Assessing Nanoparticle Risks to Human Health

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David B. Warheit, PhD, DABT, ATS, graduated from the University of Michigan, Ann Arbor, Michigan, with a BA in Psychology. He received his PhD in Physiology from Wayne State University School of Medicine, Detroit, Illinois. Subsequently, he was awarded a National Institutes of Health (NIH) Postdoctoral Fellowship, and 2 years later, a Parker Francis Pulmonary Fellowship, both of which he took to the National Institute of Environment, Health, and Safety (NIEHS) to study mechanisms of asbestos-related lung disease. In 1984, he moved to the DuPont Haskell Laboratory to develop a pulmonary toxicology research

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Preface

The first edition of this book rightly started off by focusing on the lack of data regarding the various elements in characterizing the health risks posed by various nanotechnologies. This set of novel technologies and its products poses fundamental challenges to conventional risk assessment paradigms. As I had written in the preface to that edition, "Besides a lack of data, there is deep scientific uncertainty regarding every aspect of the risk assessment framework: (i) particle characteristics that may affect toxicity; (ii) their fate and transport through the environment; (iii) the routes of exposure and the metrics by which exposure ought to be measured; (iv) the mechanisms of translocation to different parts of the body; and (v) the mechanisms of toxicity and disease. In each of these areas, there are multiple and competing models and hypotheses. These are not merely parametric uncertainties but uncertainties about the choice of the causal mechanisms themselves and the proper model variables to be used, that is, structural uncertainties. In addition, these may not be sufficient to capture all the dimensions of risk." Over the past few years, there have been rapid advances in our understanding of some of these risks, necessitating this new edition. However, the occupational environment is where the potential for human exposure is the greatest and where our focus should stay.

The book presents a coherent framework for analyzing the available information to arrive at robust decisions. It presents the latest scientific understanding of the toxicity and health effects of nanoparticles, the technical issues relating to exposure assessment and management, the ways in which the current risk paradigm can be used or modified to deal with the challenges of nanoparticle risks. It presents complementary methods for risk assessment that efficiently use existing information and expert knowledge to extrapolate risks for new nanomaterials. Finally, it discusses these risk assessment methodologies in the context of existing regulatory oversight mechanisms in the United States and Europe and suggests useful ways in which such frameworks can be modified to make these more efficient and effective.

There are some significant updates and improvements to the first edition of this book. The first chapter sets the stage by considering some of the definitional challenges in the area of nanotechnologies and how these impact risk assessment and management. There needs to be a language of engineered nanomaterial risk that clarifies rather than obfuscates the challenges

being faced, starting with the distinction among the terms *nanotechnologies*, *nanomaterials*, and *nanoparticles*, which are too often used interchangeably and inappropriately. The chapter also talks about the important issue of responsible innovation, and the nexus between definitional issues of what "nano" means, or what "responsibility" entails. The second chapter includes a discussion of several new exposure assessment strategies that have been published in the peer-reviewed literature, including an influential study by the National Institute for Occupational Safety and Health (NIOSH), and a strategy published by a group of 10 leading experts in the United States representing a consensus on the state-of-the-art for exposure assessment for nanomaterials. The last section in this chapter provides a "best practices" strategy for exposure assessment in the nanotechnology industry that takes into account these uncertainties and leverages current knowledge on toxicology, epidemiology, and instrumentation. Chapter 3 provides an updated discussion of key additional publications on the toxicology and biokinetics of nanomaterials; the available data and methods to characterize the health hazard and risk of exposure to nanomaterials in the workplace; and additional examples of the use of such data and methods to develop occupational safety and health guidance. Pulmonary bioassay studies are extremely useful for comparing the potential hazards of different test materials and for suggesting mechanisms of action, as well as for generating hypotheses to be tested. Along these lines, Chapter 4 describes the methodology and results of a subchronic inhalation study in rats with aerosolized carbon nanofibers (CNFs). Chapter 5 presents some new studies on the use of expert judgment in nanotechnology, along with further understanding of uncertainty in nano-risk assessment, and novel approaches for assessment. The uses of subjective exposure assessments and cognitive biases inherent in them are also addressed. Chapter 6 includes a "Validation" section, which has been updated to include quantitative data from the Lawrence Berkeley National Laboratory's four-phase study. A description of various Control Banding (CB) tools developed subsequent to CB Nanotool and their evaluations is also included. Chapter 7, Controlling Nanoparticle Exposures, includes new information from the literature on filtration of airborne nanoparticles, efficacy of protective gloves, protective clothing, and respiratory protection at preventing exposure to nanoparticles, and a short new section containing information on case studies that have investigated approaches that might be used together in a workplace to limit exposures to nanoparticles. Chapter 8 presents several important updates and changes, including the failure to date of efforts to amend the Toxic Substances Control Act, the status of the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) Implementation Project on nanomaterials, status of the Guidance documents, information on the Plant Protection Products Directive, which came into effect after the first edition of the book was published, European Chemicals Agency's review of nanotechnology coverage and plan to cover it more systematically after 2012, status of the applicability of the quantitative thresholds to nanomaterials, and information about exposure estimates and hazard identification and test guidelines.

