a goal that can be easily defined in the neutral and unbiased way, but a field of contestation that involves ongoing negotiations over fundamental definitions."

As with risk analysis, it is a bit far ahead for this discussion to seek a common definition of sustainable technology development, but the notion is that new technology development considers a broad set of potential environmental impacts, and seeks improvement on these. For example, some view sustainable technologies as carbon neutral — that is, they do not contribute to releases to the atmosphere of carbon dioxide, the main greenhouse gas contributing to climate change. The focus of much sustainable technology is on energy efficiency. Sustainable technology also must address human

and environmental impacts, in terms of harm to health and the environment versus improving health and environment. Technology is the development of response to a human need or want. There are choices about technologies that are developed. Why not focus on technologies that "first, do no harm," the thesis of the medical oath?

This is an idea briefly suggested earlier, that new technologies should convey benefits that our existing technologies do not. However, they also often bring new risks or tradeoffs and it is important to broadly consider the proposed benefits and risks of new technologies in comparison to existing technologies. This is the broad principle — industrial ecology — behind *life cycle analysis* (LCA).

Some refer to industrial ecology as the science of sustainability. Industrial ecology seeks to develop technologies that operate without degrading the environment. LCA is a tool to evaluate whether technologies accomplish that goal. There are many alternative definitions of industrial ecology, and these are not reconciled here. Rather, this discussion focuses on the application of LCA as a study of the flows of materials and energy associated with product development.

Many applications of LCA use *life cycle impact analysis* (LCIA). LCIA applies modeling tools to evaluate impacts of technologies broadly, from large databases for materials from their generation, or removal from the earth, to their end of use, terms used to describe the life cycle includes cradle-to-grave; or the beginning to the end of life; cradle-to-gate, the industrial process of developing products; and cradle-to-cradle, William McDonough and Michael Braungard's notion that products should be designed for systems that regenerate, that are ecological by design, and for which the end of life is a new beginning, not a waste product. The materials flowing from one technology become inputs for another, limiting impacts on the environment and on resource depletion (McDonough and Braungard 2002).

LCIA was developed through substantial efforts by the Society for Toxicology and Environmental Chemistry (SETAC) and the International Organization for Standards Technical Committee (ISO 14040) to agree on impacts and criteria for their approaches to life cycle assessment. LCIA is promoted through a variety of voluntary initiatives by the United Nations Environment Programme (UNEP), national governments, industry, and many international organizations and industry associations. Several models are currently used for LCIA, but agreement about using them varies depending on who conducts the analysis. LCIA is a key tool of the U.S. Green Building Council's Leadership in Energy and Environmental Design (LEED), a rating system for developing buildings in a sustainable way, often called "green building."

These concepts are a new way of thinking about technology development that is more holistic than simply identifying a material with new properties, and replacing existing technology. LCIA applies an indicator approach: it assesses the inputs and outputs at each stage of the life cycle to estimate the impacts of a product or technology on a set of predetermined criteria. The criteria include: greenhouse gas emissions, air pollutants (nitrogen oxides and ozone precursors), acid rain, smog, impacts on water by the path of eutrophication (overgrowth of algae in water bodies that causes lakes to die), natural resource depletion, and

effects on human and environmental species. LCIA models estimate releases of materials that impact each of these categories; the emissions are matched with material properties to estimate an overall impact that can be compared to other products, so that the product with the least impact can be identified.

One idea bred from this work is the notion of *life cycle thinking*, which "integrates existing consumption and production strategies, preventing a piece-meal approach" (UNEP 2001; EU Joint Research Centre 2007). Life cycle thinking applies the concepts of considering the broader context for a product in its design and development, without necessarily the detailed data requirements of LCA and LCIA. Some have suggested it as a tool for small and medium enterprises (SME).

Life cycle thinking for nanotechnology development is currently promoted in terms of green chemistry. One recent initiative is summarized in *Nanotechnology and Life Cycle Assessment: A Systems Approach to Nanotechnology and the Environment*, which discussed the potential for using LCA for nanotechnology (CORDIS 2007). The workshop participants agreed there currently are some serious data limitations, but that the basic methodology is applicable. They also suggested an approach for incorporating life cycle thinking into nanotechnology evaluation. It begins with a traditional check for obvious harm. Next, it conducts a traditional LCA without toxicity study, followed by toxicity and risk assessment sets of questions. Finally, the approach combines the LCA and risk analysis (RA) and conducts a scenario analysis. Risk frameworks that combine LCA and RA are discussed in Chapters 6 and 7.

Life cycle thinking forms the underpinnings for NANO LCRA, the adaptive life cycle risk assessment framework proposed in this book (Chapter 6) and the frameworks described in Chapter 7. This type of approach has broad applicability for industry, governments, and people who are genuinely interested in or concerned about understanding and managing the potential impacts of nanomaterials and nanotechnologies.

Currently, there is a situation of limited data availability for analyzing the impacts of nanotechnology and nanomaterials. Therefore, the tools of LCA, LCIA, and even risk analysis cannot provide quantitative estimates today. However, taking a *screening level approach* allows these concepts to be incorporated into assessments of new technologies and substances, to improve the ability to identify adverse health and environmental impacts. Since nanotechnology innovation is occurring so quickly, adopting a proactive, science-informed approach that formalizes life cycle thinking into the assessment and management of risk will lead toward a sustainable path for nanotechnology development.

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4

The State of the Science — Human Health, Toxicology, and Nanotechnological Risk

Brenda E. Barry

CONTENTS

At present, considerable uncertainty exists regarding risks from nanoscale materials and the products that incorporate them. This chapter gives an introduction to some of the current science and its implications regarding the effects of nanomaterials on human health. Although numerous studies have been completed, they are not reviewed comprehensively here; rather, this chapter gives an overview, focusing on carbon nanotubes as an example of a category of nanomaterials, the types of heath effects observed, and the complexities of toxicological studies with nanoscale materials.

The concerns about the potential toxicity of nanomaterials are based on their unique surface, catalytic and magnetic properties, and how these properties may be expressed in biological systems and in the environment to produce adverse effects. In one of the first articles to broadly address the impending issues related to nanotechnology, Colvin (2003) examined the causes for concern regarding the potential biological and environmental impacts of nanomaterials. Colvin's discussion of these issues highlights a main theme of this book — due to their unique composition and properties, the key questions concerning nanomaterials are: (1) whether they present new risks for health and the environment and, if so, (2) can the potential benefits of nanotechnology be realized while minimizing the potential risks?

The majority of scientific studies examining the potential toxic effects of nanomaterials have been completed within the past five years. Interestingly, the results to date suggest that the behavior and effects of nanomaterials are not always directly predictable from the results of previous studies with other types of nanoscale materials. It is becoming increasingly apparent that although they are composed of the same basic elements, at the atomic or quantum level, nanomaterials have different properties and behave differently from their bulk counterparts. For example, at the nano-scale, clusters of gold atoms appear red (Kulinowski 2004). Similarly, although both graphite and carbon nanotubes (CNT) are composed solely of carbon atoms, the results from different *in vivo* and *in vitro* test systems indicate that the properties of graphite do not accurately predict the properties of CNT. To address the specific scientific questions raised by nanomaterials, a new area of toxicology, termed *nanotoxicology* (Donaldson et al. 2006; Oberdörster et al. 2005a), has emerged. Nanotoxicology can be defined simply as the science that deals with the effects of nanostructures and nanodevices on living organisms.

One of the first steps in understanding the potential toxic effects of nanomaterials is to understand their specific characteristics. Because chemical engineers have developed several different methods for producing a wide variety of nanomaterials, a categorization scheme for nanomaterials, such as the one developed by the EPA (2007), provides a useful approach for grouping the different types according to their composition or characteristics. The EPA scheme proposes four major types of nanomaterials: (1) carbon-based, which includes CNT and fullerenes; (2) metal-based, which includes quantum dots, nanocrystals that can act as semiconductors, and metal oxides; (3) dendrimers, which are nano-sized polymers built from branched units; and (4) composites in which nanomaterials are combined with other nanomaterials or larger, bulk-type materials. Additional types of information are also useful for characterizing and understanding the potential toxicity of these different categories of nanomaterials. Some key parameters include the number or concentration of the specific nanomaterials; the size characteristics, including the length-to-width or aspect ratio; their surface area; and their chemical composition.

An overall concern about the potential toxicity of all types of nanomaterials is their large surface area relative to their size (Oberdörster et al. 2005a). This feature, which results in many of the beneficial aspects of nanomaterials, has also been linked to their increased biological reactivity. Oberdörster and colleagues (2005a) also comment on evidence that due to their small size, inhaled nanomaterials can pass through the cells of the respiratory system into the vascular system, and from there move to sites beyond the original site of deposition in the organism. Similarly, a study by Kim and colleagues (2006) reported that following injection of nanoparticles into the abdominal area of mice, the particles penetrated the blood–brain barrier, yet did not appear to affect brain function or produce toxicity.

A basic concept of toxicology is that the dose makes the poison (Klaassen 2001). Even materials essential to life itself, such as oxygen and water, can cause death in organisms if provided in excess. Examples include ingestion of excess water that can produce an imbalance in the ionic composition within cells, termed hyponatremia, which can result in brain swelling and possibly death (Cotran et al. 1999). Similarly, inhalation of high concentrations of oxygen, such as in a clinical setting to treat lung damage, can result in the production of reactive oxygen species (ROS) in the lung tissues (Cotran et al. 1999). ROS are reactive, unstable forms of oxygen that can damage and kill these tissues, an effect called oxygen toxicity. The point here is that the type of nanomaterials as well as the exposure amount, or dose, that may produce adverse effects in organisms and the environment are an active area of nanotoxicology research and are not yet well understood.

Nanotoxicology has drawn together toxicologists from a variety of discipline areas to apply their previous knowledge and expertise to questions about the potential toxic effects of nanomaterials. They include inhalation toxicologists with backgrounds in particle toxicology, who have studied the adverse effects of nano-scale particles emitted as air pollutants from stationary industrial sources, such as smokestacks, as well as from mobile sources, such as motor vehicles (Oberdörster et al. 2005a; Nel et al. 2006). Fiber toxicologists with backgrounds in the toxic effects of natural mineral fibers, such as asbestos; synthetic vitreous fibers, such as fiberglass; and other fibrous materials are interested in studying the potential effects of carbon nanotubes (CNT) based on the similar aspect ratios and the durability of CNT (Donaldson et al. 2006; Borm and Kreyling 2004; Mossman et al. 2007). Similarly, dermal toxicologists are interested in learning whether the small size of nanomaterials increases their potential to penetrate the skin layers and to produce changes in the dermal cells and tissues, and how these changes compare with dermal exposures to other types of materials (Monteiro-Riviere and Inman 2006).

4.1 Mechanisms of Toxicity

A toxicologist evaluates a number of factors to understand a potential toxic effect. One important determinant factor is the likely route of exposure for the material of interest. The pathways for exposure to nanomaterials as well as any other material include inhalation, dermal contact, and ingestion. In some cases, ingestion can occur following dermal contact, when the material sticks to the skin and is later transferred to the mouth. For nanomaterials, the eyes may also be an area of concern, when nanomaterials on the skin are transferred by hand contact with the eyes.

The exposure dose that an organism receives depends on the concentration of the material of interest, including a nanomaterial, and the duration

and frequency of the exposure. Following an exposure, the fate of that material in an organism is a product of several different processes, including its absorption, distribution, metabolism, or breakdown in the organism, and how effectively it is subsequently eliminated from the system. For many materials, the site or sites where a toxic material causes damage, called a target tissue, may be identified. This target tissue may be specifically affected by exposure to the toxic material, perhaps due to buildup of the material or the particular sensitivity of that tissue or area to the material. It is important to keep in mind that the target tissue may not always be at the initial deposition site, because the material or one of its breakdown products could be transported to another location in the organism that becomes the target tissue.

The mechanisms by which a compound or material, such as a nanomaterial, produces a toxic effect can be grouped into several broad categories because cells, tissues, or an organism have a relatively limited number of ways to respond to an exposure. The material of interest may cause direct irritation that produces a reaction at the site of contact. Alternatively, the material may produce oxidative stress due to the generation of ROS. As mentioned previously, ROS are unstable forms of oxygen; they can cause cell injury by interacting with cell membranes, breaking them, and causing the cell contents to leak. Both of these events can result in the release of a number of different protein factors — including cytokines, chemokines, and cell growth factors — that can initiate more complex reactions involving immune and inflammatory cells, the release of additional factors, and more reactive processes occurring at the site of initial injury. This overall process is called inflammation, a protective response by the organism that is designed to rid it of the foreign material that is the cause of the injury (Cotran et al. 1999). The most severe response to a toxic material is cancer, which results in uncontrolled cell growth at the site of damage.

A recent review by Donaldson and colleagues (2006) discusses a number of different features of one type of nanomaterial, specifically CNT, that may affect potential mechanisms of toxicity, particularly related to pulmonary toxicology. Drawing upon the authors' previous extensive experience in particle and fiber toxicology, they suggest that previous studies in this field can provide a basis for understanding the effects of nanoscale particles and fibers. They comment that if CNT are longer than 20 μm, they would likely cause the same type of pathological damage as mineral fibers, such as asbestos, and synthetic vitreous fibers, such as fiberglass. The damage can include inflammatory responses, as previously described, and possibly cancer. They also note that several classes of impurities, such as small amounts of metals, organic residual matter, and support materials, may be present in CNT samples following the production processes. As observed following exposures to different types of fibers, pro-inflammatory effects produced by CNTs may be caused by their length, their reactive surfaces, or the release of metal ions that may be toxic to the cells or tissues (Figure 4.1). These processes can cause

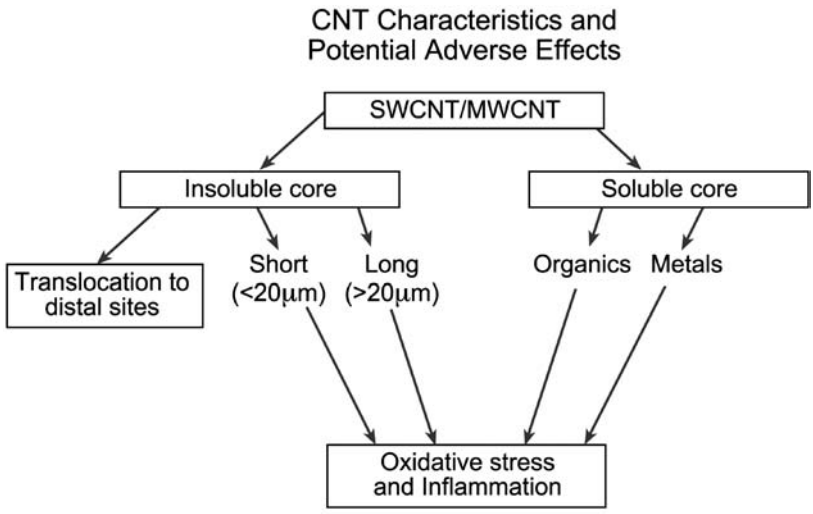

FIGURE 4.1
Carbon nanotube characteristics and potential adverse effects. SWCNT — single-walled carbonnanotube. MWCNT — multi-walled carbon nanotubes. Figure adapted from Donaldson et al. (2006). (See color insert following page 76.)

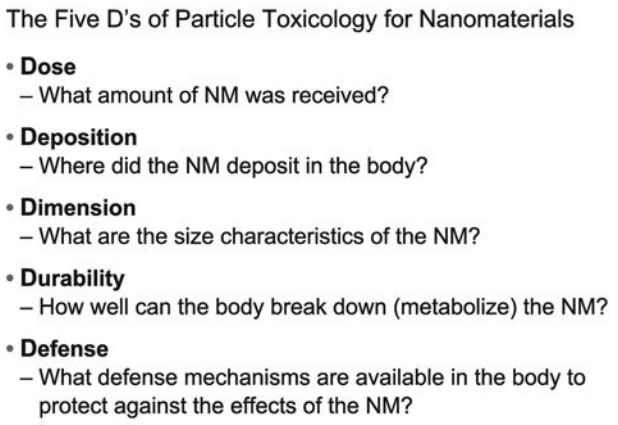

FIGURE 4.2
The five Ds of particle toxicology for nanomaterials. Adapted from Borm and Kreyling (2004).

oxidative stress to the affected cells and tissues, similar to the toxic effects previously reported for mineral and synthetic vitreous fibers.

The Five D's of particle toxicology (Figure 4.2) can provide important perspectives for consideration of the toxic effects of nanomaterials (Borm and Kreyling 2004). Although developed primarily for inhalation toxicology, the

five D's — dose, deposition, dimension, durability, and defense — are relevant characteristics for examining the responses to nanomaterials in other types of toxicological studies. These characteristics are particularly appropriate in light of the noted stable properties of nanomaterials. Certainly dose is a critical factor, as discussed previously, as well as the site of nanomaterial deposition, because this impacts the cells and tissues in direct contact with the nanomaterials. The dimension and durability properties of nanomaterials are specifically relevant for CNT, whether single-walled or multi-walled. Some investigators have suggested that the durability and dimensions of CNT resemble those of asbestos fibers, raising concerns about the persistence of these nanomaterials in biological systems once they have entered the organism, termed biopersistence. These concerns become increasingly important as chemical engineers continue to refine methods for producing longer CNT many microns in length, such that they have both the dimensions and durability of asbestos fibers.

In his recent review article, Hardman (2006) discussed the toxicity of quantum dots (QDs), which are semiconductor nanocrystals that have unique optical and electrical properties. Based on his review, he concluded that QDs cannot be viewed as a uniform group of substances with a specific toxicity. As noted for other nanomaterials, the specific properties of QDs are of interest and how these may affect their potential toxicity must be evaluated. Because bioconjugated QDs — that is, QDs linked with biological materials, such as proteins and antibodies — are under consideration for biomedical applications as tools for site-specific gene and drug delivery, as well as *in vivo* biomedical imaging, the potential human health and environmental risks of their use must be considered carefully.

4.2 Types of Toxicological Studies

Oberdörster and colleagues (2005b) have proposed a screening strategy for evaluating the toxicity of nanomaterials that includes a comprehensive array of *in vitro* and *in vivo* assays and a two-tier approach for *in vivo* studies, described in Section 5.6. This strategy employs traditional toxicology and assay techniques to understand the potential toxicity of nanomaterials under defined test conditions. The different types of testing systems and their advantages and disadvantages will now be considered.

In vivo models use whole animals to study the effects of exposures to nanomaterials. One model is intratracheal instillation, in which a nanomaterial suspended in a fluid is injected directly into the trachea and to the lungs of an anesthetized experimental animal. A concern with this model is that it delivers the nanomaterial as a one-time, concentrated amount of material, termed a bolus, into the lungs, in contrast with the more natural inhalation mode of entry, in which small amounts of a material are progressively

delivered to the lungs with each breath. The one-time delivery of a large amount of the nanomaterial may produce effects more related to the delivery method than the material. Pharyngeal aspiration is an approach that attempts a more physiologically natural mode of entry of nanomaterials into the lungs. A small amount of the nanomaterial solution is placed on the back of the tongue of an anesthetized animal; with its next breath, the animal aspirates the nanomaterial solution into its lungs.

Another potential *in vivo* exposure approach is the use of inhalation chambers, in which test animals are exposed to a measured concentration of an aerosolized nanomaterial for a specified exposure period. This approach can be costly because a large amount of nanomaterial is needed to generate the aerosol and this may be expensive. In addition, the physiochemical properties of nanomaterials can complicate generation of the aerosol as well as maintenance of the desired aerosol characteristics in the chamber, due to the tendency of the nanomaterials to agglomerate due to static forces. Although results from inhalation chamber studies with nanomaterials have yet to be reported, such studies are either in the planning stages or underway.

In vitro approaches allow the study of the mechanisms of action and biological effects of nanomaterials on cells and tissues under controlled conditions. Such studies can include the use of cells derived from a variety of sources, such as lung or skin, that have been grown in media on plate surfaces or in test tubes, to which nanomaterials can be added. Other types of *in vitro* exposure systems can utilize sections of selected tissues obtained from animals or humans. Examples of these "test tube" assays include flow-through diffusion cell studies (Ryman-Rasmussen et al. 2006) and skin flexion model studies (Rouse et al. 2007).

The disadvantages of *in vitro* test systems require consideration when interpreting study results because the effects observed *in vitro* are difficult to compare to possible effects that may occur in the naturally more complex *in vivo* systems. These systems include defense systems, as well as feedback and immune response mechanisms designed to deal with foreign matter in the body. For example, immune and inflammatory cells, which can contribute a variety of cell mediators to a toxic response *in vivo*, are absent. In addition, *in vitro* systems do not have the normal clearance or dissolution mechanisms that usually operate *in vivo,* which may reduce the amount of available nanomaterial and the observed effects. Such factors can complicate extrapolating the effects of a delivered *in vitro* test dose to an *in vivo* exposure dose.

Teeguarden and colleagues (2007) reviewed aspects of pharmacokinetics, an approach used in pharmacology to determine the fate of materials, such as drugs, in an organism, and how this approach may affect interpretation of cell dose of nanomaterials under *in vitro* conditions. Based on the specific properties, nanoscale particles can diffuse, settle, and agglomerate in the culture media; as a result, simple representatives (surrogates) of dose, such as the amount of a nanomaterial directly added to the *in vitro* test system, may be an inappropriate reference marker for evaluating uptake of nanomaterials and responses of the cells in *in vitro* test systems. The authors propose

that use of pharmacokinetics and principles of dosimetry (the relationship between dose and observed response) can improve the validity of nanomaterial *in vitro* toxicity assessments.

For both *in vivo* and *in vitro* toxicity studies, the validity of using specific assays to evaluate the parameter of interest should also be verified, to ensure that the results are relevant and that false positives are not produced. An example of the latter point is the colorimetric MTT assay routinely used for evaluation of *in vitro* cell viability. It is based on the reduction of yellow 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide to purple MTT-formazan due to the release of enzymes from damaged cells. Wörle-Knirsch and colleagues (2006) reported that in *in vitro* assays, single-walled carbon nanotubes (SWCNT) could directly interact with MTT to give a positive purple result that was not related to cell enzyme release. The positive colorimetric result indicating cell damage due to SWCNT exposure was not evident in results from the WST cell viability assay, another test that is commonly used to determine whether cells are damaged or killed by a treatment. This means the MTT assay is not a valid test for SWCNT.

Another factor that currently complicates interpretation of results from both *in vivo* and *in vitro* studies is a lack of nanomaterial reference standards. At present, considerable variability can exist within the same type of nanomaterial, such as CNT, depending on who manufactured it, as well as if and how the nanomaterial was chemically treated after synthesis. As an example, a sample of CNT can contain variable amounts of metals as contaminants from the manufacturing process. The presence of these metals may affect the responses of the cell or tissues because of the toxic effects attributable to the metals. The lack of nanomaterial reference standards can also confound comparison of the results of toxicological studies by different investigators using the same category of nanomaterial, but which were manufactured differently and with a different composition.

4.3 Findings

4.3.1 Pulmonary Toxicity Studies

Pulmonary toxicity studies comprise a sizeable segment of the recent and current research designed to understand the toxic effects of nanomaterials. The practical basis for this research is the potential for inhalation of nanomaterials, particularly in regard to worker exposures through handling and managing nanomaterials. Results from several *in vivo* studies reported within the past few years have provided some of the first evidence that exposures to nanomaterials could cause injury in the lungs of experimental animals. The *in vivo* studies reported to date have primarily focused on the effects of

exposures to metal oxides and to carbon-based particles such as SWCNT and multi-walled CNT (MWCNT).

Studies by Lam et al. (2003) and Warheit et al. (2004) used intratracheal instillation as the method to deliver SWCNT to the lungs of rats and mice, respectively. From their short-term (acute) toxicity study, Lam et al. (2003) reported that the instillation of SWCNT produced granulomas, small nodules of cells that may include macrophages, lymphocytes, and a variety of inflammatory cells in the lung tissues and that their appearance increased with the dose of SWCNT, suggesting it was dose-dependent. Based on their 2004 study, Warheit and colleagues also reported the presence of granulomas in a number of areas in the lung tissues of exposed rats, but their appearance was not dependent on dose. Unexpectedly, the reported changes also occurred in the absence of increases in markers of inflammation and cell division within fluids obtained when the lungs of the experimental animals were rinsed with saline. These markers include cell enzymes normally found only inside cells, and are indicators of dividing cells, both of which are usually detected in the lung fluid following these types of studies. Subsequent studies that also used intratracheal instillation of CNT as the treatment method (Muller et al. 2005; Grubeck-Jaworska 2006) indicated inflammatory changes and the appearance of scar-like, or fibrotic, areas in the lungs of exposed animals.