The book is aimed at practitioners of risk assessment in corporate and regulatory sectors, who are in the position of making decisions about nanoparticle risks in the absence of definitive evidence of the health risks posed by nanomaterials. The primary audience for this book, as for the previous edition, will likely be corporate risk assessment managers at large chemical and electronics manufacturing industries; insurance company risk assessors; health and safety managers in large, medium, and small industries that manufacture or use nanoparticles; and public policy analysts/advisors at regulatory agencies, nanotechnology business groups.
The secondary audience will be academics in the area of risk assessment, public policy, occupational health and safety, environmental management, and technology policy, at various universities.

CHAPTER 1

The Challenge of Nanomaterial Risk Assessment

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Chapter Outline

1.1 Introduction

In 1990, two consecutive papers appeared in the *Journal of Aerosol Science* asking whether inhaled particles smaller than 100 nm in diameter are more harmful than an equivalent mass of larger particles (Ferin et al., 1990; Oberdörster et al., 1990). On a mass-for-mass basis, nanometer-scale particles of titanium dioxide (TiO_2) and aluminum oxide (Al_2O_3) were shown to elicit a significantly greater inflammatory response in the lungs of rats compared with larger particles with the same chemical composition. At the time, this research was little more than a curiosity—a novel response to relatively benign materials. But with the advent

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of the field of nanotechnology, the importance of understanding how the physical form and chemical composition of increasingly sophisticated nanoscale materials influence human health risk factors has escalated. Now, the ability to identify, assess, and address potential impacts from intentionally engineered nanomaterials is seen by many as critical to the success of an increasing range of nanotechnology-based products.

Ferin and colleagues attributed the size-specific effects they observed by to an increased rate of interstitialization of nanometer-scale particles in the lungs. They concluded: "Phagocytosis of particles in the alveoli counteracts the translocation of particles into the interstitial space. Alveolar macrophage death or dysfunction promotes translocation from alveoli into interstitium. Particles of about 0.02–0.03 μm in diameter penetrate more easily than particles of *ca.* 0.2–0.5 μm. Small particles usually form aggregates. Their aerodynamic size determines the deposition in the airways. After deposition, they may deagglomerate. If the primary particle size is *ca.* 0.02–0.03 μm, deagglomeration may affect the translocation of the particles more than for aggregates consisting of larger particles" (Ferin et al., 1990). This simple statement outlined two emerging aspects of materials that potentially mediate their impact: particle size and dynamic behavior. In follow-up studies, further associations between the composition and form of materials and their effects were uncovered—most notably the role of particle surface area in mediating pulmonary toxicity. Using TiO_2 samples consisting of two distinct sizes of primary particles, Oberdörster et al showed that while inflammatory response following inhalation in rats depended on particle size, normalization by surface area led to a common dose-response function (Oberdörster, 2000). Moreover, this response seemed to depend only weakly on the composition of chemically inert materials: using surface area as the dose metric instead of the more conventional mass concentration, Maynard and Kuempel, for instance, showed that a range of insoluble materials typically classified as "nuisance dusts" followed a similar dose-response curve for pulmonary inflammation in rats. However, more chemically active materials such as crystalline quartz demonstrated a markedly different dose-response relationship (Maynard and Kuempel, 2005).

This early research was largely driven by occupational aerosol exposures. There were concerns that the hazards associated with fine dusts, ranging from welding fume to metal and metal aerosol powders, were not predictable from the chemical composition of these materials alone. What began to emerge was an understanding that the physicochemical nature of inhaled particles was more relevant than previously thought in eliciting a response following exposure and that materials with a nanometer-scale biologically accessible structure (whether they were discrete nanometer-scale particles or had a nanometer-scale surface structure, as in the case of aggregates of nanoparticles) had the potential to show previously unanticipated biological behavior. That this new research on what were termed "ultrafine aerosols" was associated with occupational health is perhaps not surprising, given the field's long history of addressing hazards associated with exposure to aerosol particles with varying sizes, shapes, and compositions (Maynard, 2007).

While research into occupational exposure to ultrafine aerosols was developing, environmental epidemiology studies were also beginning to uncover associations between ambient aerosol particle size and morbidity and mortality. Starting a the six-cities study (Dockery et al., 1993), evidence emerged suggesting that ambient particles smaller than approximately 2.5 μm (PM2.5) had an elevated impact on human health (Schwartz and Morris, 1995; Pope, 1996; Schwartz et al., 1996). As small particles were implicated in pronounced pulmonary and cardiovascular effects following inhalation exposure (e.g., Seaton et al., 1995), researchers began to correlate impacts with exposure to ultrafine particles (Wichmann and Peters, 2000; Brown et al., 2002; Pekkanen et al., 2002; Chalupa et al., 2004). Although clear associations between ultrafine particle exposure and health impacts remained uncertain, this research hinted at a link between aerosol inhalation and health impacts mediated by particle size as well as chemistry, with smaller particles exhibiting a higher degree of potency.

In the late 1990s, toxicology and epidemiology research on ultrafine aerosols began to come together. But it was the formal advent of the field of nanotechnology toward the end of the 1990s that galvanized action toward developing a more complete understanding of how material physicochemical characteristics impact on material hazard and how nanoscale materials might lead to previously unanticipated health impacts. In the 1990s, federal research agencies in the United States began looking to identify and nurture a new focus for science, engineering, and technology that would stimulate research funding and lead to economic growth. At the time, advances across the physical sciences were leading to breakthroughs in understanding how material structure at the near-atomic scale influenced functionality and how this nanoscale structure might be intentionally manipulated. Recognizing the potential cross-disciplinary and cross-agency significance of these breakthroughs, the Interagency Working Group on Nanotechnology (IWGN) was established within the federal government of the United States to promote the science and technology of understanding and manipulating matter at the nanometer scale (IWGN, 1999)—the scene was set for the global emergence of nanotechnology.

Although not fully realized until late in the twentieth century, the field of nanotechnology had its roots in the advances during this century in materials science and high-resolution imaging and analytical techniques. As techniques such as X-ray diffraction and transmission electron microscopy (TEM) began to illuminate the structure of materials at the atomic scale—and how this structure influences functionality—interest grew in improving materials through manipulation of this structure. The fields of materials science and synthetic chemistry began to explore how small changes in structure at the atomic and molecular levels could alter behavior at the macroscale. But it was perhaps physicist Richard Feynman who first articulated a grander vision of nanoscale engineering. In a 1959 lecture at Caltech, titled "There's plenty of room at the bottom," Feynman speculated on the revolutionary advances that could be made if scientists and engineers developed increasingly sophisticated control

over how substances were built up at the nanoscale (Feynman, 1960)—a level of control that had then remained largely out of reach. Despite Feynman's lecture often being considered the foundation of modern nanotechnology, there is little evidence that it had much impact at that time (Toumey, 2008, 2010). However, the advent of scanning probe microscopy in 1982 (Binnig et al., 1982), together with advances throughout the physical and biological sciences in imaging and understanding matter at the nanometer scale, began to open up the possibility of altering the functionality of a wide range of materials through nanoscale engineering.