Shvedova and colleagues (2005) used pharyngeal aspiration to deliver SWCNT to the lungs of mice. They reported that their treatment produced not only a strong inflammatory reaction shortly after treatment but also progressive and dose-dependent development of fibrotic changes in the lung tissues. Surprisingly, this fibrotic reaction occurred in the absence of signs of persistent inflammation and at sites distant from the SWCNT deposition sites. More recently, this team demonstrated that inflammatory effects were mitigated when exposed mice were also given vitamin E, an antioxidant (Shvedova et al. 2007).

The results of all of the studies briefly reviewed here suggest that the SWCNT may be capable of producing fibrotic alterations in the lungs similar to those reported following exposures to other types of fibrous materials. However, as discussed in Chapter 3, there are numerous uncertainties in the dosing of these studies that affect their interpretation. In particular, the presence of iron contamination and the sheer number of nanotubes used in the experiments make interpretation of these findings to real world exposures difficult. Studies are underway at the U.S. National Toxicology Program to develop experimental protocols for SWCNT by inhalation (NTP 2007).

4.3.2 *In Vitro* Studies

Numerous *in vitro* studies have been conducted using a variety of nanomaterials and cell types to understand the mechanisms and potential toxic effects concerning exposures to nano-scale materials. In 2004, Sayes and colleagues reported that the cell toxicity of water-soluble fullerenes was a function of the nature of their surface, and that fullerene toxicity was caused by lipid

peroxidation of cell membranes due to generation of ROS. Using alveolar macrophages (the respiratory defense cells present in the air spaces in the lungs), Jia and co-workers (2005) evaluated several types of nanomaterials and reported that in their cell assay system, SWCNT were more toxic than fullerenes. Bottini and colleagues (2006) observed that MWCNT oxidized by treatment with a strong acid were more toxic than untreated, or pristine, MWCNT; while Brunner and co-workers (2006) concluded that solubility was a strong influence in the cell toxicity observed in their assays following cell exposures to silica, asbestos, and several different nano-scale materials. Limbach and colleagues (2007) quantified oxidative stress through the release of ROS from human lung epithelial cells treated with nano-scale silica particles that contained a variety of metals. They reported that the nanoparticles could act like Trojan horses carrying the metals inside the cells and that the specific chemical composition of the particles was the most influential factor for causing the oxidative stress.

In vitro studies have also demonstrated that alteration of the nanomaterial surface by the addition of functional groups can modify the toxic properties of nanomaterials. Sayes and colleagues (2004; 2006) reported that attachment of different chemical groups to the surface of CNT and fullerenes could change their properties and decrease their toxicity.

4.3.2.1 Dermal In Vitro *Toxicity Studies*

Investigators have increasingly focused on skin, or dermal, contact as an important route of exposure to nanomaterials. In one of the first occupational studies attempting to understand potential exposures to nanomaterials under actual worker conditions, Maynard and colleagues (2004) obtained measurements for aerosol concentrations of SWCNT and evaluated potential for dermal exposures. They reported that aerosol concentrations of SWCNT were low and that energetic processes would likely be needed to increase airborne concentrations. It is important to note the study was conducted in a simulated work environment and therefore may not reflect conditions in a manufacturing facility. Maynard et al. (2004) also observed that the gloves of workers were contaminated with SWCNT, indicating the importance of dermal contact as a source of worker exposures to nanomaterials. These findings have been followed by a number of *in vitro* studies to determine the potential effects of nanomaterial exposures on dermal cell systems and whether nanomaterials behave similarly or dissimilarly to other types of nano-scale materials, such as beryllium (Tinkle et al. 2003).

In a study using human epidermal keratinocytes (HEK) — cells in human skin that produce the protein keratin — Shvedova and colleagues (2003) reported that exposures to unrefined SWCNT produced oxidative stress and cellular toxicity in the HEK. They concluded that their findings suggested that exposures to unrefined SWCNT may lead to dermal toxicity in the skin of workers. A study by Monteiro-Riviere and colleagues (2005) also using HEK determined that chemically unmodified MWCNT were taken up

by the cells and that the nanomaterial exposures caused the release of pro-inflammatory cytokines. This suggests that, although the skin is normally a good barrier to keep many materials from entering the body, nanomaterials, due to their very small size, may be able to enter the skin and produce toxic responses. This penetration capability may be a beneficial aspect, if the nanomaterial is a drug or a cosmetic treatment; however, it may not be beneficial if the nanomaterial entry results in a toxic response in the skin, or allows a nanomaterial to enter the body and subsequently be transported to another site where a toxic effect may occur.

In a study to examine the potential toxic effects of QDs on skin, Ryman-Rasmussen and co-workers (2006) reported that in their flow-through diffusion system, QDs with different shapes, sizes, and surface coatings could penetrate intact porcine skin at occupationally relevant concentrations. In a study using a porcine skin flexion model, Rouse and colleagues (2007) described dermal penetration of fullerene nanoparticles and their presence within the spaces between cells in a sub-layer of the skin called the stratum granulosum.

4.4 Future Directions

As illustrated in this section, both *in vivo* and *in vitro* systems can provide useful information for understanding the mechanisms of toxicity as well as the toxic responses of organisms, tissues, and cells following exposures to nanomaterials. As noted earlier, a disadvantage of *in vitro* test systems for evaluating nanomaterial toxicity is the difficulty in correlating the findings with effects that may occur in the naturally more complex *in vivo* systems. The type of nanomaterial, its chemical (or functionalization) treatment prior to addition to the *in vitro* assay system, the types of cells used, the assay system, and other factors can all contribute to the sometimes contradictory results from different investigator groups.

In a recent study, Sayes and colleagues (2007) asked how well the results from *in vitro* assays could predict the toxicity results produced *in vivo* for several different types of nano-scale and fine-scale particles, including silica and zinc oxide. Using a variety of *in vitro* assays and an intratracheal delivery method for their exposure systems, they noted little correlation between the results from the *in vitro* and *in vivo* assays. They concluded that *in vitro* cellular assay systems require further development, standardization, and validation to provide useful and reliable screening data to assess the toxicity of inhaled materials. This conclusion dovetails well with the future needs described by Teeguarden and colleagues (2007) for development of high-throughput *in vitro* assays that can reliably predict the toxicity of nanomaterials. Ultimately, the results from such an *in vitro* assay should also be relevant to those effects that may occur *in vivo*. Such test systems will be invaluable for efficient evaluation of the potential toxicity of the thousands of types of

nanomaterials likely to be produced in the near future. This is because reliance on a traditional toxicology battery of both *in vitro* and *in vivo* assays for each of these nanomaterials would be both time and cost prohibitive.

This brief review of recent reports concerning the potential toxicity of nanomaterials identifies some of the variability and inconsistency in the reported findings using similar test systems and even the same category of nanomaterials. Variability among the results is likely due to the fact that toxicological assays for nanomaterials have only been conducted within the past few years, and relatively few nanomaterials have been studied thoroughly. Some of these differences may be attributed to the current absence of nanomaterial reference materials that could be used to standardize results with different test systems and among different research laboratories that conduct the testing. Nevertheless, the trend of current findings for exposures to several different types of nanomaterials is that they can produce toxic and unexpected responses in the various test systems used to date.

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5

The State of the Science — Environmental Risks

Jo Anne Shatkin

CONTENTS

Even in the built environment, reliance on water, air, and natural resources is the basis of the high quality of life people aim to enjoy in modern society. Everyone requires clean water for drinking, cooking, irrigation, and recreation. When the air is polluted, it affects everyone's breathing, in some people stimulating respiratory distress and affecting heart functioning. The food supply is impacted when land and water resources are contaminated. As humans we exist as part of earth's ecosystem — as animals in the food chain. Humans are not quite at the top, but we are near it, particularly urban

dwellers. We rely on all of the lower levels of the ecosystem to function in order for us to survive.

Beyond the food chain, people are impacted by the health of plants and animals in many ways. Consider the following issues: (1) environmental contamination can change the health of the world around us, and thus the resources humans depend on; (2) people rely on the environment, and because human activities often affect the environment, attention to the impacts of development on the world around us is necessary; (3) ecological impacts can be sentinels — that is, observation of toxicity to fish and other aquatic organisms can be an indicator of adverse effects on people; (4) with global trade, the world's food supply is complex and relies on technology and food grown in different parts of the world can be impacted if pollution or disease outbreaks affect the complex food web of an ecosystem, with unpredictable effects; and (5) there is a lack of equity between the wealthy who enjoy a clean environment, and those who are poor and live in a dirty environment. Protecting the environment is also a social justice issue.

There are many reasons to be concerned about whether nanomaterials affect the environment, not the least of which is stewardship. Here is a synopsis of what is known about the effects of selected nanomaterials on the environment. Scientists and regulators study the effects of substances on the environment to assess impacts on specific populations or representative organisms, as indicators of the extent of effects.

5.1 Antimicrobial Properties

Many types of nanoparticles have been investigated for antimicrobial properties. What is an antimicrobial property? It is the ability of a substance to kill or inhibit the growth of microbes, or microbiological organisms. Microbes include bacteria, such as *Escherichia coli* and Salmonella, which cause gastrointestinal illness, and also *Lactobacillus acidophilus*, the active ingredient in yogurt that improves digestion. Bacteria tend to be microns in size (although nanobacteria are an emerging area of research), whereas viruses are also microbes, but are of nanoscale size.

Not all microbes cause diseases. Those that do are called pathogens. Pathogens can cause disease by infecting the food, water, and air that people eat, drink, and breathe. Microbes that are not disease causing (non-pathogenic organisms) are important and often necessary components in the digestive tract, in soil, and in complex ecosystems. Non-selective killing of microbes can be harmful to health and the environment. While it is good for public health to kill pathogens, killing non-disease-causing environmental microbes can disrupt the natural processes of complex food webs in which microbes play a vital role, for example creating food for higher organisms, and breaking down dead organic matter into soil components.

The development of nanoscale materials for use as antimicrobials applies the greater reactivity and surface area of the smaller particles for more effective killing of pathogens. Applications include fabric coatings, food packaging, kitchen products, water taps, food contact surfaces, medical instruments, and other consumer products such as sporting goods, electronics, and door knobs (WWCS 2007). There are benefits to antimicrobial products — pathogens are not transferred from the treated surfaces, increasing food safety, and decreasing the likelihood of contracting an infection during hospital visits, or from doors, handrails, waiting rooms, bus seats, and other surfaces in public places. If you are a poor cleaner, anti-microbial treatment of appliances and kitchen counters in your home can reduce the presence of pathogens and resulting illnesses.

Because they only target microbes, some nanoparticle antimicrobials may be less toxic than the current alternatives, such as the chemical triclosan, which is now in hundreds of products, and may be hormonally active (Jacobs et al. 2005; Veldhoen et al. 2006), disrupting the endocrine systems of larger animals, including people. Since not all microbes are pathogens, wide use of antimicrobial coatings on consumer products could have some unintended effects, for example the development of antimicrobial resistance to microbes, which has occurred as a result of the wide introduction of antimicrobials in soaps and cleaning products (Pruden et al. 2006). Some pathogens that cause common hospital infections are resistant to antibiotics as a result of overuse for medical purposes and in products, and their subsequent wide occurrence in the environment. Increasing the frequency with which antimicrobials are used, will increase microbial resistance to antibiotics, decreasing our ability to treat infections. As a result, society increasingly is at risk of an outbreak of disease caused by antibiotic-resistant microbes. Generally, our immune systems can fight off these microbes, but there are sensitive subpopulations of immunodeficient people who cannot. These include people whose immune systems are weakened because of other illnesses, and also those with immune system diseases including lupus, AIDS, and others.

Studies evaluating the effects of nanoscale silver, fullerenes, titanium dioxide, and carbon nanotubes have identified antimicrobial properties associated with exposure. These types of nanoscale particles are now being tested and applied for use in numerous applications. By far, nanoscale silver is currently the most widely developed for antimicrobial use.

5.1.1 Antimicrobial Properties of Nanoscale Silver

Colloidal silver and silver ions have long been used as antimicrobials. Recently, nanoscale silver particles have been investigated as an alternative and is rapidly entering the market in a range of consumer products. Nanosilver is as effective as silver ions which are soluble and not nanoparticles, in killing *E. coli* (Sondi and Salopek-Sondi 2004); efficacy varies with the shape of the particle (Pal et al. 2007). The nano-silver particles interfere with the outside membrane of a microbe and destabilizes it, releasing the contents of

the cell, which kills it. This is specifically a microbial effect; the nano-silver does not affect mammalian cell membranes, which is part of why nano-silver can be found in upwards of 95 consumer products on the market today (WWCS 2007). Some commercial vendors claim silver is not toxic to people, although the U.S. Food and Drug Administration has banned the use of colloidal silver (FDA 1999), and has nominated nano-silver to be tested for mammalian toxicity by the National Toxicology Program (NTP 2007). The U.S. EPA requires all substances that are used for biocidal purposes to be registered, and is likely to evaluate the imports of nano-silver for its antibacterial properties.

5.1.2 Buckyballs

C_{60} fullerenes are entering the market now in a range of consumer products. C_{60} fullerenes are spherical carbon molecules with a diameter of approximately 1 to 2 nm; they have been reported to behave as antioxidants, scavenging radical oxygen molecules that have been associated with aging and stress. Antioxidants are hot market items for skin creams and nutraceuticals (e.g., vitamins and supplements). Fullerenes are in at least six skin creams currently on the market (WWCS 2007). C_{60} also appears to have catalytic effects on cell membranes, reducing cell viability, and is being investigated as an antibacterial additive for disinfectants. Some early studies on the behavior of C_{60} raise concerns about whether they might cause unintended effects.

C_{60} is not soluble in water; however, it forms soluble and stable aggregate crystalline molecules, termed nano-C_{60}, that may inhibit microbial activity in aqueous solution (Fortner et al. 2005). Depending on their mode of preparation, fullerenes suspended in water in standard assays inhibited the growth of *Bacillus subtilus,* at concentrations from 0.09 mg/L to 0.95 mg/L (parts per million). The size of the aggregated particles affected toxicity, with smaller aggregates more toxic than larger aggregates, which may be related to the level of crystallinity (Lyon et al. 2006). However, when the surface was hydroxylated (substituted), C_{60} did not show antimicrobial activity, indicating a need to better understand transformation of fullerenes in the environment (Lyon et al. 2005).

5.1.3 Titanium Dioxide (TiO_2)

One of the most widely studied nanomaterials for environmental effects is nanoscale titanium dioxide ($nTiO_2$). $nTiO_2$ is photocatalytic — that is, it becomes catalytic when exposed to ultraviolet (UV) light. It has been explored for use in water treatment to destroy chemicals such as polychlorinated biphenyls (PCBs), pesticides, and other complex organic contaminants. $nTiO_2$ has also been demonstrated to be bacteriocidal (Coleman et al. 2005; Kuhn et al. 2003; Rincon and Pulgarin 2003). Coleman et al. (2005) compared several $nTiO_2$ preparations for water treatment in a slurry and when immobilized. One commonly used type of $nTiO_2$ had a negative surface charge,

resulting in an acidic pH in the water that created additional stress in *E. coli* bacteria (Coleman et al. 2005). Rincon and Pulgarin (2003) observed a detrimental effect on the survival of *E. coli* after photocatalytic exposure; no bacterial growth was observed after UV illumination of a contaminated $nTiO_2$ suspension. UV-illuminated TiO_2 was more bactericidal to thin-walled gram-negative bacteria than thicker-walled gram-positive bacteria on surfaces, suggesting that the mechanism of toxicity is by radical hydroxyl generation on the cell membrane (Kuhn et al. 2003). Others have suggested lipid peroxidation as the mechanism of toxicity of photoilluminated $nTiO_2$ on cell membranes (Maness et al. 1999).

5.2 Short-Term Toxicity Tests

One common measure of effects of substances on the environment is evaluating toxicity to organisms in water. Several standardized tests measure the concentration of a substance required to kill or measurably decrease a population of test organisms, such as water fleas (daphnia) or small fish, like minnows. *Daphnia magna* is a species of water flea that is a filter feeder. They are small transparent organisms that grow and reproduce quickly, and obtain nutrition by filtering water through their bodies. They are thus a simple organism to study, and obtain results from, and so are used in several standardized assays (EPA, OECD, and EU) to evaluate short-term effects of substances in aquatic systems.

5.2.1 Daphnia LC_{50} Assays

Standard assays for testing the aquatic toxicity of substances in daphnia measure the concentration that is lethal to 50% of the test population, the LC_{50}, or the effects concentration, EC_{50}. The lower the LC_{50} concentration, the greater the toxicity of a substance. For C_{60} fullerenes, an LC_{50} of 460 parts per billion (ppb) was found in 48-hour toxicity tests with *D. magna* prepared with tetrahydrofuran (THF, a solvent) and 7.9 ppm for sonicated (using ultrasound to disperse) C_{60}, possibly indicating greater toxicity for the sonicated C_{60}, but some difficulties were reported in particle dispersion in the sonicated experiments so the results are not conclusive. Adult daphnids demonstrated behavioral irregularities when exposed to C_{60} (Lovern and Klaper 2006). In another study with *D. magna*, the results indicated uptake and sub-lethal effects of fullerene exposure, including altered molting and decreased reproductive output (Oberdörster et al. 2006b). Daphnids exposed to a SWCNT that was coated with a lipid (fat) layer were able to metabolize the outer layer, and excrete the SWCNT back into the water (Roberts et al. 2007), demonstrating that biological organisms can modify nanoparticles in the environment.

Material preparation was also shown to affect the toxicity of nano-TiO_2. Using standard EPA 48-hour acute toxicity tests in daphnids, Lovern and Klaper (2006) found toxicity associated with exposure to filtered tetrahydrofuran (THF)-derived 30-nm TiO_2 (P25) particles and reported a 48-hour lethal concentration (LC_{50}) of 5.4 ppm and a no-observed-effects concentration (NOEC) of 2.0 ppm. Unfiltered and sonicated TiO_2 particles that were agglomerated (stuck together forming larger particles) to 100 to 300 nm were less toxic to daphnids; mortality never exceeded 9%, and no LC_{50} value could be determined. This may have been due to differences in particle size, or perhaps the THF in the filtered experiments was the cause of toxicity rather than the TiO_2. There are some indications that daphnids can ingest nano-sized TiO_2, with particles in the gut and fatty lipid storage droplets appearing shortly after ingestion; it also appears that particles may be transported to other parts of the organism (Lovern and Klaper 2006).

In a modified standard bioassay in algae, Hund-Rinke and Simon (2006) demonstrated a difference in toxicity from UV-illuminated 25 nm TiO_2 (P25) and 100 nm particle diameter TiO_2. An effects concentration (EC_{50}) of 32 to 44 mg/L was found for the 25 nm diameter particles. According to the European Union Directive 67/548/EEC, this substance would be labeled harmful to aquatic organisms; however, under the U.S. EPA classification (U.S. EPA 2001) this result is classified as low acute toxicity. Similar to the fullerenes, for the 100 nm diameter particles, there was not enough toxicity to calculate an EC_{50}, although some toxicity was observed. Hund-Rinke and Simon (2006) compared washed particles to unwashed ones, and report slightly, but not significantly, lower toxicity with the washed particles. They further report no toxicity in experiments with daphnids; however, no measurements of particle aggregation or other properties were made. Wiench et al. (2007) compared the acute toxicity of nano- and micro-scale TiO_2 particles in daphnids using the OECD Test Guideline 202. Although the choice of test media affected the level of agglomeration and sedimentation, both particle sizes showed similarly low acute toxicity.

These findings of the toxicity of nTiO_2 can be compared to interpret the results (Lovern and Klaper 2006; Hund-Rinke and Simon 2006; Warheit et al. 2007; Wiench et al. 2007). Table 5.1 shows the toxicity levels in different test systems, and the hazard ranking according to the U.S. EPA Hazard Ranking Scale (U.S. EPA 2001). The nature of the particles and the tests vary, but generally report similar results in a low to medium hazard ranking for this substance.

Daphnids were exposed to nanoscale iron particles in water, and these were shown to be taken up into the digestive tract, but apparently not into the rest of the organism. The uptake did not affect their survival or reproduction, and nano-iron toxicity was similar to that found with larger iron particles. The only observed effects were that the antennae were clogged externally from the exposure, and that their digestive tracts were darker, because the iron produced a dark color visible through the fairly transparent

TABLE 5.1

Acute Toxicity of Nanoscale TiO_2 in Aquatic Tests

Test	Material	Study	Endpoint	Value	EPA Hazard Ranking
Acute aquatic invertebrate (daphnids)	THF 30 nm anatase	EPA 48 h tox test (Lovern and Klaper 2006)	LC_{50} (48 h)	5.5 mg/L	M
Acute aquatic invertebrate (daphnids)	THF 30 nm anatase	EPA 48 h tox test (Lovern and Klaper 2006)	NOEC	2.0 mg/L	M
Acute aquatic invertebrate (daphnids)	Sonicated >100 nm anatase	EPA 48 h tox test (Lovern and Klaper 2006)	LC_{50} (48 h)	NA	L
Acute aquatic invertebrate (daphnids)	25 nm P25 (80% anatase: 20% rutile)	EC standard algal assay (Hunde-Rinke and Simon 2006)	EC_{50}	NA	L
Acute aquatic invertebrate (daphnids)	100 nm anatase (Hombikat)	EC standard algal assay (Hunde-Rinke and Simon 2006)	EC_{50}	NA	L
Acute aquatic invertebrate (daphnids)	Unknown	OECD 202 (Wiench et al. 2007)	EC_{50}	NA	L
Acute aquatic invertebrate (daphnids)	140 nm 79% rutile: 21% anatase	OECD 202 (Warheit et al. 2007b)	EC_{50} (48 h)	>100 mg/L	L
Acute algal toxicity	140 nm 79% rutile: 21% anatase	OECD 201 (Warheit et al. 2007b)	EC^{50} (72-h growth)	21 ± 5 to 87 ± 4 mg/L	M
Acute algal toxicity	380 nm rutile	OECD 201 (Warheit et al. 2007b)	EC_{50} (72-h growth)	16 ± 6 to 61 ± 9 mg/L	M
Acute fish toxicity test	140 nm 79% rutile: 21% anatase	OECD 203 (Warheit et al. 2007b)	LC^{50} (96 h)	>100 mg/L	L
Acute algal toxicity	25 nm P25 (80% anatase: 20% rutile)	EC standard algal assay (Hunde-Rinke and Simon 2006)	EC_{50}	32–44 mg/L	M (harmful according to EC)
Acute algal toxicity	100 nm anatase (Hombikat)	EC standard algal assay (Hunde-Rinke and Simon 2006)	EC_{50}	NA	L

Abbreviations: NA – not applicable; M – medium; L – low.

body of the small organism (Oberdörster et al. 2006b). These studies suggest that particle size may affect the toxicity of substances to aquatic organisms.

Templeton et al. (2006) tested the toxicity of SWCNT in a salt water organism, *Amphiascus tenuiremis* (also known as copepods), using a standard toxicity test (ASTM Method E-2317-04) and demonstrated that purified nanotubes were not toxic during a chronic (long-term) exposure. The SWCNT were prepared by washing in nitric acid, which removed impurities. In contrast, the unpurified SWCNT was toxic at the highest dose of 10 ppm, a higher concentration than would likely occur in the environment. A third experiment found that a smaller fraction of the produced material, which the authors called fluorescent nanocarbon, was also toxic to the copepods at 10 mg/L. This study demonstrated differences in the uptake of SWCNT by size and purity. The larger purified nanotubes did not cross the gut, nor did they cause toxicity. The copepods excreted SWCNT as condensed clusters, transforming them into a new shape. The study also showed that impurities (i.e., the fluorescent nanocarbon) may be important contributors to toxicity and that organisms can transform nanomaterials in the environment (Templeton et al. 2006).

These studies indicate that material preparation affects the toxicity of nanomaterials, and that test conditions also affect the results of toxicity testing. These initial results can be considered indicators, but not definitive findings. At this moment, the limited data only allow the conclusion that some nanoparticles may be toxic to small aquatic organisms. Much work is needed to understand what factors affect the study results, and to produce reliable studies that can be considered more conclusive. According to the EPA, $nTiO_2$ would be of low to medium ecological toxicity in short-term tests.

5.3 Studies of Nanomaterial Toxicity to Fish

Relatively few studies have looked at the effects of nanomaterials on larger aquatic organisms such as fish. In this section, we discuss a few of the current studies.