Some of the more extreme and speculative possibilities of building materials and even devices molecule by molecule were captured by Eric Drexler in his book *Engines of Creation*, inspired by shrinking human-scale materials engineering down to the nanoscale (Drexler, 1986). Although many of the ideas put forward by Drexler were treated with caution and sometimes skepticism by the scientific community, there was a groundswell of excitement through the 1980s and 1990s over the possibilities offered by emerging techniques in enabling systematic manipulation of matter at the nanoscale, which allowed nanoscale structure-mediated functionality to be exploited at the macroscale. This excitement was buoyed up by the formal discovery of carbon nanotubes (Iijima, 1991)—a new and functionally unique allotrope of carbon—and the demonstration of single-atom manipulation using scanning probe microscopy (Eigler and Schweizer, 1990). Working at this scale, new opportunities began to arise, including enhancing the structure of materials; engineering materials tailored to exhibit specific physical, chemical, and biological behaviors; exploiting novel electron behavior in materials; and building increasingly sophisticated materials that could demonstrate multiple and context-specific functionality. The door was being opened to a new era of enhancing existing materials and products and creating innovative new ones by intentionally manipulating the composition and physical form of substances at the nanoscale.

Riding the wave of this cross-disciplinary "revolution" in science, engineering, and technology, President Bill Clinton announced a new U.S. initiative to explore and exploit the science and technology of the nanoscale on January 21, 2000 (Clinton, 2000). In an address at Caltech on science and technology, he asked his audience to imagine "materials with 10 times the strength of steel and only a fraction of the weight; shrinking all the information at the Library of Congress into a device the size of a sugar cube; detecting cancerous tumors that are only a few cells in size" and laid the foundation for the U.S. National Nanotechnology Initiative (NNI). Since then, the NNI has been at the forefront of national and international research and development in nanoscale science and engineering.

As nanotechnology began to gain ground, however, it did not take long for concerns to be raised over the potential health and environmental implications of the technology. In 2000, Bill Joy, the co-founder of Sun Microsystems, wrote an influential essay for the magazine *Wired* titled "Why the Future Doesn't Need Us," in which he raised concerns about the impacts of nanotechnology (Joy, 2000). This was followed by calls for a moratorium on

research until more was known about the possible adverse impacts by one Civil Society group (ETC Group, 2003). Concerns were also raised by the reinsurance company Swiss Re in 2004 (Hett, 2004), and later that year, the U.K. Royal Society and Royal Academy of Engineering launched a highly influential report on the opportunities and uncertainties of nanotechnology (RS/RAE, 2004). At the center of the Royal Society and Royal Academy of Engineering report were concerns that engineered nanoscale materials with unique functionality may lead to unexpected exposure routes; may have access to unanticipated biological compartments; and may exhibit unconventional biological behavior associated with their size. In particular, concern was expressed over materials intentionally engineered to have nanoscale structure—nanomaterials—and particles and fibers with nanometer-scale dimensions—nanoparticles and nanofibers.

The Royal Society and Royal Academy of Engineering report marked a move toward a more integrated approach to the potential risks associated with nanotechnology. As global investment in nanotechnology research and development has grown (it has been estimated that global research and development investment in nanotechnologies exceeded $18 billion as far back as 2008), so has interest in identifying, understanding, and addressing potential risks to human health and the environment (e.g., Luther, 2004; Chemical Industry Vision 2020 Technology Partnership and SRC, 2005; Oberdörster et al., 2005; SCENIHR, 2005, 2009; Maynard et al., 2006; Nel et al., 2006; ICON, 2008; Klaine et al., 2008; RCEP, 2008; NNI, 2010; PCAST, 2010; NRC, 2012; Westerhoff and Nowack, 2013). This interest has been stimulated by concerns that novel materials have the potential to lead to novel hazards and risks. But fueling it has been the research, as noted earlier, on the role of particle size, physical form, and chemistry in mediating biological interactions and responses. With the advent of nanotechnology and the production of increasingly sophisticated engineered nanomaterials, research strands developing an understanding of the potential human health impacts of fine particles were thrust into the mainstream and became the basis of new thinking about how potential risks associated with new materials can be addressed.