5.3.1 Buckyballs and Bass

Nano-C_{60} was shown to induce oxidative stress (lipid peroxidation) in the brain of juvenile largemouth bass (Oberdörster 2004). There has been much discussion about this study, in part because exposure conditions were not well defined. Importantly, a solvent mentioned previously, tetrahydrofuran (THF), which causes neurological, or brain, effects, was used to help transfer the C_{60} particles into water because they are insoluble. Several studies have shown that using THF to solubilize C_{60} in water results in THF becoming

part of the nano-C_{60}. Thus, the observed brain effects may have been a result of the THF, not the fullerenes (Oberdörster et al. 2006a).

Oberdörster and colleagues (2006b) also evaluated the effects of C_{60} on the benthic (mud-dwelling) invertebrate *Hyalella azteca*, marine organisms, fathead minnows, and Japanese medaka (fish). As with TiO_2, LC_{50} values in invertebrates could not be determined using the doses tested (exposure to nano-C_{60} resulted in less than 50% of the population dying). These studies leave open the question of whether nano-C_{60} in water is toxic to larger aquatic organisms.

5.3.2 TiO_2 in Arsenic and Carp

Recently it was demonstrated that arsenic strongly binds to nanoscale titanium dioxide ($nTiO_2$) in water. Further, the presence of $nTiO_2$ more than doubled the uptake of arsenic in carp (Sun et al. 2007). The $nTiO_2$ also accumulated in the fish and correlated with arsenic absorption. The presence of $nTiO_2$ did not alter the distribution of arsenic in the fish, however. Arsenic with $nTiO_2$ accumulated preferentially in the intestine, stomach, gills, liver, skin, and scales, and least in the muscle. While not quantitatively characterized in the study, the accumulation of $nTiO_2$ was much greater in the presence of arsenic compared to $nTiO_2$ alone. However, the fish were sacrificed to assess uptake, so no toxicity can be inferred from these experiments. These findings suggest a secondary environmental affect; increasing the uptake of other environmental contaminants, altering their environmental behavior.

These few studies indicate that while nanoparticles might be harmful to aquatic organisms, the way the studies were conducted affected the results. In some cases, the material preparation affected the measurements. As with the human toxicity studies, the impacts may be related to the smaller size of the particles, their increased reactivity as a result of greater surface area per particle, or the greater number of particles in a dose. Also as with human toxicity studies, new ways are needed to describe the doses of nanoparticles, to allow more accurate interpretation of findings.

5.4 Field Studies

One of the complexities in assessing environmental effects of substances is that in the environment, conditions are much more complex than in a laboratory. For example, in a water body, there is much more interaction of substances with components of the water, such as natural organic matter that may be dissolved, plants, and other substances. In a laboratory, one usually just includes a substance combined with pure water, and the test organisms. This is one reason it is difficult to extrapolate laboratory results to the real world. On the one hand, in field studies, it is hard to relate a substance as a

cause to an outcome as an effect because of the complexity of the ecosystem and other factors. On the other hand, in laboratory studies, natural feedback systems, or other factors likely to affect toxicity, are not considered. One can relate the results of exposure to effects more directly, but cannot as easily interpret their meaning for the real world.

Very little information is published on the effects of nanoparticles on soil organisms. A study of the effects of C_{60} fullerenes on a soil microbial community did not identify any toxicity to the soil community structure, either when exposed as a solid material or as n-C_{60} in aqueous solution (Tong et al. 2007). Another study, not yet published in the peer reviewed literature, found that fluorescent-labeled SWCNT were not absorbed by a commonly studied worm, *Caenorhabditis elegans* (Oberdörster et al. 2006a).

A recent study of MWCNT demonstrated that natural organic matter (NOM) can stabilize a generally insoluble substance in water. Hyung et al. (2007) demonstrated that laboratory solutions of NOM, as well as actual river water containing NOM, kept the normally insoluble MWCNT in solution for four months. Using an instrument called a Thermal Optical Transmittance Analyzer, this group was able to quantitatively measure the concentration of the MWCNT in solution, and showed that with additional NOM, increasing amounts of MWCNT were suspended as individual nanotubes.

Since most natural waters contain some NOM, this is an important finding. It suggests that under the right conditions, CNTs can be dispersed, rather than bundled; thus, they would be at the size that aquatic organisms could ingest them with food, and they potentially could travel long distances in water bodies. Previously, it was thought that nanomaterials would aggregate in water, as has been shown for nanoparticles in air. Recall, however, that there are many different types of nanotubes, and there are an equally diverse number of ambient water conditions.

5.5 Environmental Exposures

Many people argue that, unless nanoparticles are free particles, there is no need to worry about their effects in the environment. That is, when nanoparticles are embedded in a product matrix, there should be no concern about exposure to them because the material is no longer at the nanoscale — the particles cannot be absorbed because they are bound up in the product. However, there is evidence from other types of materials that embedded ingredients of products can be released to the environment.

For example, flame retardants are used in many consumer products. Clothing, chairs, tables, carpets, furniture, electronics, and other products are coated with flame retardants, often required by law to limit their flammability and save lives. One category of flame retardants that have been widely used is polybrominated diphenyl ethers (PBDEs), which are not

nanomaterials, but are illustrative of potential environmental exposure concerns. Several recent studies measured the levels of PBDEs in dust in people's homes, airplanes, indoor air, and home electronics (Rudel et al. 2003; Stapleton et al. 2005; Wilford et al. 2005; EST Science News 2007a,b). These studies demonstrate that there is widespread exposure to some PBDEs from consumer and electronic products. As products are used, small amounts of coating wear off and enter the environment. PBDEs have been measured in high levels in human blood in the U.S. population (Schecter et al. 2005); they have also been measured in polar bears — who are not sitting on couches treated with flame retardant fabrics, but are exposed because PBDEs were released to the environment, and moved from North America and elsewhere to the Arctic regions. PBDEs are now banned, and it is possible in the foreseeable future that some nanomaterials could replace them as flame retardants. The point here is that it is necessary to test materials to see if they enter the environment, not simply to assume that they will not.

In 2007, in the inaugural issue of the journal *Nanotoxicology*, Maynard and Aitken summarized the work of many who are calling for new measurement approaches to characterize exposure for nanoscale materials. The state of the science is that there are few, if any, measurements of environmental exposure to engineered nanoparticles. Currently, many types of nanomaterials are now used in the environment, including nano-iron, nano-silver, and nano-cerium oxide, but there are no agreed-upon methods to analyze how these substances are entering the environment (Maynard and Aitken 2007). The following sections summarize what is known now about environmental exposures for some nanoscale materials.

5.5.1 Nanoscale Zerovalent Iron

Nanoscale zerovalent iron (NZVI) is being used at a number of hazardous waste sites to clean up chlorinated solvents that have contaminated ground water. The metallic iron is pumped into the ground, stimulating the breakdown of compounds that are in water below ground. Specifically, NZVI is introduced in the ground water to catalyze the removal of chlorine molecules from common solvents perchloroethylene and trichloroethylene (PCE and TCE). The dechlorination of these substances eventually breaks down the PCE and TCE to carbon dioxide. Many hazardous waste sites are contaminated with these chlorinated solvents that were once widely used for cleaning, degreasing, and other purposes, and which persist in the ground water. NZVI is accelerating the cleanup of these sites. NZVI has also been shown to immobilize arsenic, chromium, and lead, three highly toxic metals that have many industrial uses, which are also common at hazardous waste sites. In the cleanup process, as the NZVI particles oxidize and become rust particles, they reduce the contaminants in the ground water to forms that are less mobile and less hazardous.

From an environmental perspective, a concern is whether engineered nanoscale iron particles behave similarly to larger iron particles when

released to the environment. Iron is prevalent in the environment, making up about 5% percent of the earth's crust. However, iron generally occurs as minerals such as iron oxides and iron sulfides, not as pure metal. Zerovalent iron does not occur naturally. One study was located on the toxicity of NZVI, described in Chapter 6. Oberdörster et al. (2006b) showed that nanoparticles of iron have similar toxicity to larger iron particles. However, there is so much naturally occurring iron in the soil, rock, and ground water, it would be very difficult to detect nanoscale iron above these background levels.

NZVI has been shown to last as long as a year in ground water under certain conditions (Liu and Lowry 2006). However, the effectiveness of the NZVI is diminished by aging of particles, even during shipping and storage. NZVI is reactive and as it oxidizes, it releases hydrogen ions, which could create an explosion hazard if stored under confined conditions (Liu and Lowry 2006). There is little concern about hydrogen generation in water as an explosion hazard; it makes the water more acidic, but cannot build up as a gas that could explode. In addition, researchers at Carnegie Mellon University measured the behavior of a specific type of NZVI particle and determined that in the laboratory, they are magnetic and quickly stick to one another, within minutes forming particles that are no longer at the nanoscale. That is, the aggregates are larger than 100 nm (Phenrat et al. 2007). This happens more quickly when there are more iron particles. At lower concentrations, there is less aggregation, and the individual nanoparticles last longer. As larger molecules, NZVI cannot travel far in ground water, and become stuck between soil particles; they are also less reactive because the surfaces are stuck to each other, and thus cannot react with and reduce the chlorinated solvents.

These new data suggest that NZVI is not traveling far in the ground water. The implication is that researchers are now seeking ways to enhance the mobility of NZVI so that particles will last longer as nanoparticles, continuing to reduce the solvents, and will travel further from the point of origin to cleanup more pollution. As the performance of NZVI is enhanced, its potential to migrate in the environment also increases.

5.5.2 Cerium Oxide

As discussed in Chapter 3, cerium oxide nanoparticles are being used for diesel fuel applications. Already part of catalytic converters, nanoscale cerium oxide particles added to fuel improve burn efficiency, so the fuel produces fewer carbon particles, reduces particulates, and improves fuel economy (HEI 2001). There is a net benefit from reducing the overall number of particles associated with vehicle exhaust. There are many elemental components of particulates released from automobile exhaust. The Health Effects Institute (HEI) reports that currently the air concentration of cerium is less than 1 nanogram per cubic meter of air (<1 ng/m^3), but that model estimates suggest the concentration could rise to around 1 microgram per cubic meter (1 $\mu g/m^3$), 1000 times more (1 μg equals 1000 ng), if cerium oxide is added to fuel. While the current data do not suggest cerium oxide is toxic at these

concentrations, the issue still merits careful consideration because it would substantially increase the concentration of cerium oxide in the environment. Inhalation exposure might not be an issue, but it is unclear whether particles that land on soil could adversely affect the environment. This is how urban environments ended up with lead in soil, by adding it to fuel. A risk assessment would have to consider the multiple pathways of exposure to cerium oxide to fully grasp its potential impact.

5.6 Risk Assessments

Having surveyed some of the toxicity and exposure data for nanoparticles, let us now consider how these data can be used for risk assessment.

5.6.1 NIOSH — TiO_2

The National Institute for Occupational Safety and Health (NIOSH 2005) recently reviewed animal and epidemiological studies of TiO_2, but these primarily pertained to pigment-grade TiO_2, as manufacturing of ultrafine TiO_2 did not start until the 1990s. The draft document (NIOSH 2005) stated that tumorigenic effects of TiO_2 in rats "appear[ed] to be a function of particle size and surface area acting through a secondary genotoxic mechanism associated with persistent inflammation." The draft indicated that insufficient evidence exists to designate TiO_2 as a potential occupational carcinogen (cancer-causing substance), but noted concern about the potential carcinogenicity of ultrafine (nanoscale) TiO_2 if exposure levels are at the current occupational limits. According to the draft, studies in rats demonstrated a dose-response relationship for pulmonary effects when the dose of TiO_2 was expressed on the basis of surface area. Based on this information, a draft exposure limit of 1.5 mg/m^3 for fine (<2.5 μm) and 0.1 mg/m^3 for ultrafine (<0.1 μm, i.e., <100 nm) TiO_2 was recommended (NIOSH 2005).

5.6.2 The International Life Sciences Institute — Risk Sciences Institute Approach

At the request of the U.S. EPA, the International Life Sciences Institute — Risk Sciences Institute (ISLI-RSI) convened an expert panel, mainly of toxicologists, to develop a risk screening approach. The screening framework recommends that all toxicology work include detailed characterization of the physical and chemical properties of materials — nearly 20 types of properties — and then recommends *in vitro* tests ("in glass," as in a test tube) to be conducted in conjunction with *in vivo* (in whole animal) assays.

The reason so many physical and chemical properties are identified in the ILSI screening strategy is the poor current understanding regarding which

TABLE 5.2

Estimates of Particle Number and Surface Area per 10 μg/m^3 of Airborne Particles

Particle Diameter (μm)	Particle Concentration (#/cm^3)	Particle Surface Area (μm^2/cm^3)
0.005	153,000,000,000,000,000	12,000,000
0.5	153,000,000,000	120,000
5	153,000,000	12,000
500	153	120
5000	0.153	12

Adapted from Oberdörrster et al. 2005a.

of these parameters actually relate to toxicity. However, the work of the toxicologists on this panel has shown that the following parameters may be predictive of toxicity. The first is particle size and size distribution. It is important to know whether exposures are in fact occurring to nanoscale particles, and to characterize the range of particle sizes. Some studies have shown that upwards of 90% of particles thought to be at the nanoscale (<100 nm) aggregate to form particles larger than the nanoscale. But a small fraction of the entire distribution is free particles. As shown in Table 5.2, the number of particles varies greatly depending on the particle diameter, thus it is important to characterize the size and distribution for toxicity.

The shape of the particles could be important as well, because this could impact how the particles can move in biological systems. Shape is also an important parameter to describe, particularly for non-spherical particles; nanotubes, for example, can have any number of combinations of length-to-width ratios. The dimensions of other novel structures may have even more complexity. For example, they may be spirals or horn shapes, and these characteristics are important to describe when testing toxicity, since the results may be specific to the shape and are often compared across different substances and test systems.

The surface area of particles has been shown by many researchers to be an important predictive parameter of particles affecting toxicity. One group led by David Warheit of DuPont demonstrated that inhaling nanoscale titanium dioxide is not more toxic to lung tissue than inhaling larger particles of titanium dioxide, when considered on the basis of surface area rather than mass (Warheit et al. 2007). As discussed earlier, nanoparticles have much less mass compared to surface area than larger particles. This means that on a mass basis nanoparticles have much more surface area than larger particles, indicating surface area equivalents may affect toxicity.

The composition of the material is also significant. Carbon nanotubes, for example, can be grown from a number of substrates, and those substrates may contribute to toxicity, so it is important to know the type of substrate used and how much of that raw material is still present in particles.

The surface of nanoparticles may be quite reactive; therefore, characterizing the surface chemistry of nanoparticles is also recommended. The surface contamination and surface charge of the nanoparticles is also important. One reason is that the surface charge can affect whether particles can bind to or cross cell membranes. If the charge structure is unfavorable, there may be no interaction with cell membranes. Surface charge would also affect solubility of particles in different biological media.

Researchers have also demonstrated differences in toxicity based on crystal structure. For example, it has been shown that for titanium dioxide, the crystalline structure of anatase particles has greater catalytic activity than the rutile crystalline structure form (Sayes et al. 2006). Other parameters that may be important include how agglomerated (stuck together) the particles are. Nanoparticles tend to be very sticky — they will often form loose or tight bonds (generally referred to as *agglomerated* or *aggregated*, respectively). Agglomerated particles are sticky, in the way that dry laundry will stick together because of static cling. Aggregated particles are considered to be fused together, as if someone poured glue into the dryer before spinning the clothes. Agglomerated particles will be larger than free unbound particles, and probably will behave differently in the human body. It is unclear whether biological or other media can de-aggregate either the agglomerated or more tightly fused aggregated particles.

There is considerable uncertainty regarding the role of size of nanoparticles in toxicity. This topic has been considered by those participating in the voluntary standards community (discussed in Chapter 9) with respect to defining nanoparticles. Many want to limit the definition of a nanoparticle to one with at least two dimensions less than 100 nm. It is not clear yet that 100 nm has significant biological relevance. Some studies, already discussed, demonstrate size-dependent differences in behavior of nanoparticles between 25 nm particles and 100 nm particles, for instance (e.g., Hunde-Rinke and Simon 2006). However, from a biological perspective, 100 nm holds no special designation. It is not as if particles larger than 100 nm cannot be absorbed into the body. But for the branch of science now called nanotoxicology, there might be reason to exclude some particle size ranges from consideration in nanotoxicology studies. Actual size ranges of concern for specific effects are likely to be elucidated when comparative studies are conducted.

Other possible parameters that ILSI recommended measuring include: porosity; method of production; physico-chemical structure of the particles; preparation process; heterogeneity; prior storage; and concentration. It is interesting that concentration is listed last on the list. Normally, that is the only parameter one would measure in toxicology experiments. The detailed evaluation of particles may prove useful for other branches of toxicology. It may be helpful for understanding how substances interact with the human body to have detailed knowledge of the whole range of these parameters.

All of these tests represent the physicochemical properties that one should measure when planning *in vitro* or *in vivo* assays. As a screening strategy, the group at ILSI recommends *in vitro* assays before detailed *in vivo* assays,

which can be quite costly. They divided *in vitro* assays into cellular and non-cellular groups. Cellular assays are tests that generally occur in a cell culture, in a dish, where the cells are grown and then exposed to a particular material. The cells can be human or nonhuman cells and can be from any part of the body. They may be skin cells, cancer cells, blood cells, or lung cells; for these, specific assays are recommended.

In addition, the ILSI report recommends some non-cellular assays as part of the screening strategy. These can include interactions with specific proteins or enzymes, activation assays, as well as reactive oxygen species (ROS) assays. These tests might also be called *ex vivo* because they are outside of a biological system; they are intended to be predictive of effects that might occur in live cells or whole organisms. Recent work at UCLA has shown that *ex vivo* assays are not necessarily predictive of what happens in cells (Xia et al. 2006). However, the screening strategy was published before this work had been completed (Oberdörster et al. 2005).

Finally, the ILSI screening approach recommends two tiers of *in vivo* assays. Tier 1 assays are: evaluations for pulmonary, oral, dermal, and injection exposure, inflammation, oxidative stress, and cell proliferation. These endpoints have been commonly observed in tests with a range of nanoparticles. Second-tier evaluations are more complex evaluations of deposition, translocation, toxicokinetics, multiple exposures, reproductive effects, alternative model studies, and mechanistic studies.

Studies of deposition and translocation measure how much of inhaled particles will deposit in the lungs; whether inhaled particles can cross lung tissue, enter the bloodstream, and enter other tissues. Toxicokinetics describes the timing and pathways of the deposited particles and resulting effects.

Multiple exposures would consider a more realistic scenario where animals, including people, could be exposed to nanoparticles by many pathways. That is, if you are in a work environment where nanoparticles can enter the air, you can breathe them. But they may also settle out of the air onto surfaces such as table tops and chairs. So you may touch them with your hands or other body parts and they may be absorbed across your skin, or you might accidentally put your hands in your eye, mouth, or nose and ingest the particles via that indirect route. Studies of reproductive effects would look at what kinds of effects might occur from exposures in various parts of the reproductive system. Other endpoints are also important, including studies of neurological effects, immunology, and cancer.

The ILSI screening strategy is quite comprehensive although it focuses only on human health and toxicology, and primarily inhalation toxicology. The authors do point out that not all tests may need to be conducted for all materials, and that we may learn more about the relationships between the physicochemical properties and the endpoints to measure. But until we do, the characterization should be fairly broad. Unfortunately, much of the current approach to characterization involves optical methods; that is, using high-end microscopes to study particles. This can be problematic because different laboratories may have different equipment, different people may

interpret findings differently, and it is very difficult to be quantitative when using primarily qualitative, or visual, tools.

5.7 Summary and Conclusion

The complexity of issues to address in risk assessment for the broad class of nanomaterials and nanotechnologies currently in development requires a comprehensive approach. The ILSI framework not only includes the factors contributing to human health effects that need to be evaluated, but also ecological effects; and not simply the raw material, but the material as it is used, and as it may be transformed in the environment. This requires a detailed understanding of the behavior of materials in the environment. It requires adopting a life cycle approach to risk analysis, and it requires more focus on exposure assessment early in the evaluation process. Chapters 6 and 7 describe NANO LCRA and several other proposed frameworks for assessing and managing nanoscale materials across their life cycles.

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6

NANO LCRA — An Adaptive Screening-Level Life Cycle Risk Assessment Framework for Nanotechnology

Jo Anne Shatkin

CONTENTS

"Good risk assessment is essential for good risk management."

NSET, 2007

This chapter brings together many of the central concepts developed in the preceding chapters to arrive at the core theme of this book — adopting life cycle thinking and risk assessment for managing the hazards of nanomaterials and nanotechnology. Building on the basic understanding of risk assessment given in Chapter 2, it describes the concepts of adaptive management and screening-level analysis, and explains NANO LCRA, the proposed adaptive screening-level risk assessment framework that incorporates life cycle thinking.

NANO LCRA is based on adaptive management and involves revisiting the framework and reevaluating prior decisions with new information. The screening-level, or qualitative, assessment process is targeted to today's decision making, that is, in the current state of uncertainty about the environmental and biological behavior of nanomaterials. As with any

emerging issue, sound management is imperative, but there is too much uncertainty to devise science-based regulation. This framework provides a sound scientific basis for sustainable nanotechnology development.

Following the discussions in Chapters 4 and 5 of the state of the science, it is clear that the scientific understanding of nanomaterial behavior in terms of health and environment is in an early stage. It is not infancy because much of what has been learned about the behavior of other types of particles and chemical substances is applicable to nanomaterials, but it is not matured either, due to the complexities of atomic level effects with which health and environmental scientists have little experience. Nanoscience in relation to biological effects is so poorly understood that resolving key uncertainties will take time, experimentation, and deliberation, yet technology development is rapid and demands action now.

As we have discussed, nanotechnology is developing outside of a regulatory structure. It is, in fact, too early to understood how to regulate nanotechnology, what the potential effects are, and how best to manage them. The uncertainty in scientific assessment holds implications for managing the potential risks, such that definitive regulatory actions taken today may not be effective for the concerns that do emerge. That is, even if regulations could be implemented now, they may be ill informed. More likely, the process would take years to develop regulations governing nanotechnology in the workplace and in the environment. Nanotechnology risks need to be managed now. Hence, an adaptive approach, that is developed with the best available information, targeted to learning more and improving nanotechnology management, is the best path forward to protect health and the environment and allow the benefits of nanotechnology to be enjoyed today.

The level of knowledge about nanoscale material impacts might be compared to the experience of learning to ride a bicycle. In this comparison, the current state of knowledge might require training wheels. It is probably beyond a tricycle, but certainly not confidently rolling down a road. To relate this level of understanding to risk assessment is somewhat like the understanding one gains from a "screening-level" or "back-of-the-envelope" qualitative analysis. Full quantitative risk assessment is comparable to a cyclist clipping his feet into clipless pedals and racing with the peleton in the Tour de France (minus the transfusions) or at least to a club ride at sunrise. It is not that risk assessment is so complex, it is that the level of effort, knowledge, and experience required to conduct full risk assessments is much more extensive. In other words, it makes sense to learn how to ride a bike before attempting to race with the best of the best. An adaptive approach, an iterative analysis with increasing levels of understanding, skill, and quantitation, presents a path forward for evaluating and managing the risks of nanomaterials. This path allows adaptation to new information, decision making under uncertainty, and a manageable process for identifying and prioritizing concerns about health and environmental risks.

Identifying the potential implications in technology development and evaluating their likelihood requires both a risk-based approach, and life

cycle thinking. The adaptive life cycle risk assessment approach is founded in the use of science for environmental decision making. It is also inherently a "win-win" economically, environmentally, and socially, the so-called triple bottom line (Elkington 1998). The approach is also a proactive way to manage technology.

6.1 Adaptive Management for Nanomaterials Using Risk Analysis

The NANO LCRA framework applies *adaptive management* for nanomaterials; it adopts the tools of risk analysis and life cycle thinking to characterize the potential for exposure and risk to nanomaterials in specific applications. Adaptive management in this context means making the best decisions with the available information, ensuring that these decisions can be updated when new information becomes available, and ensuring that timely re-evaluations occur. Adaptive management *requires* building re-evaluation into the process. That is, conduct an analysis initially when available information may be scarce, with the intention that the results of this initial analysis will involve conservative and protective actions to manage any identified risks. This drives the need for further data gathering and analysis to better characterize the potential for human and environmental exposure and risk.

Adaptive environmental management integrates environmental, economic, and social aspects of complex issues, as an alternative to traditional, reactive management solutions. It represents an approach to managing complex systems with several key attributes relevant for nanoscale materials and nanotechnology. Designed for situations that are poorly understood and somewhat unpredictable, adaptive management identifies key uncertainties and conducts experiments to better understand and manage them. The main objective of adaptive management is to adapt and learn, improving the process or intervention. Responses are developed that represent opportunities to learn about uncertainty, and these responses are routinely revisited with the learning that has taken place. Conceived of in the 1970s as an approach for ecosystem management in forests and other complex systems, adaptive management is widely used in a range of situations with social as well as environmental complexity.

The concept of experimenting to learn about how to manage risk might seem disconcerting, but in fact this approach is fairly common. A problem is identified and evaluated, and a solution proposed, but often it is later learned that new problems arise from the solution, that in turn must be managed, and the initial solution also requires revision. Some argue that the world is so complex that introducing new technology is akin to conducting experiments that no one can fully grasp and manage (Giddens 1998). As a result, to

achieve a sense of control over the environment, many of us are preoccupied with calculating and managing risks (Beck 1998), which inherently is adaptive management.

The current situation with nanomaterials and nanotechnology is uncertain and complex, begging for solutions that use the best available knowledge to address risks, while continuing focus on learning about the key variables affecting exposure, toxicity, and risk. The ecological and societal impacts of technology result from diverse uses in consumer products that are used by many people, and ultimately disposed of in the environment. Dispersed not only in spatial terms, technology also evolves so quickly that its rapid obsolescence means more and more electronics enter the environment, and the technological impacts require nearly continual adaptation. Managing the human and environmental aspects of technology in an adaptive manner means that society as a whole can benefit from learning how best to manage technological risk, but empowers those who are preoccupied with understanding and managing risks to participate.

There is one aspect of adaptive management that is not well-suited to nanotechnology, that is, the spatial scale. In a global economy, with technology and nanomaterials being introduced across economic sectors and geographic boundaries, it is difficult to envision a global scale for adaptive management. Most effective environmental management occurs at a local or regional scale, where the key stakeholders and participants are committed to a solution because they are directly impacted by it. Adaptive management approaches for nanotechnologies might not be universal, and might be implemented differently for different sectors, allowing additional learning from the diverse implementation. Perhaps by the time most nanotechnologies achieve global integration, risk assessments for them will be fairly routine.

6.2 Screening-Level Risk Assessment and Adaptive Management

The philosophy for an adaptive framework incorporating life cycle thinking into risk assessment for nanotechnology is based on the view that an early *screening-level analysis* with considerable uncertainty and a lack of available data will have two valuable outcomes: it develops the information needed to make sound decisions; and also offers an opportunity to make decisions amid uncertainty. There are three unique components to the NANO LCRA framework: *adaptive management*, *life cycle thinking*, and *screening-level risk assessment*. The framework is applied as a screening tool to identify and prioritize potential risk concerns, and develop strategies for investigating and managing them further.

Before presenting a step-by-step explanation of the NANO LCRA framework, first we consider the rationale, main principles, and how such an approach came to be developed, including some of the significant issues it addresses for risk assessment of nanomaterials. While detailed risk analysis and life cycle impact assessments require a lot of data, for emerging contaminants the needed data are generally not available. Some argue that complete data sets are necessary before nanomaterials can be comfortably allowed into commercial products that will enter into the environment. It has been demonstrated that combining available information with professional judgment can be used to guide decision making and to prioritize the gathering of more complete information, sometimes called "back-of-the-envelope." An excellent reference is the book, *Consider a Spherical Cow: A Course in Environmental Problem Solving (*Harte 1998). Harte describes how solutions to complex environmental problems can be simplified by initial estimation. As suggested in the title, defining the surface area of a cow can be estimated by assuming it is spherical (Harte 1988). This approach is particularly valid under conditions of uncertainty. Conducting screening-level analysis does not suggest that the available information is adequate to answer all questions, but allows estimation to approximate the significance of potential impacts. Detailed quantitative estimates may not be calculable initially, but order-of-magnitude estimates may be, and this is often adequate for informing control strategies. Stepping through the analysis identifies what is unknown, and important to know, in terms of who may be exposed and how; how significant those exposures may be; and where in the environment concerns may exist regarding the presence of nanomaterials. In particular, it is clear from looking at a few examples that across their life cycle there may be limited or no exposure to nanoparticles or nanomaterials at certain stages. For example, manufacturing nanotubes in an enclosed process limits exposure to them. A screening-level analysis can help to document and identify which life cycle stages may be of concern and require further investigation, or management policies to prevent exposure. The screening-level approach of NANO LCRA adopting life cycle thinking into risk analysis helps to establish priorities for future work.

One key issue to address is how, indeed, a screening-level approach can satisfy the concerns of those who wish to adopt a precautionary approach; that is, conducting a full analysis of all aspects of a substance before it is developed into products. As Tukker points out, there is an inherent difference in philosophy regarding sustainability and the level of confidence in technology management, between those who prefer an analytic versus a precautionary approach (Tukker 2002). Adopting the NANO LCRA approach for risk analysis can address the concerns of these divergent views. The reason is that the initial screening provides some level of confidence because in situations of greater uncertainty, risk management and decision making will address the uncertainty by adopting more risk-averse measures. This approach motivates further actions to better characterize and understand health and environmental impacts.

To summarize, adopting a screening approach acknowledges that there is not enough information to make definitive determinations of the health and environmental risk associated with new materials and technologies, yet provides a clear path forward to incorporate the available information into risk management and decision-making. The available data is supplemented by adopting tools from *risk analysis* for addressing *uncertainty*. The *adaptive management* aspect allows learning from the analysis and allows decisions to be made that make sense today, allowing for the possibility that these decisions may need to be adapted as new information becomes available. *Life cycle thinking* means that unintentional releases and the potential for indirect exposures are broadly considered with reference to what is known from past examples. *Risk assessment* means formal consideration of both the likelihood and the significance of potential exposure.

Even without a quantitative evaluation a lot can be learned about potential risk to inform nanotechnology management going forward. Even when quantitative estimates of risk are made, they are just that — estimates — and they tend to be very conservative. By making assumptions to quantify risk, consistent procedures for evaluation allow characterization of new materials similar to substances with greater familiarity. Early consideration of the potential for exposure and risk will guide science to better understand the potential risks associated with nanomaterials.

6.3 NANO LCRA: An Adaptive Screening-Level Life Cycle Risk Assessment Framework for Nanotechnology

Figure 6.1 shows the proposed NANO LCRA framework for nanotechnologies. The concepts are quite similar to Comprehensive Environmental Assessment and the other assessment approaches described in Chapter 7 that conceptualize the life cycle of a product when conducting exposure assessment.

The key difference is that the adaptive risk framework is a screening tool to identify and prioritize key health and environmental issues, which may be applied at a very early stage of nanomaterial development when little information is available for risk assessment. The first application of the NANO LCRA framework identifies what information is really needed to make a better decision; however, it also allows early decisions to be made, with the intention that they will be revisited when more information becomes available. This dynamic approach is applicable to a broad array of hazards, materials, and technologies. In fact, there is nothing specific to nanoscale about it. It allows an evaluation to occur at any stage of the supply chain; it can be equally applied to a raw material producer, or to a downstream user of a product containing a nanomaterial in a composite, or both.

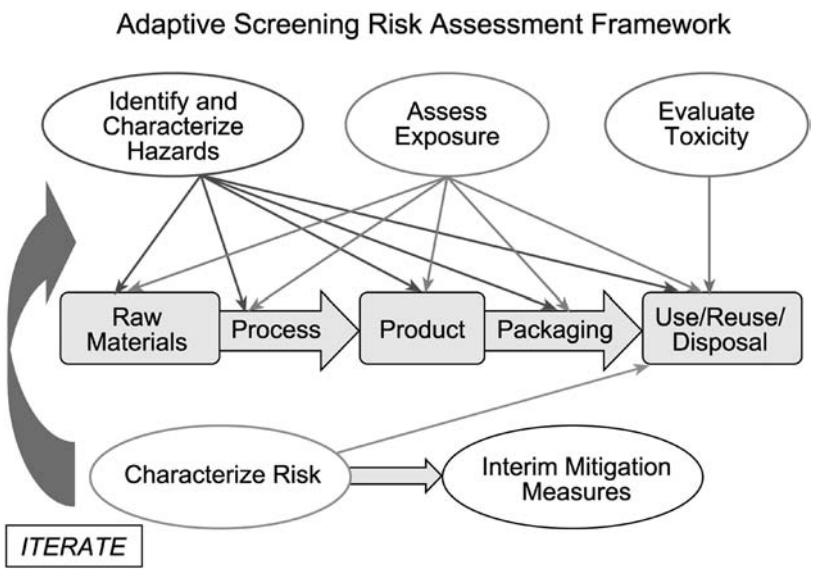

FIGURE 6.1
Proposed NANO LCRA framework. (See color insert following page 76.)

In a situation of significant data gaps, *exposure* is the place to start the evaluation. Of course understanding the toxicity of new materials is important, but time and significant resources are required to develop toxicity data. Considering the potential for exposure first makes sense. It means detailed toxicological evaluations for materials or products where exposure may be low or nonexistent (for example, when carbon nanotubes are embedded in a solid composite material) may not be required. Instead, resources are focused on toxicology evaluations in the life cycle stages when potentially significant exposure to nanomaterials may occur. Without exposure evaluation, however, these concerns will not even be identified. The analyses are systematic evaluations to ensure comparability of one type of material, or exposure, to another. The comparisons across materials, products, and technologies are the initial steps of quantifying exposure and risk.

Moving on now into the specifics of each stage of the process will help clarify the overall significance of adopting this adaptive approach. The idea is to step through the risk analysis process, and for each step of the life cycle to conduct a mini hazard assessment and an exposure assessment — the first two steps of risk analysis. These steps identify where to focus future activities in order to evaluate the toxicology and to conduct a risk characterization. The early evaluation can help to identify mitigation measures that ought to be used, but it also will pinpoint what information is missing in order to develop a more detailed characterization of risk. That information then becomes part of an adaptive approach.

6.3.1 The Ten-Step NANO LCRA Framework

1. Describe the life cycle of the product.
2. Identify the materials and assess potential hazards in each life cycle stage.
3. Conduct a qualitative exposure assessment for materials at each life cycle stage.
4. Identify stages of life cycle when exposure may occur.
5. Evaluate potential human and non-human toxicity at key life cycle stages.
6. Analyze risk potential for selected life cycle stages.
7. Identify key uncertainties and data gaps.
8. Develop mitigation/risk management strategies and next steps.
9. Gather additional information.
10. Iterate process, revisit assumptions, adjust evaluation and management steps.

The NANO LCRA framework starts at the beginning of the manufacturing process. If you are a raw material producer of nanomaterials, then the starting material may not be a nanomaterial. For example, if you manufacture carbon nanotubes, you may start with iron and carbon black as raw materials. Step 1 describes in detail the manufacturing process and life cycle of the product, from generation to ultimate disposal. The framework is flexible enough to evaluate products at any stage of the supply chain. The product may be a nanomaterial; the incorporation of a nanomaterial into a composite; the incorporation of a composite material into a product; a component of another product, such as a switch; or the final assembled unit, such as an airplane.

In step 2, the hazards associated with packaging the product are identified and characterized; and finally how the product is used, and how those uses might lead to new hazards when the product or material reaches its end of life, including how it is disposed of, or, if it is recycled. The potential hazards (e.g., contamination, reuse) associated with all of these steps are identified. Hazards might include: the presence of free nanoparticles, fire, explosion hazards, equipment failure, accidental or intentional releases of nanomaterials.

Step 3 conducts an exposure assessment looking entirely across the life cycle. First, exposures to raw materials are assessed; for example, is mining involved to obtain raw materials? How are the raw materials handled and managed once they reach a processing facility? Who might be exposed, how frequently, and how much? Is there no exposure to nanomaterials in the raw materials?

Next we look at the process of manufacturing a product: when and what types of exposure might occur? Can free particles be released to the air? Is the process entirely enclosed, so that no exposure to particles could occur, unless a problem arises? Does the process involve touching the material or otherwise coming into contact with it? Is a lot of waste material produced

that might be put in the trash or otherwise disposed of, outside of the facility? Does the process allow particles to be entrained into a ventilation system and released elsewhere?

The framework continues to step through the exposure scenarios that could occur once a product is produced. Next is to focus on the packaging step in manufacturing and evaluate whether exposures might occur. If the product is a powder, the packaging step might be the most significant. In some manufacturing designs for the packaging step, the only opportunity for exposure may be if the equipment requires periodic maintenance, or breaks and needs repairs.

With the first three steps completed, the life cycle, hazard assessment, and exposure analysis, step 4 evaluates which parts of the life cycle have the greatest potential for exposure and should be the focus of the product risk assessment. This requires careful consideration of all potential pathways and the likelihood that human or environmental exposure could result. Step 5 then identifies the available toxicology data to assess the types of potential adverse effects. As discussed in Chapter 4, little information is currently available about the levels of nanomaterials that may adversely affect health. The screening-level evaluation may identify some preliminary concerns, but may also include data gaps, particularly for specific routes of exposure, such as oral ingestion of nanoparticles.

Step 6 compares the toxicology data with the exposure and hazard data to characterize risk. It is likely because of data gaps that early evaluations will be more qualitative than quantitative in describing risk. One way to get a sense of the potential for significance of risk is to compare it to other risks, including alternative technologies and/or materials. Another is to obtain expert input regarding the potential risk. Another tool is to use bounding analysis, that is, using estimates or probabilistic tools to generate minimum, most likely, and reasonable high-end estimates (these are more relevant than "worst case" scenarios) of risk levels.

Step 7 evaluates the level of confidence in the assessment, by identifying key sources of uncertainty, and documenting the level of confidence in the results. Whether this is a quantitative exercise depends on the availability of data. With little data, it sometimes makes more sense to use "low-medium-high" as a scale describing the confidence of the assessment, the data themselves, and the weight of evidence generally. When more detailed information becomes available, the uncertainty/confidence assessment becomes increasingly quantitative.

Step 8 applies what is learned from the analysis to develop alternatives for how to manage the risks. Using information from the analysis, control measures may be developed. It is important to realize that as an adaptive management process, these may be interim steps, until more detailed information is developed. However, the management strategy is informed by the prior steps of the assessment. The analysis has likely identified some uncertain and crucial areas for further investigation. The management strategy

includes a plan for addressing the uncertainties, and this becomes a living document, that is, it is updated as the framework is reiterated.

With management/mitigation measures implemented, the last two steps reiterate the entire process. This may include gathering additional data, but certainly includes evaluating the efficiency of management efforts to mitigate risk, and also identifies the next set of priorities to be addressed. Some data gathering may take time, so appropriate intervals are set for iterating the life cycle risk analysis, and updating the mitigation measures in the management strategy.

Thus, having conducted a screening-level risk evaluation has helped to focus on the key exposure and risk issues of that particular material and/or technology and its life cycle. The process has identified the next steps, such as finding more information or implementing mitigation measures — for example, changing the packaging process to prevent exposure, or perhaps conducting toxicity evaluation for exposures at a particular life cycle step. With the additional information gathered, the steps of the NANO LCRA framework are revisited to evaluate the impact of the mitigation measures, which could indicate, for example, that the next greatest concern regards the raw materials, and identifies the next set of priorities.

The output of applying the framework initially will be more qualitative than quantitative in describing the potential risks. It will describe the identified stages of exposure to nanomaterials that might occur for the entire life cycle of a nanomaterial or nanotechnology. Using this qualitative approach creates a sound basis for decision making, and a set of data needs that require greater focus going forward to characterize the risk.

For example, a nanopowder has greater potential for inhalation exposure and also for dermal contact (by touching the powder) and ingestion exposure (by a worker or consumer accidentally putting contaminated hands in or near the mouth). A toxicology evaluation can then focus on those pathways and on the direct exposure to the powder. If toxicity information needed for evaluation is not available, the analysis has still identified an important next step for characterizing risk: that a more detailed evaluation of this particular exposure scenario is needed. That in itself is a significant finding — enough initial information to allow "thinking through" how to mitigate, or even prevent, exposure during that step. Thus, even in the absence of key information, the process still yields the ability to characterize risk and document the characterization for management options.

One of the benefits of conducting a screening analysis using the NANO LCRA framework is that it identifies the important information to document what is known, but also to learn what is not known and may require investigation in order to make sound science-informed decisions. Stepping through this process may lead to the discovery that potential exists for exposures that are unacceptable, even if these cannot be quantified. This may lead to changes in the manufacturing process or redesign, even before any equipment is purchased. As discussed in Chapter 3, that is also an important

finding and an important benefit (both environmental and economic) of using this framework.

The NANO LCRA framework has direct application to health and safety concerns. Applying this process of looking at the life cycle of a material considers health broadly, including occupational exposures, consumers, and health of the environment. Considering exposure first will help to identify hazards and assess exposures in a way that will elucidate safety concerns.

Another feature is that the framework leads to management decisions linked directly to the potential for risk. The rationale for taking certain actions over others is clearly identified. Whether this becomes the basis for a regulatory policy, a company policy, or a voluntary activity that can be used to certify technologies, this process demonstrates proactive management of risks, both within an organization and to stakeholders. It allows clear communication of efforts taken to mitigate risk, and the rationale for doing so. Further, because risks are assessed in real time, for novel materials early in their innovation process, adaptive approaches allow early decisions for managing risks based on sound science, even under conditions of uncertainty.

The NANO LCRA framework steps sequentially through processes across the product life cycle, evaluating risk at each step. It focuses on exposure potential, and addresses the "worst things first" mentioned at the beginning of the book. It allows prioritizing concerns. As an adaptive approach, it iterates new information and with changes to a process or product. It allows great flexibility in designing management systems to address potential exposure.

The NANO LCRA framework is transparent because it documents the assumptions and analysis and allows comparison of different products and processes amid uncertainty. During the research and development process, there is still an opportunity for testing alternative manufacturing methods that could be used when scaling up from research and development to manufacturing. Further, using the framework allows comparison of the types of environmental health and safety issues that would need to be addressed under alternative manufacturing scenarios; for example, evaluations to assess whether to capture nanomaterials in a liquid matrix or in an air filter, what types of management will be required for those materials in one media versus another, or whether a process can be designed to capture the materials for reuse versus disposal. Finally, the NANO LCRA framework offers a proactive, dynamic approach which because of its simplicity can be reevaluated regularly.

6.3.2 Examples using the NANO LCRA Framework

Some products are intended to create nanoparticle exposure during use, sunscreen for example. The active ingredient in sunscreen may be a nanoparticle that blocks ultraviolet rays from reaching the skin; thus, exposure is intended during use in this application.

In assessing product use, it is important to consider what happens to the materials in a product after its disposal. With drugs, for example, the

American Medical Association (AMA) used to recommend that when the course of treatment is finished, unused prescription drugs should be flushed down the toilet, to limit the potential for accidental exposures by others and thus prevent their consumption by people for whom they had not been prescribed. However, after pharmaceuticals go down the toilet or the drain, they can then flow into a wastewater treatment system, which is not necessarily designed to capture them. Thus, after the water is treated the drugs can be released into other water bodies. With a number of pharmaceuticals beginning to appear in water bodies, U.S. EPA has recently released guidance recommending that people dispose of their used prescriptions in the trash. A recent survey by the U.S. Geologic Survey measured a number of pharmaceuticals in streams and other water bodies downstream of wastewater treatment systems. It also measured substances such as caffeine that were clearly associated with human use (Kolpin et al. 2002). Thus, if nanomaterials are part of drugs, they too could be released into waters. Even if unused portions of prescription drugs are thrown into the trash, they can still enter the water cycle when excreted in urine or feces of the people using them.

Materials such as product packaging that are not necessarily recycled also go in the trash, and their ingredients can also make their way into the environment. Sometimes trash is incinerated, and materials can be released into the air or associated with the ash after burning. Trash that goes to a solid waste landfill can break down and release components into the environment via gases or liquids (leachate). Modern landfills treat the leachate, but it is currently unclear whether nanoparticles would be adequately captured during that treatment.

There are many other pathways for potential exposure. As discussed in Chapter 5, cerium oxide added to fuel could be released with engine exhaust. Putting silver nanoparticle coatings on fabrics in public areas will eventually release the silver to the environment during laundry, as fabrics break down or are discarded, or during reupholstering of furniture. Nanomaterials added to building materials for self-cleaning or antibacterial use, electrical conductivity, or for strengthening structures will most likely eventually make their way into the environment.

Many materials that we use now, particularly for food packaging, *are* recycled, and if these materials contain nanoparticles, what will be the fate of the nanoparticles when the material is recycled? What types of exposure could occur during recycling and in these materials' secondary uses? It is important during the use, reuse, and disposal steps of the analysis to determine how exposure to nanoparticles might occur.

This has all been fairly abstract thus far, so let us walk through a case study.

- Step 1: Describe the Life Cycle
  - A start-up company is located in a shopping mall with office space, two small labs, and warehouse space outfitted with an air handling system, several benches for mixing materials, and

several types of high-energy machines used for generating and processing nanoparticles. The main process uses a proprietary enclosed plasma arc process to generate nanoparticles of various metals. The product in fabrication is nanoscale iron particles. These are made from iron pentacarbonyl and argon gas. Iron pentacarbonyl is heated to become gaseous. The argon gas carries the iron pentacarbonyl to the high energy plasma, which cleaves the iron-carbon bonds and produces iron nanoparticles. The argon gas carries the iron nanoparticles to a collection chamber, which is surrounded and cooled by liquid nitrogen. The iron is reactive in air; that is, it very quickly forms iron oxide (rust), and the speed of this reaction can cause the iron to spontaneously combust, so argon gas continues to flow over it as it cools to keep oxygen out of the collector. The iron powder is kept under gas and transferred to a machine that condenses the powder to remove the space between the particles, and prevent them from aggregating into larger particles and from forming iron oxide. The surface of the condensed powders form a 25 nm thick layer of iron oxide. The pressed powder is used for treating ground water contaminated with chlorinated solvents.

- The powder is immersed in high purity water diffused with nitrogen, packaged in an airtight container, and shipped to the field under nitrogen gas. Upon arrival, the material is mixed with a dispersing agent and injected into the deep ground water through a series of airtight well encasements. The iron begins to travel with the ground water, and quickly breaks down the tetrachloroethylene and trichloroethylene (PCE and TCE), until it locates enough oxygen molecules to form iron oxide, which is poorly soluble and adheres to soil particles.

- Steps 2 and 3: Hazard Identification and Exposure Assessment
  - At the production stage, iron pentacarbonyl is flammable, and is used in a high-energy environment. The production of iron nanoparticles creates a combustion hazard; and if the iron particles spontaneously combust, they could break the glass container at the end of the column, releasing nanoparticles into the work area. The removal of the powder at the end of the process creates a hazard because it must be handled and could spontaneously combust. The packaging step requires manual handling of the powder on a bench, and so could include dermal contact with the powder, which could lead to inhalation or ingestion of nanoparticles if personal protective equipment is not worn properly. Although immersed, the iron nanoparticles could be released during transfer to the field. Field workers using the iron could

come in contact with the iron particles. The iron could travel far from the site underground once injected into ground water.

- Step 4: Identify the Life Cycle Stages for Risk Assessment
  - This step finds the highest potential for exposures are in the raw material stage, for iron pentacarbonyl, and the packaging phase, post-production, where significant handling of the iron nanopowder can lead to exposure. Accidental release from manufacturing process upsets, during shipment, and in the field are also exposure pathways of potential concern. The potential for environmental exposure when the iron is released into ground water requires evaluation.
- Step 5: Toxicology
  - Iron pentacarbonyl is highly toxic when inhaled, and can be absorbed through the skin. Information regarding effects associated with exposure to iron nanoparticles can be gleaned from studies of poorly soluble dusts, but there are few studies for iron dust only. One unpublished study suggested low toxicity of iron nanoparticles to one aquatic test species (Oberdörster et al. 2006). Potential secondary effects from the iron particles in ground water could go undetected, but may affect downstream species.
- Step 6: Risk Characterization
  - The synthesis process has both physical and toxicological hazards associated with the handling of iron pentacarbonyl and iron nanoparticles. The packaging step has potential for exposure to unbound nanoparticles, which may spontaneously combust. Field workers could be exposed to nanoparticles in preparing for deep well injection. There is potential for downstream environmental exposure from use of the iron nanoparticles.
- Step 7: Identify the Uncertainties and Important Data Gaps
  - Exposure levels in the packaging process are not measured, and health effects associated with those exposures are poorly characterized. The frequency and intensity of process upsets and accidental releases is a data gap to address. The behavior of the iron nanoparticles in ground water remains a key area of uncertainty. These data gaps can be addressed by adopting measures to mitigate the potential exposure, or by initiating studies to better characterize their potential significance.
- Step 8: Develop the Risk Management Strategy
  - Many steps must be taken to improve the safety of the manufacturing process, including encasing the equipment to limit injury

potential; working with iron pentacarbonyl in a ventilated environment, such as a fume hood; and building protective layers around the gas handling in and out of the plasma generator to avoid direct contact with the nanopowder. The packaging step needs to be part of the same enclosure, to prevent the possibility of spontaneous combustion and human exposure to the nanoparticles. Risks from field use can be mitigated through careful communication and worker training. Information on the behavior of iron nanoparticles in ground water was not located.