1.2 The Nature of the Nanomaterial Challenge

As awareness has grown over the emerging human health issues raised by engineered nanomaterials, questions have revolved around their potential impacts at every stage of a material's life cycle—from production to transport for use, to disposal, and even to recycling (Klöpffer et al., 2007; Gottschalk and Nowack, 2011; Westerhoff and Nowack, 2013). This has been stimulated by increasing awareness over the need for a life-cycle approach in addressing any human or environmental health risk from physical, chemical, or biological agents. But it has also been forced by the dynamic nature of many engineered nanomaterials. Where potential impact depends on physical form as well as chemistry, changes in physicochemistry—along with availability or exposure potential—across a

material's life cycle, can have a profound impact on risk within different contexts. Thus, the risk presented by just-generated carbon nanotubes, for instance, may be markedly different from the risk presented by processed or purified nanotubes, which not only represent altered physicochemistry but also a different exposure potential. Likewise, once these carbon nanotubes have been incorporated into a product—say, an epoxy resin matrix—the exposure potential and the physicochemical nature of any material that is released is profoundly different from that of the starting material (Harper et al., 2015). And as the resulting product is used and eventually disposed or recycled, the hazard and exposure potential differ yet again. Thus, the risk profile of a nanomaterial over its life cycle is complex—even if that material is relatively stable. However, when nanomaterials undergo transformations through their life cycle—as many do—through processes such as agglomeration, dissolution, surface adsorption/desorption, chemical reaction, or other interactions with close-proximity materials, the challenges of evaluating and addressing risk become commensurately more difficult.

Within this complex challenge, much attention has been placed on exposure potential as a first order determinant of potential risk. And this, in turn, has led to the workplace being an area of particular concern, as an environment where inhalation of, dermal contact with, and possibly ingestion of engineered nanomaterials before they are incorporated into products could be significant (Maynard and Kuempel, 2005; NIOSH, 2010). Much of this concern has focused on nanoparticles—nominally particles smaller than 100 nm in diameter—as being most likely to enter the body and cause unanticipated harm. However, this is an environment where airborne nanostructured materials that are micrometers in diameter can be inhaled and enter the upper airways and lungs, placing an onus on understanding interactions with relatively large aggregates and agglomerates of nanoscale particles, as well as micrometer-scale particles with biologically accessible nanoscale features (Maynard, 2007).

The importance of workplace exposures to engineered nanomaterials is reflected in the growing literature on it and expanding research initiatives on occupational exposure, hazard, and potential risk (e.g., Maynard, 2007; Schulte et al., 2010, 2014). In the United States, for example, the National Institute for Occupational Safety and Health (NIOSH) has developed a detailed research strategy addressing the evaluation, characterization, and management of workplace health risks associated with engineered nanomaterials (NIOSH, 2012). This has been developed in response to growing concerns over the safety of workers as nanotechnology and the production and use of engineered nanomaterials continue to grow. But it has also been prompted by a number of evaluations that highlight the workplace as a critical area where further research on potential risks and their mitigation is needed.

Research that is now being pursued is beginning to help address the safe handling of nanomaterials in the workplace. Yet, more generally, there is a sense that the key human health questions associated with engineered nanomaterials remain elusive. Numerous reports have listed specific research gaps with regard to engineered nanomaterial safety (e.g.,

SCENIHR, 2005, 2009; Maynard, 2006; EPA, 2007; ICON, 2008; NNI, 2008, 2011; RCEP, 2008; Aitken et al., 2009; EFSA, 2009; ENRHES, 2010; UK House of Lords, 2010; NRC, 2012). However, few of these manage to establish key research gaps within a compelling strategic framework that relates research challenges to real-world decision making. This was perhaps most obvious in the 2008 engineered nanomaterials risk-research strategy published by the NNI (NNI, 2008), which was criticized by a National Academies of Science review panel for failing to be strategic enough (National Academies, 2009). Although the criticisms were hard hitting, the NNI report was not the only one failing to clearly identify the nature of the problem or a viable route to its resolution. (The NNI also responded to the critique in the follow-up 2011 strategy (NNI, 2011).) This lack of clarity is indicative of the nanomaterial safety research community, as a whole, struggling to formulate the problems assumed to be caused by these new and often novel materials. In effect, although a clear definition of the problem is the first step to assessing and addressing risks (National Academy of Science, 2008), many years of efforts to develop an understanding of the potential risks presented by engineered nanomaterials attest to the difficulties in characterizing the problem, let alone the solution, when dealing with complex and novel materials. There is a possibility, however, that these difficulties have been compounded by an adherence to definitions of nanotechnology and engineered nanomaterials that are not directly relevant to human health risks. To understand how definitions may have obfuscated research into potential risks and to explore the possible roots of the resulting definition rut, it is worth examining what is generally meant by the term "engineered nanomaterial."