- Steps 9 and 10: Adaptive Aspects
  - Several unknowns require more detailed evaluation. Areas for further research include: inhalation, dermal exposure, and ecological toxicity of iron nanoparticles; particle concentration in workplace air; and the environmental behavior of nanoscale iron in ground water, particularly in the presence of solvents. Workplace enclosures should be installed, and the process revisited. Finally, as changes are implemented in step 8 the process is reiterated. Steps 9 and 10 require gathering additional information, iteration of the prior steps, and adjustment of the evaluation and management steps.

6.4 Summary

The NANO LCRA framework is an assessment and management tool. The NANO LCRA framework is iterative and adaptive, allowing decision making under uncertainty, and presents a path forward to address the uncertainties. It is a framework that applies now, to our current level of understanding for most nanomaterials, and can be broadly applied to any emerging substance. The novel aspects of nanomaterials require adaptive management — we must make decisions today, but today's decisions may not be in line with our thinking tomorrow. There is substantial overlap between the NANO LCRA framework proposed here and the frameworks discussed in Chapter 7, for understanding the occupational and environmental risks from nanomaterials.

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7

Alternative Approaches for Life Cycle Risk Assessment for Nanotechnology and Comprehensive Environmental Assessment

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CONTENTS

A number of parties have converged on the idea of integrating life cycle thinking and risk analysis as a path forward for evaluating nanotechnology risks. Several alternative frameworks have been proposed, and it is clear that life cycle thinking is an important attribute of substance and technology management amid uncertainty. Broadly considered, there is nothing specific to nanotechnology about the frameworks discussed in this chapter. Simply, they represent current thinking and may become broadly applicable for nanotechnology because no existing frameworks are adequate to address the breadth of concerns about impacts on health and the environment.

Analyzing and managing risks from materials, products, and technology across the life cycle represents a novel approach to sustainable materials development. Under the Toxic Substances Control Act, submitters of new substances must make preliminary assessments of the potential for persistence and bioaccumulation, along with other chemical property data, to look for early indications of persistent, bioaccumulative, and toxic compounds.

Under REACH companies must consider exposure scenarios for workers, consumers, and the environment. However, the approaches described here and in Chapter 6 incorporate life cycle thinking more broadly and explicitly. A necessary step is public vetting of the various frameworks and their implications, requiring broad participation in establishing how to adopt a life cycle risk assessment approach for nanomaterials and nanotechnology risk management.

7.1 Adopting a Life Cycle Approach to Risk Analysis

The idea behind this book originated in 2005, with Shatkin's work on the NANO LCRA framework, described in Chapter 6. That is, while the data needed for quantitative risk assessment are not yet available, the need for risk assessment is great, requiring an approach to evaluate what is known, and what needs to be known, to make decisions about how to manage the risks, prior to having data available to quantify them. Experience shows that "back of the envelope" or screening-level evaluation is a valid step before embarking on complex and detailed assessments.

Although it is difficult to pinpoint exactly where and when the idea to integrate LCA and RA first arose, an early focal point was the 2000 Society for Risk Analysis (SRA) Annual Meeting in Washington, DC. The meeting became the backdrop for interdisciplinary discussions between life cycle analysts and risk assessors to discuss common themes (Evans et al. 2002). This led to a series of papers published in the journal *Risk Analysis* (Volume 22 (5) 2002).

There have been broad calls for adopting a life cycle approach to nanotechnology (COM 2004; Sweet and Strom 2006; EPA 2007; Sass 2007). Shatkin first introduced the NANO LCRA framework for nanotechnology at the Foresight Institute Nanotechnology Conference, "Advancing Beneficial Nanotechnology," in October 2005 (Shatkin 2005), and later at the NSTI Nanotech 2006 meeting in Boston (Shatkin and Barry 2006), among other forums. At NSTI, three other presentations also described life cycle approaches to risk analysis for nanotechnology. At that time, Davis was developing a manuscript on comprehensive environmental assessment for nanotechnology (Davis 2007). The seemingly independent developments on LCA and RA spurred us to organize a symposium at the 2006 SRA Annual Meeting in Baltimore, to discuss the alternative frameworks and their applicability to nanotechnology. The broad and convergent interest in this approach suggests a correlative need to evaluate these and other frameworks to understand how to integrate life cycle thinking in a risk assessment. The frameworks themselves require research, evaluation, and public discussion and debate over

their implementation. The following is a brief summary of the life cycle risk frameworks presented there.

7.2 Society for Risk Analysis Symposium on Life Cycle Approaches to Risk Assessment of Nanoscale Materials

The SRA symposium was a forum to discuss alternative frameworks, the roles they might play in risk management of nanomaterials and nanotechnology, opportunities and research needs for their development as policy tools, as well as potential consequences of their introduction in voluntary and regulatory decision making processes. Building on the body of work developed at the 2000 SRA Annual Meeting, the symposium included invited presentations of recently proposed life cycle/risk assessment frameworks for nanotechnology under development across diverse organizations representing government, academia, legal, and risk/policy entities, and a collaborative chemical industry/NGO team. At a round table discussion following the presentations, speakers discussed ways in which a life cycle/risk assessment framework could inform risk management and regulatory decision making and the steps necessary for implementing such an approach.

J. Michael Davis, Senior Science Advisor from the National Center for Exposure Assessment at the U.S. Environmental Protection Agency, described his proposed *Comprehensive Environmental Assessment* (CEA) Framework that incorporates life cycle thinking into a risk analysis framework. Olivier Jolliet of the University of Michigan described a life cycle framework for nanomaterials that evaluates health and environmental risk. James Votaw of the legal firm Wilmer, Cutler, Pickering, Hale, and Dorr discussed life cycle thinking for legal decision making. Environmental Defense (ED) and DuPont described their joint framework, and Shatkin presented an adaptive risk assessment framework for management of poorly defined materials intended to identify and prioritize research.

Davis described CEA, a framework that combines the risk assessment paradigm with a product life cycle framework. The CEA approach expands on the exposure component of risk characterization (discussed in Chapter 2) by considering life cycle stages, environmental pathways, and transport and fate processes throughout product life cycle, comprising feedstocks, manufacturing, distribution, storage, use, and disposal (including reuse if applicable). Exposure is partly a reflection of product life cycle, transport and transformation, and exposure media, but goes beyond characterizing the occurrence of contaminants in the environment. Exposure implies actual contact between a contaminant and organisms, regardless of whether the receptors are biota or human populations. Among the many aspects of exposure characterization are routes of exposure (such as inhalation, ingestion,

and dermal absorption), aggregate exposure across routes (the multiple pathways and sources), cumulative exposure to multiple contaminants, and various spatiotemporal dimensions (e.g., people's activity patterns, diurnal and seasonal changes). These are linked with ecological and human health effects, which can encompass both qualitative hazards and quantitative exposure-response relationships. Also important are considerations such as analytical and measurement methods and control technologies. CEA is described in more detail in section 7.4.

Jolliet, one of the key developers of Life Cycle Impact Analysis through SETAC, discussed life cycle risks and impacts of nanotechnologies. Jolliet's framework adopts a life cycle perspective to analyze the trade-offs between risks and benefits of nanotechnologies, as a replacement for conventional technologies, focusing on the impacts on human health. A matrix approach is used to identify risks associated with nanotechnologies over the whole product life cycle (raw material extraction, manufacturing, use phase, disposal, and recycling). It looks at (a) the additional risks and benefits directly due to nanotechnologies, and (b) the indirect risks and impacts of nanotechnologies compared to (c) those avoided with conventional technologies, and identifies influence factors. A comparative risk model combines a multimedia model with pharmacokinetic modeling of nanoparticles, to analyze different nano-applications.

Votaw, a legal scholar, described an approach, "applying general 'life cycle assessment' concepts, … to identifying where the risks lie for a particular organization, and a practical approach to developing a legal risk management strategy for navigating these uncertainties until the potential environmental, health and safety risks, and related regulatory and business risks, are better understood" (Votaw 2006).

The SRA Symposium also included a presentation about the draft Environmental Defense DuPont "Nano Risk Framework." The ED DuPont framework is intended to help organize what is known; assess, prioritize, and address data needs; and communicate how risks are managed (ED DuPont 2007). ED and DuPont's framework is intended to be comprehensive. The framework is information driven, and considers product life cycle. The terms are different from CEA, but the life cycle stages are similar: material sources, production, use, and end-of-life disposal/recycling. A key feature is the development of base data sets at the outset. Five steps are outlined that include: (1) describing the material and its application; (2) profiling the material life cycle in terms of properties, potential safety, health, and environmental hazards, and opportunities for human or environmental exposure at each step of the product lifecycle; (3) evaluating risks, either with available data or by assuming the "reasonable worst case;" (4) assessing risk management options, including engineering controls, protective equipment, risk communications, and process or product modification; and (5) decide, document, and act (ED DuPont 2007).

At SRA, Shatkin presented the NANO LCRA framework and its application to two case studies described in Chapter 6. The following is an

overview of Shatkin's SRA presentation. Each word of the adaptive screening level life cycle risk framework conveys meaning. *Adaptive* means this approach utilizes adaptive management. *Adaptive management* is important when making decisions under uncertainty. The assumptions and decisions need to be revisited, particularly when new information becomes available. The framework uses a *screening-level* approach to inform decision making. It does not necessarily complete entire quantitative risk assessments at each step, an important aspect distinguishing this framework from others that have been proposed. *Risk assessment* means taking a stepwise approach, looking first at the potential hazards, then the potential exposure at each step of the life cycle. After this level of analysis, the need for information about toxicology can be considerably narrowed to the key pathways leading to human and ecological exposure, and information obtained about the specific health effects associated with these exposures. The available information is used to conduct an assessment, which may or may not be quantitative. Preliminary decisions can be made at this step about the immediacy of need for additional data, how to protect workers, and whether and what types of steps should be taken to protect product users and the environment.

7.3 Perspective on the SRA Symposium and Alternative Frameworks

Both the NANO LCRA and CEA frameworks focus on exposure assessment before considering the toxicology of nanomaterials, and both seek a transparent assessment process. The main differences between the frameworks proposed by Davis and Shatkin are that Shatkin focuses on a screening-level assessment that builds to greater levels of detail, for risk management decisions, using adaptive management. CEA is a risk assessment methodology that can also be qualitative and incorporate adaptive features and, because of its interdisciplinary nature, incorporates the collective judgment of a range of experts. Jolliet offered that industrial ecologists begin with a different frame in mind. They tend to focus on a broad range of outputs related to the use of water, energy, contribution to climate change, and impacts on ecosystems (such as eutrophication) in addition to toxicity, which focuses on cancer and non-cancer effects. The units of analysis, whether per mass of material or on the basis of annual use, affect the resulting rankings. ED and DuPont's joint framework is intended to be comprehensive. A key feature is the development of base data sets at the outset. Both Jolliet and ED DuPont approaches rely on significant data collection and analysis. CEA intends to be comprehensive without necessarily conducting all necessary research

upfront. NANO LCRA incorporates modeling and bounding analysis to characterize impacts.

The SRA symposium raised many good questions about how to incorporate life cycle thinking into risk analysis. An issue that arose in the SRA Symposium is that how one frames the problem determines the results of the process. The life cycle assessment process can compare risks across two different materials in units of health, environment, or energy, and how this is done can affect the results. For example, when in the life cycle of a nanomaterial is there potential for exposure to nanoscale particles? Again, how the problem is formulated affects the results. Regulators and other risk managers have not typically made risk management decisions based on the life cycle of a material — although increasingly they are considering the potential for substances to be persistent and bioaccumulative. Regulations typically involve decisions about a substance in a specific context, i.e., in drinking water, or a microbe in a food product or process. There is a need to evaluate how to accomplish the task of being comprehensive in assessing the risks of a substance or product, and to address what its meaning is in a risk management context.

Some issues arise with the ED DuPont nano risk framework. The first is that the framework as proposed requires such significant effort, it is difficult to imagine anyone except an organization with the resources of DuPont implementing it. For example, the ED DuPont framework includes evaluation of the risks at each stage of the life cycle for all products associated with a nanomaterial, across the entire supply chain. This suggests a complex, investigational approach for managing risks under uncertainty, in the absence of regulation. The framework also requires a significant level of expertise in many different fields. One could envision an engineer without training in toxicology or environmental science might try to do the evaluations and reach wrong conclusions about an environmental fate evaluation or the significance of a toxicology study. The ED DuPont framework requires a lot of upfront analysis in developing the base data sets, suggesting it may take a significant level of effort to develop the data for the analysis. It is unclear how these data relate to product development.

An interesting phenomenon happened after ED and DuPont released their draft framework for public comment in February 2007. In response, a group of about 20 non-governmental, public interest, and labor organizations published a letter responding to the framework, saying that because it was developed privately, it was invalid, and they would not acknowledge it by commenting on it. A coalition of non-governmental organizations, including the AFL-CIO, United Steelworkers of America, Friends of the Earth, Greenpeace, the International Center for Technology Assessment, and the Natural Resources Defense Council (NRDC) wrote an "Open Letter to the International Nanotechnology Community at Large," urging all to reject the "public relations campaign" (Coalition Letter 2007). In a press release, the coalition expressed concerns about the lack of broad participation in the framework development: "We strongly object to any process in which broad

public participation in government oversight of nanotech policy is usurped by industry and its allies" (Coalition Letter 2007). The coalition denounced the framework as "fundamentally flawed" because it was developed by industry and their allies without government oversight or public involvement. Their key concern was that the framework could become a voluntary approach, which could delay legislation and forestall public involvement. Shortly thereafter, NRDC produced their own analysis recommending a life cycle approach to evaluating the risks from nanotechnology (Sass 2007).

At the June 2007 public release of the framework, ED and DuPont presented a somewhat revised framework, concluding that in some situations, it was unrealistic to be quantitative and that one does not necessarily want to collect data in some situations. In fact, using the framework led to a decision by ED and DuPont not to go forward with an evaluation of one material because they could not obtain the base set of data (nanoriskframework.com).

Perhaps by the time you are reading this, another forum for public discussion of the various frameworks and how a life cycle approach to risk analysis could be adopted either on a voluntary or a regulatory basis will occur. Developing a new approach to managing the risks of new substances requires significant discussion and communication. Therefore, it is disappointing to see the negative reaction to the ED DuPont framework, which said that "the DuPont-ED proposal is, at best, a public relations campaign that detracts from urgent worldwide oversight priorities for nanotechnology…" (Coalition Letter 2007). An alternative view is that these two organizations used their collective extensive resources to define for them what information is needed to make sound decisions for managing nanotechnology risks in the absence of regulation. It is to their credit that ED and DuPont put up their own resources and put the framework in the public domain for debate, discussion, and potential adoption.

The positions of some non-governmental organizations regarding nanotechnology raise serious concerns about the potential for using a science-informed approach in environmental decision making. If there were a clear path to regulation, and it were clear that regulating nanotechnology now would improve public health and the environment, governmental colleagues in a regulatory role would be working diligently toward this end. In fact, many health and environmental organizations with regulatory responsibilities have reported on internal evaluations regarding whether the new regulations are needed for nanotechnology (EC 2007; EPA 2007; FDA 2007; Environment Canada 2007). If new regulations are necessary, the rule-making process generally requires years of development. In the interim, it is imperative to be managing risks, and voluntary approaches are an important step toward that management. It is greatly hoped that some integration of the frameworks discussed here will occur, which can be adopted as tools for transparent evaluations of nanomaterials and nanotechnologies by developers, users, and risk managers in the public and private sectors, and that these evaluations can inform science-based

sustainable technology development and management. In the next section, CEA is discussed in detail.

7.4 Comprehensive Environmental Assessment

The idea of Comprehensive Environmental Assessment (CEA) was first developed in reference to fuels and fuel additives (Davis and Thomas 2006), although its applicability to other technological issues, including nanotechnology, has been apparent (Davis 2007). Its origins in relation to fuels/fuel additives (F/FAs) owes a great deal to the Alternative Fuels Research Strategy (U.S. EPA 1992) that was developed by the EPA's Office of Research and Development to lay out a framework for assessing the benefits and risks of various F/FAs. In essence, both the Alternative Fuels Research Strategy and the CEA approach combine a life cycle perspective with the risk assessment paradigm (described in the following).

The advantage of a life cycle perspective is that it allows a broader, more systematic examination of the trade-offs associated with a product. This point is well-illustrated by the case of methyl tertiary butyl ether (MTBE), a fuel additive that has been widely used to increase the oxygen content and octane number of gasoline. As discussed in Chapter 3, during the 1990s, MTBE use grew dramatically in the United States mainly in response to provisions in the 1990 Clean Air Act Amendments that called for the use of oxygenates in gasoline to address certain air quality problems. Although MTBE was at one time used in approximately one third of U.S. gasoline, its use declined precipitously because of concerns about its potential to contaminate water resources when leaking from underground fuel storage tanks (USEPH 1998; USEPH 1999). Thus, a product that was intended to improve air quality ended up being unacceptable due to water contamination issues.

The Alternative Fuels Research Strategy (U.S. EPA 1992) presciently warned about potential problems with MTBE (and a related oxygenate, ethyl tertiary butyl ether [ETBE]) when it stated: "Compared to gasoline, the ethers MTBE and ETBE have relatively large aqueous solubilities and would likely leach more rapidly through soil and groundwater. Also, limited data suggest that ethers may be persistent in subsurface environments." And, "Very little is known about emissions and releases from MTBE and ETBE storage and distribution, making this area an appropriate target for research. Effects on existing equipment and controls…need to be evaluated" (U.S. EPA 1992).

As it turned out, the propensity of MTBE in gasoline to leak from underground fuel storage tanks and thus foul groundwater proved to be the Achilles heel of this product. But correctly anticipating this problem was not a fluke or coincidence; rather, it was the result of a collective effort by EPA scientists to think through various implications of MTBE and other F/FAs in relation to the entire life cycle of the fuels, not just their intended end use.

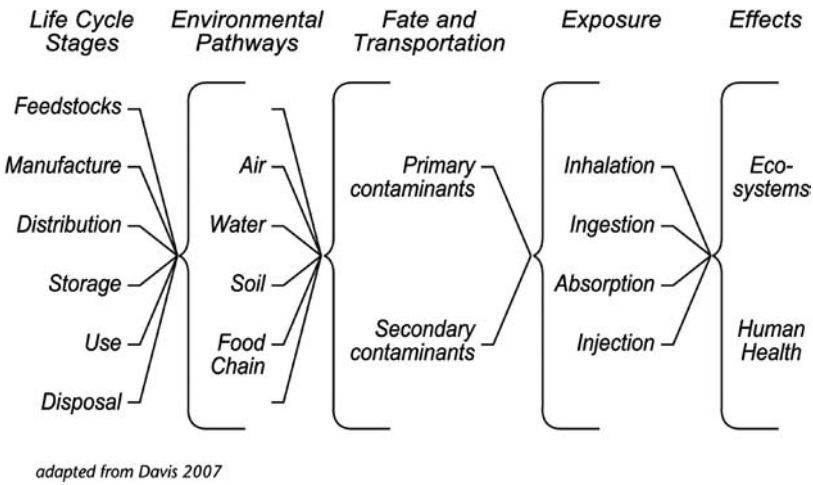

FIGURE 7.1
Comprehensive environmental assessment framework. (Adapted from Davis 2007). (See color insert following page 76.)

The CEA concept extends and formalizes the approach that was used in the Alternative Fuels Research Strategy.

7.4.1 Features of Comprehensive Environmental Assessment

The CEA approach, shown in Figure 7.1, is an expansion of the basic risk assessment paradigm. It encompasses identification of both human health hazards and ecological stressors, but it also elaborates the exposure component of risk characterization. First, various stages of the product life cycle are considered. Typically this would include feedstocks, manufacturing, distribution, storage, use, and disposal/recycling. At each of these stages some potential may exist for releases/emissions of materials into the various environmental media (air, water, soil, and food web). Of interest here are the primary materials as well as by-products such as manufacturing waste. Both primary and secondary contaminants may undergo transport and transformation processes, which in turn may yield additional by-products. Aggregate and cumulative exposure of biota and human populations would thus potentially involve multiple environmental media and pathways, with multiple routes of exposure to not only the primary material but secondary by-products.

Adequate empirical data may not exist for such complex characterizations of exposure. Again, *as with the NANO LCRA framework, in lieu of quantitative information, the CEA approach relies on qualitative characterization*. Indeed, the use of qualitative information distinguishes CEA from the much more quantitative analyses generally employed in life cycle assessment (LCA) and life cycle impact assessment (LCIA). Thus, even if numeric estimates of material

releases/emissions are unavailable, it should be possible to describe such contamination in qualitative terms.

The importance of doing this is illustrated by the statements about MTBE quoted from the Alternative Fuels Research Strategy (EPA 1992). Even though no quantitative estimate of the likelihood of MTBE leakage and water contamination was feasible at that time, the qualitative potential was at least a warning signal that could have resulted in closer monitoring, better control technology, or other steps that could have mitigated the problem of water contamination. The fact that such preventive actions did not occur is not an indictment of the ability to anticipate potential problems, as much as a lesson to risk managers to heed the insights of technical experts in their attempt to think through the environmental implications of a new technology.

Reliance on collective judgment is another distinguishing feature of the CEA approach. Given the complexity and lack of data on the health and environmental implications of nanomaterials, it is clear that no single individual or even small group of persons can have the breadth of knowledge needed to consider the many facets of a CEA of nanomaterials. Instead, an array of technical experts and stakeholders is needed to support a CEA. It is also important that the knowledge and judgments of these individuals be tapped in a structured manner. A "free for all" discussion does not provide as much benefit as formal, controlled discussions under the leadership of trained facilitators using techniques such as expert elicitation and multi-criteria decision analysis.

7.4.2 Illustration of CEA Applied to Selected Nanomaterials

The importance of the product life cycle is quickly evident in considering the potential impacts of a nanomaterial such as titanium dioxide (TiO_2), which is used in numerous applications ranging from coatings to water treatment agents and in closed industrial settings to general consumer products. The opportunities for exposure to TiO_2 are likely to be quite different, depending on whether or not the substance is tightly bound in a matrix. For example, TiO_2 used in light-emitting diodes would appear to pose less potential for dispersion in the environment than TiO_2 used as a water treatment agent. As a water treatment agent, there could be several opportunities for a powder of nanoscale particles to be released to the environment subsequent to manufacturing, including spillage during distribution, storage, and use. In addition, differences in manufacturing processes have been found to yield different physical and even toxicological properties of nominally equivalent nanomaterials (Dreher 2004). Thus, to evaluate the full range of potential ecological and health impacts associated with any given nanomaterial, it is necessary to consider the broader life cycle context for the material in question.

Using water treatment applications of nanoscale TiO_2 as an example, the product life cycle begins with the feedstocks from which the material is produced. Either titanium chloride or titanium sulfate can serve as feedstocks for producing nano-TiO_2, with the possibility of some contamination of the

end product related to these respective compounds (e.g., chlorine contamination of TiO_2 produced from $TiCl_4$). As part of a CEA, one would want to consider the potential for environmental releases of contaminants related to feedstock procurement and processing. Although this may not necessarily pose a significant issue in the case of feedstocks for nano-TiO_2, it is conceivable that other types of nanomaterials such as cadmium (e.g., in quantum dots) could be more problematic in this regard. This would depend in part, however, on the magnitude of feedstock use for nanoscale material production. For example, if the mass of nanomaterial-related feedstock is trivially small in relation to use of the same feedstock for bulk products, then the differential in environmental contamination from the feedstock for nanomaterial production would presumably be correspondingly small.

Manufacturing of nano-TiO_2 may be accomplished by various processes, including hydrolysis of a sol-gel (a solution of suspended colloids which forms a gel) or solution of titanium sulfate or, for larger scale production, chemical vapor deposition. The latter may in turn involve a variety of methods for vapor generation, but whether these different methods yield different physical or toxicological properties is unknown. Post-production processing of the materials, e.g., through use of sonication, a technique using ultrasound waves, or surfactants, to achieve or maintain nanoscale properties of the particles, could introduce yet another variable affecting the characteristics of the end product. Although worker exposure to a nanoscale product is the most salient concern, whether by inhalation, dermal absorption, or ingestion (e.g., resulting from hand-to-mouth activity), exposure to waste by-products associated with the manufacturing process should also be considered as part of a CEA evaluation. In addition, releases of material, both the primary product and waste by-products, outside the confines of a manufacturing facility need to be included in the scope of a CEA.

Distribution of the manufactured product involves packaging and transportation of the material. In the case of nano-TiO_2 used for water treatment, it appears that one commercial form of the product may be shipped as a powder in 10-kg "multilayer ventilated paper bags, equipped with an additional polyethylene lining when required" (Degussa 2007). This raises questions about the potential for accidental as well as routine spillage during packaging and subsequent transport of the material, with implications for workplace as well as broader environmental contamination. Similar issues would apply to product storage, with added concerns about the breach of packaging or containment material by vermin. The latter scenario would have possible relevance to wider environmental contamination through introduction of the material into the food web.

Nano-TiO_2 can be used in various ways as a water purification agent, e.g., to inactivate bacteria or a means to remove arsenic from water by converting arsenite [As(III)] to arsenate [As(V)]. These differing uses could have different implications for releases to the environment. However, assuming the product is mixed with water as a slurry (other scenarios are possible), one could envision the release of particles to air in the micro-environment as the

powder is being prepared for mixing and/or is actually being mixed with water. After a slurry is formed, the particles could behave in various ways, but assuming the particles are not destroyed by the water treatment process itself, some portion of the particles might remain in solution in the treated water. Another possibility is that a portion of the nano-TiO_2 could settle with floc (the suspended water treatment chemicals) in the sedimentation stage of water treatment and be subject to removal as sludge.

The disposal of sludge created in the water treatment process could follow several environmental pathways, including landfills and land applications. The latter conjures scenarios such as application to land used for growing crops, grazing animals, recreational uses such as parks, and numerous other uses that could pose direct and indirect opportunities for exposure of humans and other biota. Transport and transformation processes could also come into play through surface runoff, plant uptake, and a host of other conceivable events.

The previous discussion highlights some examples of points that warrant consideration in a CEA of nanomaterials, but in no way does justice to the complexity of the exposure component of such an assessment. For example, it is important to recognize that exposure may be both cumulative and aggregative. *Cumulative exposure* refers to the multiple contaminants, including waste by-products and secondary transformation products that could be associated with a given nanomaterial such as nano-TiO_2. *Aggregate exposure* refers to the multiple environmental sources, pathways, and routes through which exposure to a nanomaterial might occur. For example, given that nano-TiO_2 may be found in various consumer products such as toothpaste, sunscreen lotions, cosmetics, foodstuffs, etc., any exposure to nano-TiO_2 in connection with its use as a water treatment agent should be understood in relation to the total potential exposure to nano-TiO_2 across sources, pathways, and routes. Further complexities arise when time and activity patterns of exposed organisms are considered.

Exposure characterization provides a context and premise for considering the effects of nanomaterials on both ecological receptors and human populations, for without exposure there can be no effects. As discussed in Chapter 5, with regard to ecological effects, some studies using standard testing assays indicate that nano-TiO_2 may be toxic to water fleas (*Daphnia magna*), a key aquatic indicator species (Lovern and Klaper 2006; Wiench et al. 2007). Also, nano-TiO_2 has bacteriocidal properties (Coleman et al. 2005; Rincon and Pulgarin 2003; Kuhn et al. 2003), which may be desirable under controlled conditions but undesirable if beneficial bacteria in the environment are affected. Such effects may be modulated by various factors, including particle size (Hund-Rinke and Simon 2006) and material preparation (Lovern and Klaper 2006). It also appears that nano-TiO_2 can affect the uptake of other substances. As described earlier, Sun et al. (2007) found that As(V) strongly binds to nano-TiO_2 in water and that the presence of nano-TiO_2 more than doubles the uptake of arsenic in carp. Although toxicity was not assessed in that study, the increase in arsenic uptake alone suggests that interactive/secondary effects warrant careful attention as part of a CEA of such nanomaterials.

Information on the health effects of nano-TiO_2 is not as plentiful as one might prefer, but it is growing and can only be highlighted here to make a few general points. A key point is that extrapolation from bulk or microscale TiO_2 to nano-TiO_2 is inadvisable, given the notable differences in physicochemical properties of nanoscale and microscale TiO_2. Oberdörster et al. (1994) observed differences in particle retention, translocation, pulmonary inflammation, and impairment of alveolar macrophage function between nanoscale (ultrafine) and microscale (fine) particles of TiO_2 after 12 weeks of inhalation exposure in rats when compared on the basis of the mass of the dose. However, when compared in terms of total particle surface area (given that nano-TiO_2 has a greater surface area per mass than microscale TiO_2), a linear dose-response curve was apparent for the nano-TiO_2. Other studies have demonstrated that surface area may account for differences in respiratory toxicity effects between nanoscale and microscale TiO_2 (e.g., Bermudez et al. 2004; Warheit et al. 2007). However, other factors, including surface coatings or contamination, surface charge, and primary particle size, may also contribute to toxic properties of nano-TiO_2 (Warheit et al. 2007; Kreyling et al. 2002). In addition, some high-dose respiratory effects in rats may have been confounded by particle overload due to species differences in lung clearance mechanisms and thus not be representative of effects in humans under occupational or general environmental exposure conditions (Bermudez et al. 2002, 2004).

Data for other target organs are quite limited, especially for reproductive, developmental, and immunological endpoints. However, some information indicates that nanoparticles such as nano-TiO_2 may cross the blood–brain barrier, be taken up in the brain, and induce certain effects in brain cells (microglia), at least *in vitro* (Long et al. 2006, 2007). In some cases, transport to the brain may occur directly via the olfactory nerve (Oberdörster et al. 2004). As with other nanoparticles, oxidative damage appears to be a common mechanism of toxicity associated with nano-TiO_2 (Long et al. 2006, 2007; Xia et al. 2006).

The available data do not appear to be sufficient at present to derive quantitative hazard assessments for nano-TiO_2 or for nanomaterials in general. However, the above highlights of effects information for both ecological receptors and experimental animal subjects suggest that assessments may soon be feasible, if research is targeted in a manner to yield clear indications of dose-response (stressor-effect) relationships. It is important to keep in mind, however, that a full comprehensive environmental assessment requires a broader consideration of the indirect as well as direct impacts associated with nanomaterials such as nano-TiO_2.

7.5 Summary

Several alternative frameworks for evaluating the risks from nanomaterials and nanotechnologies across their life cycle have been proposed. While each is proposed specifically to deal with the unique challenges of substances at

the nanoscale, there is little in any of the frameworks that is uniquely relevant for nanotechnology. In other words, adopting life cycle thinking into risk analysis could be broadly applicable to managing the potential risks from many substances and products. Each of the frameworks described provides key information that can be used for decision making and risk management under uncertainty. This chapter broadly considered risks from occupational and environmental exposures. In the remaining chapters we explore the current state of practice and international efforts to address occupational and environmental risks issues.

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8

Current and Proposed Approaches for Managing Risks in Occupational Environments

Brenda E. Barry

CONTENTS

This chapter focuses on a vitally important topic: current efforts and future directives to protect workers from health hazards that may result from handling and managing nanomaterials in occupational settings. National and international governmental agencies, companies, and research organizations increasingly are recognizing the clear advantages of taking proactive steps — both to understand the potential adverse health consequences of nanomaterials, and to minimize the potential hazards from nanotechnology and nanomaterials in occupational environments (National Nanotechnology Initiative 2006; OECD 2006).

An obvious benefit of this approach is avoiding the familiar history of identifying the negative health and environmental impacts of industrial and commercial materials only after years of their extensive production, use, and release into the environment. A few notorious examples from the latter half of the twentieth century include asbestos, lead (discussed in Chapter 3), silica, and a variety of toxic solvents.

Nanomaterials have unique mechanical, electrical, catalytic, magnetic, and imaging properties that differ dramatically from the same elemental materials in bulk form. These properties, some of which have been described in earlier chapters, provide nanomaterials with numerous novel applications for products in the commercial, medical, military, and environmental fields. However — in keeping with the major theme of this book — recognition of these advantageous properties must be counterbalanced with efforts to understand whether engineered nanomaterials present new and unique risks for the health and safety of workers, and whether the potential benefits of nanomaterials can be achieved while minimizing the possible risks.

Although a general consensus exists regarding the importance of identifying potential occupational hazards for nanomaterials, the financial impetus and commitment of resources to support this initiative to date have been inadequate, compared to those directed toward nanomaterials research and development efforts. For example, although $32 billion worth of products incorporating nanomaterials were sold in the U.S. in 2005, funding for nanomaterials research and development through the National Nanotechnology Initiative (NNI) dwarfs funding to evaluate nanomaterials health and environmental risks — $1.3 billion versus $31 million (Maynard 2006).

As noted by Maynard and colleagues (2006), the risks presented by not understanding or identifying the potential hazards of nanomaterials are numerous. They include unanticipated health effects and diseases from nanomaterials exposures among workers and the general public, fears and the loss of confidence among the public regarding the use of products and materials containing nanomaterials, and finally, the financial costs of liability and litigation due to personal as well as environmental exposures. This chapter describes the challenges to understanding the potential health

hazards of nanomaterials for workers as well as current initiatives and directions for efforts to address this issue.

8.1 Current Concerns about Occupational Exposures to Nanomaterials

Linkage of the word *engineered* to the word *nanoparticles* creates the essential distinction that separates these particles from particles of similar size that are naturally produced or manmade, such as those in emissions from forest fires or motor vehicles. The word engineered reflects that the atomic components were intentionally combined to create nanomaterials with the unique properties noted above. However, these combinations can produce materials that have unpredictable properties regarding their interactions with biological systems and potential health impacts not only for workers, but also the general public and the environment.

As discussed in Chapter 5, the elements of a research screening strategy to understand the potential health effects from exposures to the different types of nanomaterials have been described (Oberdörster et al. 2005b). The authors note that a number of physiochemical properties of nanomaterials are likely to be important in understanding their toxicity, including particle size and size distribution, agglomeration state, shape, crystal structure, chemical composition, porosity, as well as surface area, charge, and surface chemistry. The screening strategy proposes a comprehensive array of *in vitro* and *in vivo* assays and a two-tier approach for *in vivo* studies. These types of studies are essential for evaluating the mechanisms of action and biological effects of nanomaterials on cells and tissues under controlled conditions, and for understanding how the results may relate to possible adverse health effects of worker exposures to nanomaterials.

8.2 A Framework for Evaluating Current Concerns about Occupational Exposures to Nanomaterials

A recent report from the National Institute for Occupational Safety and Health (NIOSH) in the U.S., *Progress toward Safe Nanotechnology in the Workplace* (NIOSH 2007), provides an excellent framework for outlining the broad categories of concerns regarding worker exposures to nanomaterials in occupational settings. This framework generally follows the elements of classical risk assessment (described in Chapter 2, and related to nanotechnology in Chapters 6 and 7) and allows a stepwise examination of the different issues

related to occupational concerns. Several steps also highlight significant challenges in approaching/conducting risk assessment for nanotechnology overall. The elements of this framework, with a focus on worker exposures to nanomaterials, are summarized in the following sections.

8.2.1 Hazard Identification

The first step of the framework is hazard identification, a procedure that identifies those conditions and scenarios that may result in worker exposures to nanomaterials. The potential hazards from nanomaterials can include not only direct and indirect exposures to nanomaterials, but also safety hazards, such as fire and explosions, that may occur while managing and handling these materials.

The three primary routes of exposure examined by both toxicologists and industrial hygienists serve as the starting point for identifying potential health hazards of nanomaterials in the workplace. These exposure routes are identical to those for chemicals and dusts, and include inhalation, skin or dermal contact, and ingestion. A crucial point is that, although classical toxicology approaches can be appropriately applied to evaluate risks from exposures to chemicals and dusts, they may not be applicable to nanomaterials. The activity and fate of nanomaterials once in the body likely depend as much on their shape and electrical charge characteristics as on their chemical composition.

To specifically address the occupational, health, and environmental concerns related to nanomaterials exposures, a new area of toxicology, termed *nanotoxicology* (Donaldson et al. 2004; Oberdörster et al. 2005a) has emerged. Nanotoxicology can be defined simply as safety evaluation of engineered nanostructures and nanodevices, and as the science that deals with the effects of nanomaterials on living organisms. The goal of nanotoxicology research efforts regarding worker concerns is to identify whether or not those who manufacture nanomaterials as well as those who produce products incorporating nanomaterials are at risk for adverse health effects.

Recent research studies to understand the potential adverse effects of exposures to engineered nanoscale materials have revealed some interesting and unexpected results about the potential hazards of nanomaterials (NIOSH 2007). Due to their unique properties that operate at the atomic level, some nanomaterials behave differently in biological systems than their bulk counterparts. The large surface area of nanomaterials relative to their volume has been linked to their increased reactivity. Results from *in vivo* studies have indicated that some inhaled nanoparticles can enter the blood stream and translocate to other organs (Oberdörster et al. 2005a; Borm et al. 2006).

Other investigators have reported that nanomaterials experimentally introduced into the lungs can cause inflammatory and fibrotic changes (Shvedova et al. 2005; Warheit et al. 2004). *In vitro* studies to understand the dermal effects of nanomaterials have indicated that multi-walled carbon nanotubes, fullerenes with modified surfaces, and quantum dots can penetrate intact

skin and produce cytotoxic and inflammatory responses (Monteiro-Riviere et al. 2005; Ryman-Rasmussen et al. 2006). Some investigators have also suggested that long, thin, carbon nanotubes have the potential to behave like asbestos fibers in the lungs (Donaldson et al. 2006), while others have linked the small size of nanomaterials with the ability to evade the respiratory defense mechanisms and to pass through the thin walls of the alveolar region of the lungs, into the blood stream and on to other organs (Borm and Kreyling 2004).

This latter observation has also raised concerns that nanomaterials may accumulate in biological systems, termed *bioaccumulation*. This brief summary of recent unpredicted research findings regarding the activity of nanomaterials in biological test systems indicates the importance of minimizing or eliminating worker exposures to nanomaterials. Further discussion of these findings and their implications were presented in Chapter 4.

With regard to safety hazards that may be associated with handling and management of nanomaterials in the workplace, NIOSH (2007) notes that little information is currently available regarding the potential fire and explosion dangers and catalytic reaction hazards of nanomaterials. The fire and explosion hazard concerns emerge from the small nanomaterials particle size that reduces the minimum ignition energy and increases their combustion potential. With regard to catalytic reaction hazards, although nano-sized materials and porous particulates have historically been used to advantage as catalysts, engineered nanomaterials may have unpredicted catalytic potential that may lead to increased fire and explosion incidents.

8.2.2 Exposure Assessment for Nanomaterials

The objective of the exposure assessment phase of the NIOSH strategy is to quantify exposures to nanomaterials under actual work conditions. In this way, the dose-response information obtained from the *in vitro* and *in vivo* research studies with nanomaterials can be linked to actual nanomaterials measurement data, and inferences can be drawn about the possible adverse health impacts of worker exposures.

As in the hazard identification step, exposure assessment also highlights challenges in applying risk assessment for nanotechnology. Although recognizing potentially hazardous conditions for exposures to nanomaterials can be straightforward for trained health and safety specialists, nanomaterials present unique challenges to traditional exposure assessment techniques. Traditional mass and bulk chemistry methods that collect particles on filters for evaluation of airborne levels may be less important than measuring nanoparticle size, surface area, and surface chemistry. Because very large numbers of nanomaterial particles represent very little mass, nanomaterials can confound usual industrial hygiene approaches and equipment for detecting and quantifying exposures to particles in workplace settings.

A variety of instruments are available for measuring nano-sized particles, but each category of equipment has its advantages and disadvantages (Maynard and Kuempel 2005; Maynard and Aitken 2006). Condensation particle counters (CPCs) have been available for a number of years and can be useful as screening tools to detect nano-sized particles. The advantages of CPCs are that they provide real-time measurements of total particle number, are easily portable, and are relatively inexpensive to purchase, generally costing less than $10K. The disadvantages include that the total count data do not resolve the particle counts by size, they cannot distinguish the nanoparticles of interest from other nanoparticles in the same size range, and the lowest range of particle size detection is 10 to 20 nm.

With increasing nanoparticle measurement sensitivity come increased equipment cost and some tradeoffs in portability. Several different types of diffusion chargers are available. These instruments provide surface area measurements that correlate with the deposition of the measured nanoparticles into the lungs. Their disadvantages include that, similar to the CPCs, the total count data are not resolved by size, they cannot distinguish between the nanoparticles of interest and other nanoparticles, and the measurements are susceptible to bias by larger-sized particles.

Scanning mobility particle sizers (SMPS) are yet another category of nanomaterial measurement equipment. They employ a continuous, fast-scanning technique that quickly provides high-resolution particle measurements. They can measure particles ranging from 2.5 nm to 1000 nm and display data using more than 150 different particle size channels. They are expensive, costing more than $50K, and again do not distinguish between the nanoparticles of interest and other nanoparticles. Development and improvement of equipment for measuring nanomaterials are ongoing activities by equipment manufacturers to meet the needs of occupational specialists for evaluating nanomaterials in workplace environments.

A limited number of field studies that include measurements for nanomaterials in occupational settings have been completed to date. Maynard and co-workers (2004) presented the results of a field study to evaluate worker exposures to single-walled carbon nanotubes (SWCNT). They reported that aerosolized concentrations during handling of unrefined nanomaterials were low and that more energetic processes would be needed to increase the airborne concentrations. They also reported that the gloves of workers who handled nanomaterials were contaminated, indicating the importance of dermal contact as a potential exposure route. More recently, NIOSH (2007) completed a number of field studies at companies involved in nanotechnology. The preliminary progress-report studies describe the different methods used for obtaining air and surface measurements of nanomaterials, qualitative evaluation of engineering controls and work practices, and recommendations to the participating companies, such as improvements in work practices and worker training.

8.2.3 Risk Characterization

The risk characterization phase of NIOSH's Occupational Health and Safety process combines the results of the hazard identification and exposure assessment phases to understand the risks from worker exposures to the nanomaterials of interest. Unfortunately, risk characterization for nanomaterials currently presents significant challenges, and can raise more questions than answers.

One reason for uncertainty about risk characterization determinations is that all of the research related to characterizing occupational risk is relatively recent and thus the extent of data, although growing each year, is still limited. As reviewed in Chapter 4, the majority of *in vitro* and *in vivo* research studies to examine the effects of nanomaterials have been completed within the past five years, and little data are available for occupational exposure studies with workers. With the exception of TiO_2, occupational exposure levels for nanomaterials have yet to be established and, as discussed in the next section, questions remain about the effectiveness of traditional personal protective equipment to provide adequate worker protection. With regard to medical surveillance for workers exposed to nanomaterials, no guidelines or requirements are currently in place. Answers to the larger question of whether nanomaterial exposures have long-term effects in workers are currently unknown.

8.2.4 Risk Management

Risk management involves an overall strategy to minimize or eliminate worker exposures to nanomaterials. Components of a strategy can include use of good work practices and personal protective equipment by workers; improvement in procedures to avoid accidents; implementation of engineering controls; and development of approaches to evaluate life cycle analysis for nanomaterials to identify potential impacts from manufacture through disposal and/or recycling (Nanotechnology Environmental and Health Implications Working Group 2006). Clearly, effective worker training on these topics, provided by employers, will be essential for the success of any risk management program.

One question that arises regarding different risk management tools is the effectiveness of traditional filter materials, such as high efficiency particulate air (HEPA) filters, to remove nano-size particles from an air stream. Theoretically, HEPA filters are least efficient for particles in the range of 0.3 μm, but they effectively capture particles both larger and smaller than this value (Wang et al. 2007). This suggests that HEPA filters should provide adequate protection against exposures to nanomaterials. However, a concern for nanomaterials less than 10 nm is that these small particles may bounce through the filter media and avoid capture due to their high thermal speed, a phenomenon called *thermal bounce* (Wang et al. 2007; Kim et al. 2007). Even if HEPA filters prove adequate for capturing nanomaterials, an additional concern is

whether these small nanomaterials will bypass the edges of filter equipment and result in worker exposures. Answers to these questions will certainly require more data from research, models, and field studies with workers.

Control banding is a risk management tool that has been proposed for managing nanomaterial risks in the workplace (Bartis and Landree 2006). In control banding, a single control technology, such as local ventilation or containment, is applied to one range, or band, of exposures to a contaminant that falls within an assigned hazard group, such as *skin and eye irritants* or *severely irritating and corrosive substances* (NIOSH undated). It focuses resources on exposure controls and can be useful for qualitative risk assessment and as a management tool.

Control banding has been used successfully in the pharmaceutical industry for managing new chemical entities that are synthesized as potential drug candidates, yet lack extensive information about their toxicological properties. A system analogous to control banding for chemicals has been successfully applied for decades to infectious agents and biological toxins by those in the field of biosafety (Centers for Disease Control and Prevention and National Institutes of Health 1999). Infectious agents and toxins are categorized into one of four biosafety levels according to their potential to cause infections or disease in humans, and by the availability of effective medical treatment if an infection or disease results from an exposure.

Control banding was included in the discussions during a recent meeting sponsored by NIOSH in coordination with the RAND Corporation to evaluate occupational health and safety concerns for nanomaterials (Bartis and Landree 2006). This approach was considered because traditional approaches for developing occupational exposure limits (OELs), such as permissible exposure limits, recommended exposure limits, and threshold limit values for nanomaterials, are likely to prove impracticable. This is based on the predicted time, cost, and expense to develop OEL values for the hundreds of nanomaterials that are likely to enter the workplace during the next few years.

A recent presentation illustrated the impracticality of developing toxicity profiles and OELs for the possible permutations of manufacturing a single category of nanomaterials, SWCNT. Colvin (2007) estimated that based on the number of different SWCNT types, and the different manufacturing options, tube lengths, purification steps, and coatings options, one could generate more than 50,000 different SWCNT samples. The time and expense to evaluate each of these SWCNT samples according to the nanomaterials screening strategy proposed by Oberdörster and colleagues (2005b), for example, would be prohibitive. Colvin (2007) also suggested that in the ideal future, key information about nanomaterial properties, such as type, size, coatings, dose, shape, and purity, could be used to determine the potential toxicity of a material. This information would be essential for identifying an appropriate band category for specific nanomaterials. Today, however, environmental health and safety (EHS) professionals and others involved in nanotechnology are at the

point of trying to identify the research that would be needed to create such a knowledge database.

8.3 Best Practices for Nanomaterials in the Workplace

The previous discussion leads to the important question about what to recommend and implement *now* to minimize occupational exposures to nanomaterials. During the past few years, NIOSH has proactively directed its program resources toward research on nanomaterials and on developing publications that provide current information regarding best practices for the handling and use of nanomaterials for workers.

NIOSH is the U.S. federal government agency responsible for conducting research and making recommendations for the prevention of work-related injury, illness, and death. In 2004, NIOSH established its Nanotechnology Research Center (NTRC) to coordinate and facilitate research in nanotechnology and develop guidance on the safe handling of nanomaterials in the workplace (NIOSH 2007). A critical foundation for the NTRC is more than 35 years of experience by NIOSH in conducting research and developing recommendations to address occupational safety and health issues for workers.

NIOSH is well positioned to utilize its extensive experience in measurement and control of non-engineered particles in the nanoparticle range of 1 to 100 nm including occupational exposures to diesel exhaust, welding fumes, and various dusts, and in understanding worker health concerns for nanomaterials. NIOSH contends that the existing large body of scientific information on exposures and responses to these particles can serve as a basis for understanding and evaluating the health risks presented by nanomaterials. In concordance with this line of thinking, Oberdörster and colleagues (2005a) have proposed that the extensive database of research on air pollution and ultrafine particles, which are now termed nanoparticles, can serve as a basis for interpretation of nanotoxicology studies.

In 2005, NIOSH outlined its strategic plan for addressing the worker concerns about nanomaterials and the goals for its nanotechnology research program (NIOSH 2005). Two recent documents from NIOSH (2006; 2007) provide an excellent review of the current concerns about nanomaterial exposures for workers, as well as summarizing research initiatives and current recommendations for best practices for nanomaterials.

The best practices for nanomaterials generally follow the traditional NIOSH hierarchy of exposure control practices used by industrial hygiene professionals to minimize harmful exposures to occupational hazards (Maynard and Kuempel 2005), shown in Figure 8.1. These practices include elimination, substitution, modification, containment, ventilation controls, work practices, and personal protection.

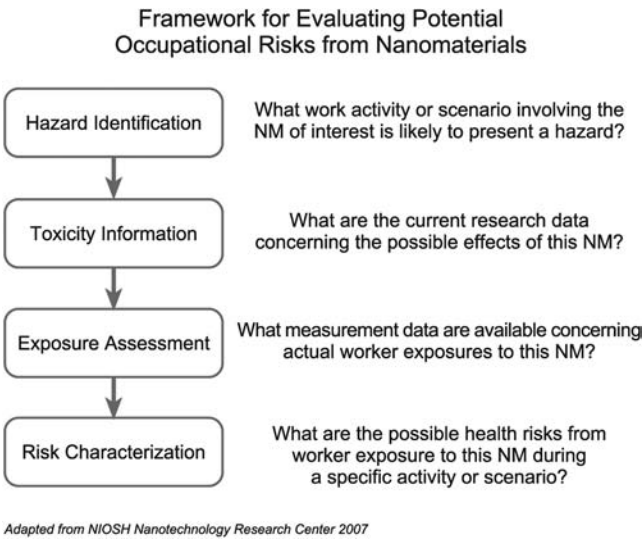

FIGURE 8.1
Framework for evaluating potential occupational risks from nanomaterials. (Adapted from NIOSH Nanotechnology Research Center 2007.) (See color insert following page 76.)

Each phase of the hierarchy for exposure control practices must be evaluated with a perspective on the unique properties of nanomaterials in mind. The first level is prevention or containment of emissions of the material of concern at its source. This approach can include implementation of administrative as well as engineering controls.

The second phase is removal of the emissions between the source and the worker. This approach can include the use of ventilation controls, such as chemical fume hoods and local ventilation exhaust. Recent studies by Lee and colleagues (2007) using nano-sized welding particles provide some initial guidance on the design of effective ventilation systems for reducing airborne nanomaterial concentrations and the potential for worker exposures.

The third approach is the use of barriers between the worker and the hazard. This approach includes the use of personal protective equipment, such as clothing, gloves, respiratory protection, and eye protection. No guidelines are currently available regarding the selection of clothing or other apparel to specifically prevent dermal exposures to nanomaterials. National Institute for Occupational Safety and Health (NIOSH) is currently developing innovative methods to evaluate the penetration of nanomaterials through clothing and gloves (NIOSH 2007). With regard to respiratory protection, NIOSH-certified respirators should provide adequate protection if properly selected and fit tested. However, their use is recommended primarily when engineering and administrative controls are inadequate to protect workers. As discussed, a concern has been raised about by-pass around the perimeter of the facemask that could allow worker exposure.

Consistent with standard industrial hygiene recommendations, work practices include maintaining clean work areas, regular hand washing, and, if appropriate, use of showers and a change of clothes. With regard to proper disposal and spill clean-up procedures for nanomaterials, recommended practices should minimize possible inhalation and dermal exposures. Finally, worker training is an essential component for insuring that workers have adequate information about nanomaterials and their potential exposure risks to implement the necessary steps to minimize exposures.

The current position of NIOSH is that manufactured nanomaterials do not have physical characteristics that suggest they would behave differently from other fine and nano-size particles that are present in numerous work environments (2007). Although this position is based on extensive existing information about the behavior of particles in the 1 to 100 nm range, NIOSH does acknowledge that this assumption requires further evaluation (NIOSH 2007). NIOSH also acknowledges that the occupational health risks associated with the manufacturing and use of nanomaterials are not yet clearly understood. Nevertheless, its research and guidance to date fill an important knowledge gap in the available information regarding how to best work safely with nanomaterials.

8.4 Current Practices for Workplace Practices with Nanomaterials

Given the limited guidance and regulations currently available regarding the handling and management of nanomaterials in occupational settings, an important question is what is being done now to protect workers from exposures to nanomaterials and their potential health impacts. In response to this question, the International Council on Nanotechnology (ICON) recently issued two related reports regarding environmental health and safety (EHS) practices currently in use by companies, researchers, and university laboratories involved in nanotechnology (ICON 2006a; 2006b). The initiative for these reports was the absence of an overall understanding of current EHS practices used for nanomaterials manufacturing activities. ICON issued a request for proposals in December 2005 to identify an organization that could conduct a survey of current practices for the nanotechnology industry, and subsequently selected an interdisciplinary team of researchers from the University of California at Santa Barbara (UCSB) to perform a two-phase study; reports for these two phases were issued in late 2006.

The report on the first phase of the project (ICON 2006a) provided an excellent summary of existing and planned efforts of current industrial practices for nanomaterials with regard to workplace safety, the environment, and product stewardship. The UCSB researchers used Internet searches and

telephone interviews to identify ongoing or recently completed research on current practices for nanomaterials manufacturing around the world including North America, Europe, Asia, Australia, Japan, Taiwan, and China. They organized their report into four categories: (1) cataloging of current practices; (2) voluntary reporting programs; (3) recommended best practices and frameworks; and (4) databases and other activities. The researchers then summarized their findings and critically evaluated the various programs for their approaches and completeness.

In the report on the second phase of the project (ICON 2006b), the UCSB team summarized their findings from a questionnaire survey they conducted regarding current EHS and product stewardship practices in the worldwide nanotechnology industry. A total of 64 of the 337 organizations invited elected to participate in the survey; the survey comprised participants from academia, industry, and research institutions from four continents, with a particular focus on those involved in nanomaterials manufacturing. The researchers used a combination of telephone interviews and a questionnaire designed specifically for the survey to identify current practices related to research, use, and manufacture of nanomaterials. Topic areas included in the survey covered EHS training, use of engineering controls, personal protective equipment and clothing recommendations, exposure monitoring, waste disposal, product stewardship practices, and risk characterization. The UCSB researchers noted that all of the information collected was self-reported and that no direct verification was performed.

The report presents a number of interesting findings regarding current practices for nanomaterials. In general, the survey participants reported that they believe there are special risks for workers associated with handling and managing nanomaterials. In response to these risk concerns, organizations have developed and are implementing EHS programs specific for nanomaterials, primarily as a precaution against its currently unknown hazards. At the same time, they continue to actively seek out updates and new information regarding best practices. The primary finding of the report is that, at present, many EHS practices for nanomaterials are based on conventional practices that have been previously developed for chemicals. Due to the limited available regulatory guidance for nanomaterials and the risk concerns, the researchers noted significant variation among the EHS practices reported by the different organizations.

Organizations that had longer histories of working with nanomaterials and greater numbers of employees tended toward having specific EHS programs for nanomaterials, as well as training programs for employees. Larger organizations more often reported that they used a variety of engineering controls, including clean rooms, separate HVAC systems for laboratory areas, and closed piping systems. In smaller companies, employees were more likely to use disposable personal protective equipment, such as dust masks and disposable body coverings, as well as less expensive control techniques for preventing exposure, such as respirators, glove boxes, and glove bags. University laboratories reported that cost concerns and a lack of

prioritization of EHS practices were major impediments to development and implementation of programs specifically for nanomaterials. Few organizations reported that they actively monitor the workplace for nanomaterials.

Geographical differences also contributed to the variations among the EHS practices reported by the different organizations. North American organizations were more likely to have EHS programs specific for nanomaterials than organizations in other parts of the world. They also reported the use of more costly engineering controls, such as clean rooms, closed piping systems, and separate HVAC systems, compared to organizations in Asia where the use of glove boxes, glove bags, and respirators was more widespread. An important conclusion of this report is that there is a strong demand for more toxicological research on nanomaterials and additional industry and governmental guidance in risk assessment and EHS practices.

8.5 Current Efforts on EHS Needs for Nanoscale Materials

The large number of reports generated during the past few years by national and international governmental agencies and research organizations on the issue of EHS needs for nanomaterials reflects both the great importance and the information gaps regarding this issue. The following sections provide brief summaries of some recent reports.

8.5.1 National Nanotechnology Initiative Environmental Health and Safety Research Needs for Engineered Nanoscale Materials

The National Nanotechnology Initiative (NNI), first formed in the mid-1990s from informal meetings among staff members from several agencies, is a federal government research and development program established to coordinate the efforts of 26 participating federal agencies regarding nanoscale science, engineering, and technology. The National Science Engineering and Technology Subcommittee of the National Science and Technology Council issued a document in late 2006, prepared as part of the NNI, to identify the research and information needed to address environmental, health, and safety issues regarding nanomaterials (Nanotechnology Environmental and Health Implications Working Group 2006). Another objective in preparing this document was to support efforts toward development of sound risk assessment and risk management strategies for nanomaterials and the products that will contain them. It was produced as a collaborative effort among the federal agencies that participate in the NNI and was informed by recommendations from industry groups as well as other reports concerning the EHS needs for nanomaterials. The section on risk management methods provides a good summary of the current research and information needs in several important areas:

- Improved understanding of the challenges that airborne nanomaterials present for process design and engineering control systems.
- Understanding and development of manufacturing approaches that minimize environmental impact to enable green design principles.
- Determination of the stages in a product's life cycle that introduce the potential for EHS risks.
- Evaluation of whether current risk communication methods are adequate for known risks and for risks that can be anticipated from currently available information.

8.5.2 U.S. Environmental Protection Agency White Paper on Nanotechnology

Under its federal mandate, the U.S. Environmental Protection Agency (EPA) has the regulatory authority to protect the environment from a variety of possible hazards, such as those that may be presented by nanomaterials. Under the Toxic Substances Control Act (TSCA), EPA can require premanufacture notification (PMN) from manufacturing companies for products containing unregistered substances. TSCA provides the EPA with the authority to identify and control "new chemicals" that may pose a threat to human health or the environment, and the EPA can determine which nanomaterials meet this criterion. As an example of its regulatory authority under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), in late 2006 the EPA required review of a Samsung clothes washer (discussed in Chapter 3) based on the manufacturer's claim to add nanoscale silver as an antibacterial agent. Other EPA regulatory authority through the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Resource Conservation and Recovery Act (RCRA), and the Clean Air Act (CAA) may also impact the manufacture of products containing nanomaterials.

The EPA recently released its final version of a White Paper on Nanotechnology (2007). This report focuses primarily on the potential environmental impacts of nanomaterials, but it has implications for companies that manufacture and use nanomaterials as part of their operations and may release nanomaterials into the environment.

8.5.3 Voluntary Standards

As discussed in Chapter 9, several organizations are developing voluntary standards for nanomaterials, and many of these include EHS standards. The American Society for Testing and Materials International (ASTM International) formed Committee E56 on Nanotechnology in October 2005 in response to the recognition by the organization that it needed to specifically

address this emerging technology area. A recent work product of Committee E56 is a terminology standard related to nanotechnology (ASTM International 2006). This document is a critical first step to define nanotechnology and the related terms that are used to describe the materials and their characteristics. The E56 subcommittee on EHS, whose focus would include worker safety issues, has not yet provided any published documents on this area. The ISO Technical Committee 229 (TC229) for Nanotechnologies working groups include: terminology and nomenclature; measurement and characterization; and health, safety, and environmental aspects of nanotechnologies. The working groups are currently developing technical reports that will contribute toward production of a standards document for nanotechnologies by the TC229. Those sections that deal with the EHS aspects of nanotechnologies will be most relevant to the concerns addressed in this chapter regarding worker exposures to nanomaterials.

8.6 Ongoing Governmental Efforts on Environmental Health and Safety

In addition to these recent reports, other EHS efforts are ongoing in the U.S. and globally.

8.6.1 Occupational Safety and Health Administration

The U.S. Occupational Safety and Health Administration (OSHA), whose mission is to assure the safety and health of America's workers by setting and enforcing standards, has not yet developed guidance documentation or specific standards for nanotechnology and nanomaterials. However, OSHA does participate in the NNI. OSHA plans to develop guidance for employers and employees engaged in operations involving nanomaterials. A clear drawback of the traditional regulatory and standards development processes by OSHA is the long timeframe and the amount of research and data required to develop standards.

In the absence of published standards or guidance documents specifically for nanotechnology, some elements of current OSHA regulations are now applicable for nanomaterials. Worker training for use and handling of nanomaterials would be needed to ensure the compliance under the right-to-know requirements. In addition, employers must comply with the general duty clause that requires them to provide each employee a place of employment that is free from recognized hazards that are causing or are likely to cause death or serious physical harm (OSH Act 29U56 654 Section 5(a)(1)). With regard to respiratory protection, OSHA has a standard (OSHA 24 CFR 1910, 134) that could be applicable to nanomaterials, but the small size of

nanomaterials may present a challenge to the effectiveness of traditional personal protective equipment designed to protect workers. As previously discussed, the adequacy of existing respiratory protective equipment and its filtration materials for protecting against nanomaterials exposures is an area of active research.

8.6.2 The European Union and Registration, Evaluation, and Authorization of Chemicals (REACH)

In Europe, one area of interest is how nanoparticles are likely to be treated under the European Union's Registration, Evaluation, and Authorization of Chemicals (REACH) program. Because nanomaterials fall within the scope of REACH, their health and environmental properties must be assessed in accordance with the provisions of this regulation. However, the EU countries are in consensus with the international recognition that methodologies for identifying hazards and evaluating risks of substances at the nanoscale need to be further refined over the next few years. The European Commission is funding research projects to assess the health and environment impacts of nanoparticles under the Seventh Research Framework Program. It will also be necessary to carefully monitor over the next few years whether the threshold for registration and the information requirements under REACH are adequate to address potential risks from engineered nanoparticles.

Other European organizations have also addressed the issue of worker safety and nanotechnology as part of their recent reports (Organization for Economic and Commercial Development 2006; Scientific Committee on Emerging and Newly Identified Health Risks 2006). Further discussion of the findings and recommendations from these reports can be found in Chapter 9.

8.7 Summary

The current perceptive awareness regarding worker health and safety and potential exposures to nanomaterials is a welcome change from the twentieth century, when the health impacts of worker exposures to numerous industrial hazards were appreciated only long after the damage had been done. Action taken in advance of extensive manufacturing and commercial use of products containing nanomaterials can avoid the previous dark history of compromised health status, disease, cancer, and even death in workers unknowingly exposed to a variety of occupational hazards. The proactive approach that is being taken, both nationally and internationally, to address worker safety issues in the nanotechnology industry is laudable.

Yet another issue is liability. As noted in the RAND-NIOSH report on nanotechnology and occupational safety and health (Bartis and Landree 2006) and as discussed in the present chapter, current gaps in knowledge about health risks for workers in nanotechnology industries raise concerns about liability from workers as well as consumer exposures to nanomaterials, such that development, production, and use of new nanomaterials may be compromised. In the U.S. and in other countries involved in nanotechnology, no standards currently exist that provide exposure limit values for nanomaterials and procedures for working safely with them; however, it is only a matter of time before they are put in place. Development of such guidance is currently impeded by a lack of information similar to that discussed throughout this chapter — that is, lack of adequate basic scientific research data on the biological effects of even broad classes of nanomaterials, as well as an absence of occupational and epidemiological studies with workers in nanotechnology industries.

It is clear that waiting for regulations is not an answer to current worker health and safety concerns for nanomaterials. The efforts by NIOSH (2006) and ICON (2006a; 2006b) to provide current information about best practices for the handling and management of nanomaterials in occupational settings, and how they are being implemented, fill a critical gap about what to do now. However, the recent ICON report (2006b) also notes that there is a strong demand for more toxicological research on nanomaterials, as well as additional industry and governmental guidance in risk assessment and EHS practices. To make progress in developing information that refines and improves the current guidance, prompt attention, as well as both cooperation and funding from governmental agencies, the public and private sectors, and the nanotechnology industry are needed.

As effectively argued by Maynard (2006), a strategic research framework is needed to address the variety of questions concerning potential risks from nanotechnology, not only for workers but also for the general public and the environment. Hundreds of products containing nanomaterials are currently on the market, and the predictions for the numbers of new products within the next 10 years alone are logarithmic. This projected increase will drive the demand for more workers in the nanotechnology industry, with corresponding potential for worker exposures to nanomaterials. Major impediments to advances in understanding the potential risks from nanotechnology are not only the absence of a clear plan with short-term and long-term research priorities, but also a lack of adequate funding to support this research. For example, although NIOSH has accomplished and continues to make commendable progress in research for a number of areas related to worker safety, the total estimated budget for its nanotechnology program in 2006 was only $4 million.

Nanotechnology presents the promise of a diverse array of manufactured goods and products that incorporate improved and innovative properties, but also presents uncertainty about the risks from exposures to nanomaterials. Workers will be on the front line of exposures to these novel and unique

materials. It is imperative that appropriate actions and funding be directed toward obtaining the information needed to develop relevant guidance to protect their health and safety.

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9

Ongoing International Efforts to Address Risk Issues for Nanotechnology

Jo Anne Shatkin

CONTENTS

The explosive growth of nanotechnology and its potential penetration into so many sectors of the economy have prompted broad international efforts to address the issues of occupational and environmental risks. Numerous organizations — governmental, non-governmental, professional, not for profit — have developed nanotechnology activities relating to its environmental, legal, societal, and ethical impacts. Much of this activity involves intergovernmental collaboration, academic liaisons, and other associations, and also includes entities developing voluntary standards. Many of these organizations and efforts are mentioned in other parts of the book, but are consolidated here to provide a fairly comprehensive assessment.

Nanotechnology is such a hot topic that it is not easy to comprehensively report on all the ongoing international activities. Those reported on in this chapter generally include a risk component. These are the organizations, or groups of organizations, that are contributing to the international dialogue on how to identify, assess, and manage the environmental health and safety aspects of nanomaterials and nanotechnology, and the list is not inclusive. The focus here is more on environmental aspects and less on occupational exposures, which are addressed in Chapter 8.

Few existing regulations apply to nanotechnology specifically. Much of the current effort in governmental organizations is evaluating whether existing regulations need to be updated to address nano-specific materials and products. For example, under the U.S. Toxic Substances Control Act (TSCA), does a material producer have to submit an application for a nanoscale particle of a substance that is already listed in the TSCA inventory for larger size particles? This might apply to silver, for example, which is already on the TSCA inventory, but which is also now manufactured at the nanoscale and used in antibacterial coatings. Governments are also funding research into the environmental applications and implications, as well as toxicology, environmental fate, and chemical property investigations.

9.1 International Federal Governmental Efforts

Australia has just authorized a $20 million national nanotechnology strategy to establish metrology (measurements), address regulations and standards, and provide advice on nanotechnology. The strategy is intended to build on current efforts and allow Australia to, "capture the benefits of nanotechnology while effectively addressing community interest about health, safety and the environment" including balanced information on benefits and impacts of nanotechnology (Industry Australia 2007). An organization called Nano-Safe Australia is assessing Australia's capacity for managing occupational safety and health (OECD 2007).

China is investing in basic scientific research on the biological interactions of nanomaterials at the cellular and organ level, in order to establish safety standards. Research includes efforts to model the behavior of nanoparticles, and building a database of properties and effects of several nanomaterials in order to establish safe approaches for managing "artificial nano-materials," which is considered part of maintaining a competitive edge (Chinese Academy of Sciences 2007).

Canada is conducting several efforts on nanotechnology. A Health Portfolio Nanotechnology White Paper is in preparation, reporting on the developments discussed in a March 2007 workshop by a breadth of governmental representatives (OECD 2007). The Council of Canadian Academies is convening an expert panel on health and environmental aspects of nanotechnology to address Health Canada's questions about the need to update their risk assessment approaches for nanotechnology. Among other activities, the Office of the Science Advisor is organizing a series of workshops to gain perspective on the most important developments in converging technologies (nano, bio, and info) for Canada, as a foresighting exercise.

The European Commission (EC) is undergoing a regulatory evaluation to determine whether any existing regulations need to be revised for

nanomaterials. The EC Nanotechnology Action Plan describes the need for research, development, and innovation, including the development of infrastructure; priorities also include interdisciplinary research that integrates societal issues including public health, safety, and environmental and consumer protection, and spells out a plan for international cooperation. In the EC's 2007 call for research proposals, U.S.-based organizations were encouraged to participate in proposals relating to health and environmental risks (CORDIS 2007). The 2007 joint solicitation by the U.S. EPA, the National Science Foundation (NSF), and the Department of Energy (DOE) also calls for European partners on research teams. A number of EU member countries also have research programs; for example, several research programs in Germany address environmental and occupational aspects of nanotechnology (OECD 2007).

Japan's Ministry of Economy, Trade and Industry (METI) recently conducted a survey of industry practices in Japan, anticipating this will lead to development of guidelines (OECD 2007). The Japanese government is invested in research on environmental health and safety aspects of nanotechnology, with a focus on facilitation of public acceptance of nanotechnology. This is new for Japan, to hold public discussions of risk, and the projects involve a number of interdisciplinary and international meetings to address various topics related to nanotechnology and risk (e.g. SRA 2007). Several Japanese organizations are participating in a series of workgroups on risk assessment for health, environmental, ethical, and societal issues, and technology assessment, which includes economic effects. This constitutes an exciting development, which is viewed by the National Institute of Advanced Industrial Science and Technology (AIST) as an innovation to incorporate issues of standardization in risk management during the process of research and development. "Attempts to position the issues, such as societal impact and public acceptance encompassing risk management and standardization, in the stages of research and development constitute an original research and development strategy of AIST, aimed at creation of innovation from core technologies" (Ata 2007).

In the United States, efforts among several agencies in the federal government are ongoing. Federal efforts are coordinated through the National Nanotechnology Initiative (NNI). NNI is coordinated by the National Nanotechnology Coordination Office, in the White House Office of Science and Technology Policy, and oversees some $1.4 billion in funding for research and development of nanoscale technology. Roughly 3% of this budget is expended on projects related to environmental, health, and safety (EHS), and to ethical, legal, and societal implications — although some within the NNI have suggested this figure is an underestimate. Many have argued this amount is far too small, given the importance of managing risks in overall nanotechnology development. A National Research Council committee reviewing the NNI recommended expanding research on environment, health, and safety (NRC 2006). Others have called for $100 million per year in EHS research funding (e.g., Air Products et al. 2007).

The U.S. EPA published a White Paper on Nanotechnology, highlighting what is known and the research necessary to manage the environmental aspects of nanotechnology. The EPA is developing a research strategy for nanotechnology. One effort is developing case studies using CEA (described in Chapter 7) to identify research gaps for risk assessment, which will then be prioritized for study. The EPA is also developing a voluntary program under the Office of Pollution Prevention and Toxics to provide guidance on Risk Management and Reporting under TSCA.

One activity in the U.S. is led by an interagency committee on Nanotechnology Environmental and Health Implications (NEHI). NEHI is part of the NNI and includes participants from the 21 agencies within the U.S. federal government which are responsible for management of nanotechnology EHS. These are: National Nanotechnology Coordination Office, Office of Science and Technology Policy, Office of Management and Budget, Consumer Product Safety Commission, Cooperative State Research Education and Extension Service, Department of Transportation, Food and Drug Administration, International Trade Commission, National Institute of Standards and Technology, Occupational Safety and Health Administration, National Science Foundation, Department of Defense, the Department of Energy, National Aeronautic Safety Administration, National Institutes of Health, National Institute for Occupational Safety and Health, Department of Commerce, Department of Agriculture, EPA, Department of Justice, and the U.S. Geologic Survey.

NEHI developed a research needs document addressing environmental health and safety research needs (NEHI 2006), and a strategy to prioritize the research needs (NEHI 2007). At the January 4, 2007 public hearing, a number of commenters, myself included, lauded the research areas identified. However, my comments expressed the view that not only is basic research needed, but also research to understand how the information will be used — in other words, such a strategy should address how the basic research results would be used to make policy decisions (NNI 2007).

9.2 Standard Setting

Setting standards for nanomaterials and nanotechnology is in the very early stages, and as we have discussed, there is only one current regulation known to the author, in Berkeley, California. In Canada, Environment Canada has posted an Advisory Note for the New Substances Program under the Domestic Substances List (DSL), which now requires reporting of nanomaterials if their structures or composition are different than bulk substances already on the DSL (EC 2007). The advisory requires reporting of unique structural

formations of existing materials at the nanoscale and novel materials. Reporting requirements are similar as for other materials.

A number of organizations are calling on U.S. EPA and FDA to develop new regulations specifically for nanomaterials (e.g., Acción Ecológica et al. 2007). National Resources Defense Council, International Center for Technology Assessment (ICTA), several legal experts, and others have weighed in on whether new standards are needed (e.g., the American Bar Association; Davies 2006, 2007). At the EPA, the Office of Pollution Prevention and Toxics has convened an advisory committee to develop a voluntary reporting system for nanomaterials. It is not clear at the moment that new standards will be required. The U.S. Food and Drug Administration (FDA) reported on its ability to address nanotechnology in the products it oversees, generally concluding that existing processes for pre-market approval of drugs, devices, and food additives address many of the challenges posed by nanotechnology, but may require revision (FDA 2007). In the EU, a committee recently determined that no special considerations are currently needed for nanomaterial applications under REACH, the Regulatory Evaluation and Authorization of Chemicals Program.

In this uncertain regulatory environment, a number of organizations are developing voluntary standards for nanotechnology. These organizations generally require membership to participate in standard setting and gain access to the standards, but tend to be open to participants from various sectors. Two organizations include the International Organization for Standards (ISO) and the American Society for Testing and Materials (ASTM International). Each of these organizations is addressing terminology, characterization of materials, and environmental health and safety. There is a nanotechnology committee within ISO, TC229, that is developing several voluntary standards for handling nanomaterials. The American National Standards Institute (ANSI) is leading the coordination of the environmental safety and health standard.

In Europe, the European Committee for Standardisation (CEN) established CEN/TC 352 "Nanotechnologies" at the end of 2005 to develop a set of standards addressing the following aspects of nanotechnologies: classification, terminology, and nomenclature; metrology and instrumentation, including specifications for reference materials; test methodologies; modeling and simulation; science-based health, safety, and environmental practices; and nanotechnology products and processes. CEN is also interacting with ISO/TC229. A terminology standard is under development.

ASTM International has a technical committee on nanotechnology (E56), with six subcommittees working on terminology, characterization standards, toxicity tests, occupational exposure standards, best practices, and others. As of May 2007, three terminology standards are completed. ASTM E 2456-06 Terminology for Nanotechnology includes 13 definitions for nanotechnology, nanoparticles, and a host of other terms, with more to be added as they are vetted by members of the committee. ASTM is also working on a best

practices standard, and several standard test methods, such as *in vitro* cytotoxicity assays (ASTM Committee E56) for nanoscale materials.

9.3 Professional Organizations

Professional societies are forming to address risks of nanotechnology. In December 2006, I led the organization of the Emerging Nanoscale Materials Specialty Group, EMNMS, of the Society for Risk Analysis (SRA). The group currently has over 130 members representing government, academia, industry, and non-profit organizations in 14 countries. Emerging nanoscale materials are agents recently identified or created that, as we have found, confer unique properties due to small size. The overarching goals of the group are:

- to facilitate the exchange of ideas and knowledge among practitioners, researchers, scholars, teachers, and others interested in risk analysis and emerging nanoscale materials,
- to encourage collaborative research on risk analysis and emerging nanoscale materials, and
- to provide leadership and play an active role in advancing issues related to risk analysis and emerging nanoscale materials.

EMNMS is actively developing collaborative efforts with other groups within and outside of the SRA (SRANANO.org). SRA was formed in 1980 (SRA 2007) and is an interdisciplinary international organization, an open forum for anyone interested in risk analysis. With hundreds of members internationally in local sections and chapters, as well as in specialty groups, SRA provides a home to analysts, communicators, decision makers, and others. SRA publishes the journal *Risk Analysis* and hosts annual meetings, conferences, and workshops on topics of risk.

The Society for Toxicology (SOT) held an organizational meeting at their 2007 annual meeting to discuss a specialty section on nanotoxicology (SOT 2007). The Nanotoxicology Specialty Section plans to serve as a focal point for its members and others interested in toxicology of nanoscale materials, and facilitate discussions about how to conduct toxicology experiments for them.

The Society for Environmental Toxicology and Chemistry (SETAC) is also active in addressing nanotechnology and environmental issues each year in their annual meeting, where numerous abstracts and papers are presented on related topics. SETAC has also organized international efforts on life cycle analysis and its application, which includes nanotechnology.

The American Chemical Society (ACS) meets semi-annually and provides a forum for chemists to discuss all aspects of nanotechnology, including environmental aspects. *Chemical and Engineering News*, a weekly publication,

provides an annual report on nanotechnology as well as regular updates on developments (CEN 2007), in addition to covering news and other events and developments.

The Materials Research Society hosts semi-annual meetings with a large focus on nanotechnology and publishes research reports. The International Association of Nanotechnology (IANANO) is a multi-disciplinary organization that promotes research and business development for the nanotechnology industry, and hosts three annual conferences: NanoBio, CleanTech, and the International Congress on Nanotechnology.

The Converging Technologies Bar Association (CTBA) is focused on the multifaceted impact of nanotechnology, biotechnology, information technology, cognitive science neuroscience, and other related sciences and technologies. CTBA seeks to foster collaborations among technical and legal experts to heighten public awareness, and educate and develop forward-thinking measures to address the societal impacts of converging technologies (CTBA 2007). The Center for Nanotechnology and Society, in Chicago, is a forum for discussion of societal aspects of nanotechnology, including conferences addressing ethics, risk, legal, policy, and business aspects (Center on Nanotechnology and Society 2007).

9.4 Non-Governmental Organizations Addressing Environmental and Risk Issues

The Foresight Nanotech Institute is among the oldest nanotechnology organizations. Its mission is to enhance the beneficial implementation of nanotechnology and seek to guide nanotechnology research public policy and education around six major challenges. The challenges include: providing renewable clean energy; supplying clean water globally; improving health and longevity; healing and preserving the environment; making information technology available to all; and enabling space development (Foresight 2007).

The Organization for Economic Cooperation and Development (OECD) Working Party on Manufactured Nanomaterials is part of the OECD chemicals committee and promotes "international cooperation on human health, and environmental safety of manufactured nanomaterials, and involves approaches to safety testing and risk assessment of manufacturing nanomaterials" (OECD 2007). Governmental activities are coordinated by convening groups to discuss and agree upon a research agenda, coordinating efforts to ensure that research funding is leveraging the efforts across agencies. The three main areas of focus are: identification and characterization, including terminology and standards; testing methods; and risk assessment, information sharing; and dissemination (OECD 2007). The report of the 2007 meeting

of the working party provides a detailed summary of member activities (OECD 2007).

The Woodrow Wilson International Center for Scholars (WWCS) Project on Emerging Nanotechnologies conducts a range of activities to address the impacts of nanotechnology on society. They have commissioned several reports on issues of regulation, life cycle analysis, greening nanotechnology, and risk research needs, and in specific sectors such as agriculture and medicine. Key staff members have published numerous reports and journal articles on issues of occupational exposure, health and safety, and research needs, including the five "grand challenges" for risk research (Maynard et al. 2006). WWCS maintains several databases, including a database of consumer products containing nanotechnology. As noted earlier, as of May 2007, there were close to 500 products in this database. A second database catalogs ongoing research on environmental health and safety of nanotechnology and nanomaterials. Other databases include research on agriculture and food, nanotechnology research and development, nanomedicine, and geographical distribution of nanotechnology activities (WWCS 2007).

The International Risk Governance Council (IRGC), based in Switzerland, addresses risk governance for emerging risk issues, including nanotechnology. IRGC has published a risk governance framework that has been applied for nanotechnology, described in Chapter 2. IRGC has held events and drafted papers addressing how the risk governance framework is best applied for nanotechnology, particularly with respect to the societal dimensions (IRGC 2006).

Building on efforts at the National Science Foundation funded Center for Biological and Environmental Nanotechnology at Rice University, the International Council on Nanotechnology (ICON) has been developing a range of resources on risk and nanotechnology. Members include governmental agencies, industry, and non-profits. ICON recently released a review of safety practices and results of a "best practices" survey described in Chapter 7 that discusses current approaches taken to mitigate EHS risks. In 2007 ICON organized workshops to identify research needs for nanotechnology and risk. ICON also hosts a virtual journal (icon.rice.edu) that summarizes research published elsewhere (ICON 2007).

NanoReg publishes the *NanoReg Report*, an electronic newsletter of regulatory and environmental health and safety aspects of nanotechnology. Nanoreg specializes in the application of laws and regulations related to the development and use of nanoscale materials throughout the nanotechnology value chain. NanoReg has been instrumental in bringing together producers and users of nanoscale materials with government policy makers and non-governmental organizations to address growing environmental, health, and safety concerns about the products of nanotechnology (NanoReg News 2007).

A multi-stakeholder effort called NANOSAFE2, which received EU funding, represents the collaboration of 22 organizations in seven countries from industry, research institutes, universities, and consulting firms. NANOSAFE2

aims to conduct research and outreach to address issues of safe industrial production, health and hazard assessments, characterization and monitoring, and societal and environmental aspects of nanomaterials. The Meridian Institute has convened and facilitated a number of nanotechnology meetings — in particular, an ongoing global dialogue on nanotechnology and the poor that looks at the impacts of nanotechnology on developing nations; and a follow-up workshop on nanotechnology water and development, held in India, which looked at the opportunities and risks of nanotechnology water purification technologies specifically for developing countries.

There are a number of industry organizations in the U.S., including the NanoBusiness Alliance, committees organized by the American Chemistry Council (ACC), the Synthetic Organic Chemical Manufacturers Association, and SEMI, the semiconductor organization, among others. While mostly focused on business issues, these groups are discussing how to address environmental health and safety for nanotechnology in the absence of a regulatory framework. The NanoBusiness Alliance (NBA) represents the small and medium enterprise nanotechnology organizations and hosts a major conference in the U.S. annually. There are Australian and Canadian counterparts. The NanoBusiness Alliance represents its members by testifying or presenting and participating in many forums that address environmental health and safety issues. ACC has been actively engaged with the EPA and others on developing a voluntary reporting program for nanomaterials under the EPA's Toxic Substances Control Act. ACC primarily represents large chemical manufacturers and has a nanotechnology group. Other industry organizations such as the Synthetic Organic Chemical Manufacturers Association also participate in many of the meetings held to discuss regulatory policy and environmental health and safety issues. SEMI is developing EHS standards for nanotechnology.

Increasingly, these diverse organizations are working together, or at least communicating regularly. It is interesting to see the partnerships formed that challenge traditional notions of working on "sides" of an issue. Some examples include: Environmental Defense and Dupont are partnering on a nanotechnology initiative; ICON members are from industry, government, academia, and non-profits; many advocacy organizations are also partnering. By the time this book is in print, no doubt many more organizations will be working in the environmental health and safety aspects of nanotechnology.

9.5 Summary and Conclusions

This volume presents a multidisciplinary evaluation of environmental and health aspects of nanotechnology. The rapid developments in this arena mean that the information herein represents a snapshot in time. The state of the science regarding nanotechnology risks is a moving target. As with any

emerging issue, the regulatory landscape, the organizations involved, and current thinking inevitably will change, perhaps outdating some information presented here. Nevertheless, the adaptive approaches proposed promise continued learning and development from past and current experiences.

The complexity of our technological world, and the rapid pace of technological evolution, demands that we pay attention and participate in efforts to evaluate and manage the risks that affect us. As new technologies develop, a crucial task is to establish processes for continued surveillance to identify and address potential risks. Only through proactive efforts to understand the health and environmental impacts can we expect to responsibly manage the potential risks from nanotechnology.

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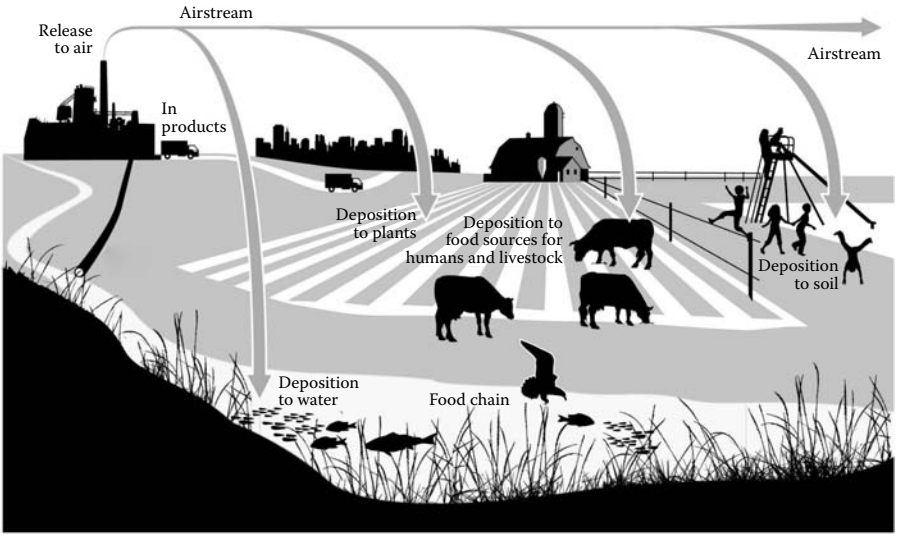

FIGURE 1.3
Potential exposure pathways for nanomaterials.

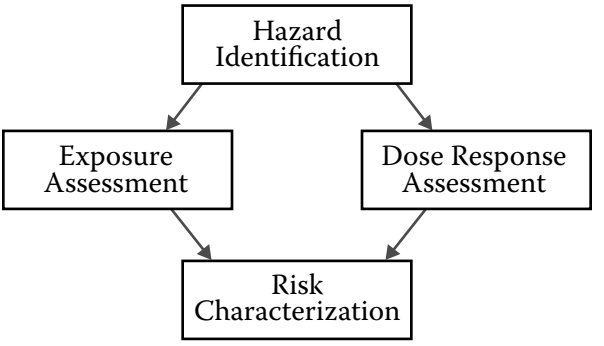

FIGURE 2.1
The four steps of the National Academy of Science risk assessment framework.

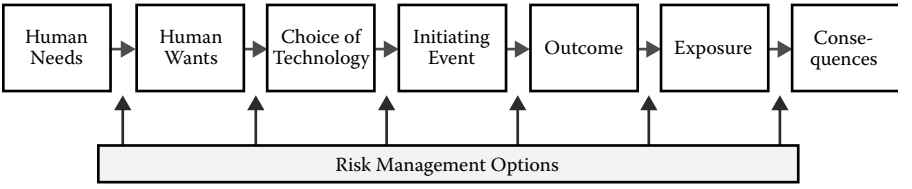

FIGURE 2.2
Technology assessment using causal chain analysis.

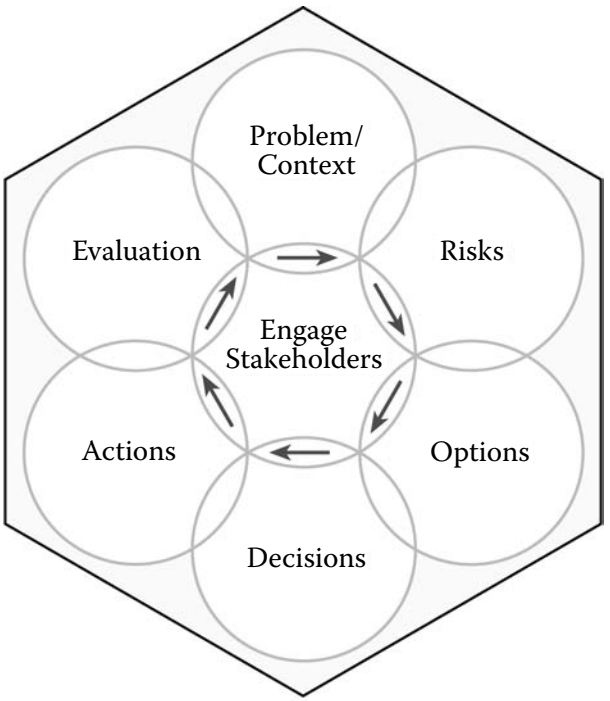

FIGURE 2.3
President's commission framework for environmental health risk management.

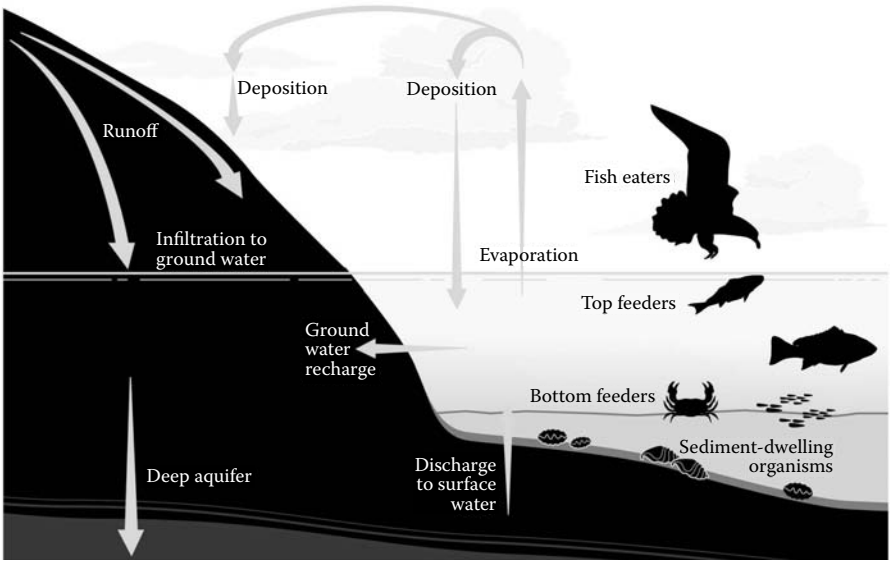

FIGURE 3.1
Environmental pathways affecting water resources.

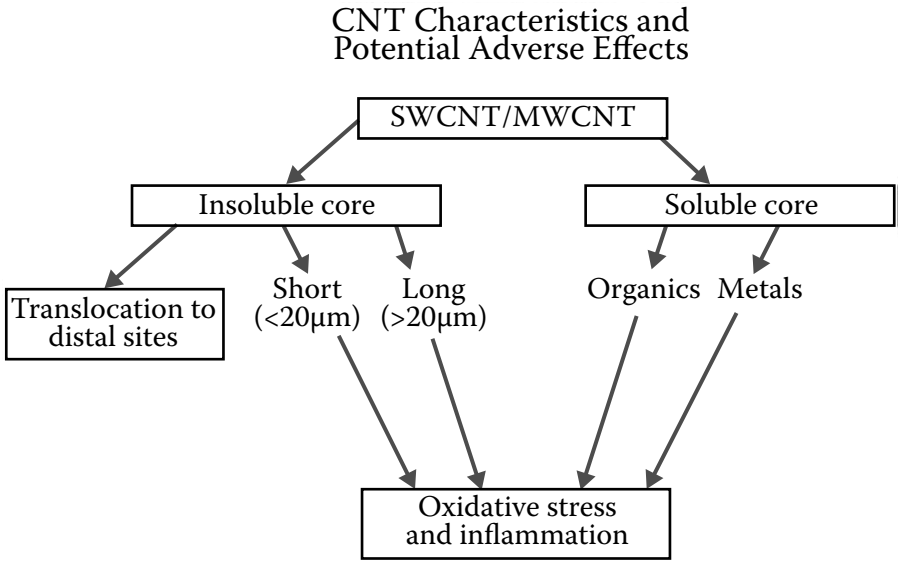

FIGURE 4.1
Carbon nanotube characteristics and potential adverse effects. SWCNT — single-walled carbonnanotube. MWCNT — multi-walled carbon nanotubes. Figure adapted from Donaldson et al. (2006).

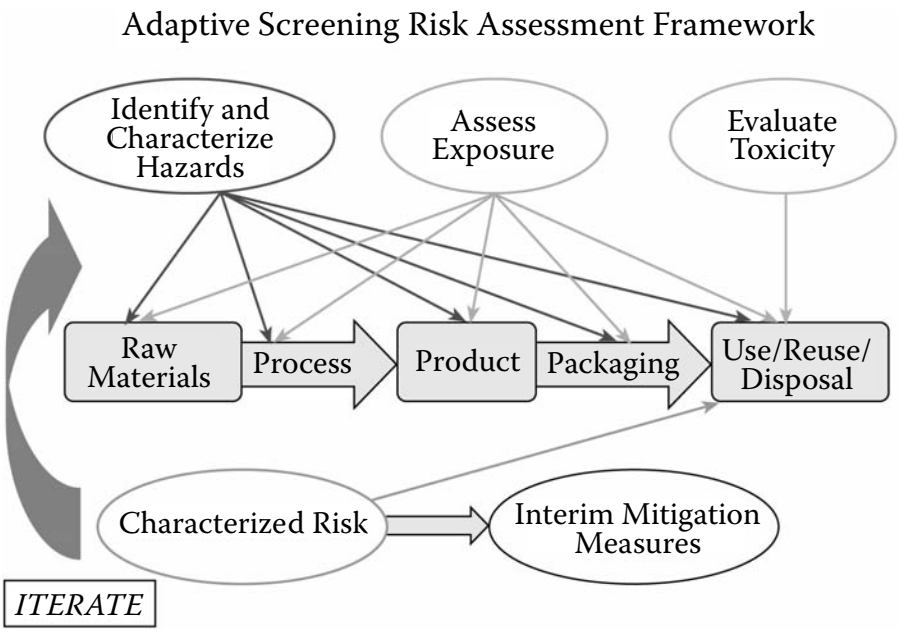

FIGURE 6.1
Proposed NANO LCRA framework.

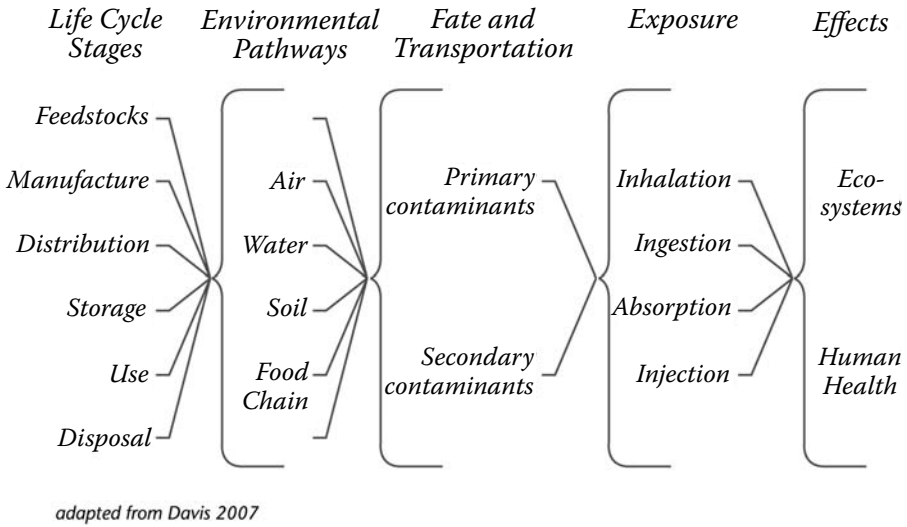

FIGURE 7.1
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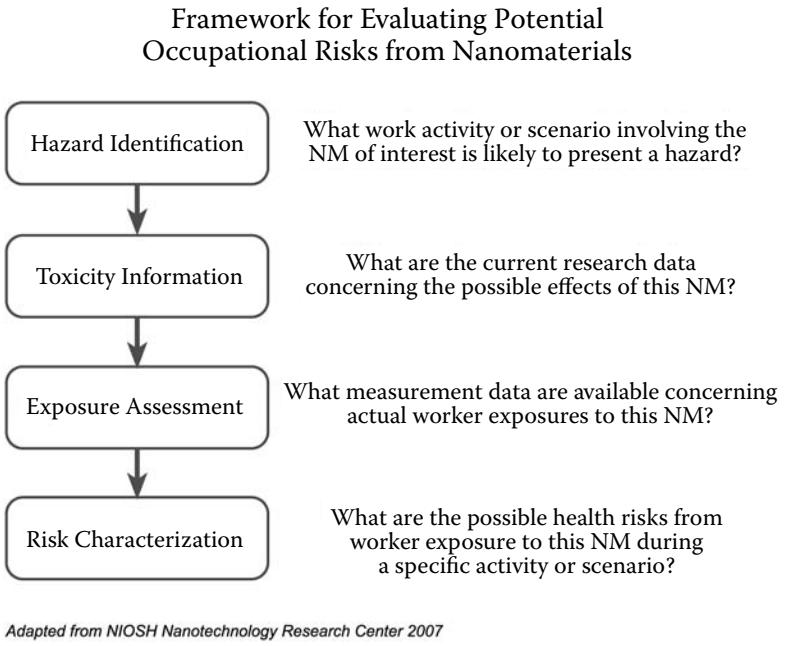

FIGURE 8.1
Framework for evaluating potential occupational risks from nanomaterials. (Adapted from NIOSH Nanotechnology Research Center 2007.)

Nanotechnology
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While reports on nanotechnology by research and marketing firms as well as governmental agencies are comprehensive and insightful, they can often be tedious to read, expensive to procure, and generally unknown to nonexperts interested in this technology. Offering a reader-friendly and affordable alternative to these options, **Nanotechnology: Health and Environmental Risks** introduces risk analysis as a tool for responsible environmental decision making in nanotechnology development and provides examples of past, present, and future technologies that demonstrate the need for and benefits of evaluating the risks of nanotechnology.

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- Discusses the present international efforts that address the risk issues of nanotechnology

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