1.3 The Problem with Definitions

"Engineered nanomaterial" is often used as shorthand for describing in qualitative terms a group of materials that have certain features in common. These materials typically have a physical structure that is of the order of nanometers in scale; their structure at this scale is intentionally engineered; and they are designed to allow product developers and producers to take advantage of this structure. They are a subset of the broader field of nanotechnology, defined by the NNI as "the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modeling, and manipulating matter at this length scale" (NSET, 2010). From this (and similar) definitions, engineered nanomaterials are often described as materials with structures that have at least one dimension approximately between 1 and 100 nm and exhibit unique or substantially enhanced properties, including scale-specific electrical, optical, and mechanical behavior. These scale-specific properties are at the center of current government and commercial investments in engineered nanomaterials: If a substance can be engineered to behave in different ways, it can potentially be used to add value to a product or used even as the basis of a completely new product. This, in turn, extends the toolbox

available to scientists and technologists to make new products and to explore new ways to address the challenges of providing people with water, food, energy, and health care and to meet a host of other pressing societal needs. Yet these same scale-specific properties are also at the center of concerns over possible new risks associated with engineered nanomaterials—if a new material behaves in novel ways, according to the argument, what are the chances of these novel behaviors leading to unexpected and unanticipated harm to people and the environment?

As concerns over the potential adverse impacts of engineered nanomaterials on human health and the environment have arisen, common definitions of engineered nanomaterials have been used to identify new materials that may present unanticipated or poorly understood risks to human health. However, since biological systems respond to a variety of physical and chemical stimuli that do not necessarily map directly onto those characteristics encapsulated in the definitions of engineered nanomaterials, these attempts have run into difficulties. As a case in point, the scale range usually used to describe engineered nanomaterials (1–100 nm) has relatively little bearing *on its own* in determining the risk a substance presents to people or the environment (Auffan et al., 2009; Drezek and Tour, 2010). In effect, risk "problems" associated with engineered nanomaterials have been formulated in terms of established "technologic" definitions of nanotechnology and engineered nanomaterials, which do not adequately reflect the potential of a material to cause harm. This is not to say that efforts to date have been wasted. Framing the potential risks associated with engineered nanomaterials in terms of established definitions does provide some insight into emergent risks. For example, potential human exposure to particles may well be enhanced as their size decreases to the nanoscale. But at the same time, this framing runs the danger of highlighting issues that may not be relevant while obscuring others that are relevant.

The problem with definitions has been highlighted, particularly in Europe, in recent years. In 2010, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) explored the scientific basis for the definition of the term "nanomaterial" (SCENIHR, 2010). As a result, on October 18, 2011, the European Commission adopted a recommendation on the definition of a nanomaterial—a move that did not garner support in some quarters (Maynard, 2011). In 2014, the European Commission Joint Research Center published an extensive review of the definition, running to over 300 pages (EC, 2014a,b). Despite this evaluation, there remains no widely accepted, scientifically grounded definition of engineered nanomaterials for the purposes of identifying and managing potential risks.

If future research and action on risks presented by engineered nanomaterials is to be relevant and responsive, careful consideration is needed on what leads to a new material presenting new, unusual, or poorly defined human health risks. In effect, the challenge is how to develop an approach to differentiating between materials that present conventionally understandable and addressable risks from those that present novel risks that require new understanding and methods to ensure their safe use.

1.4 Principles-Based Problem Formulation for Engineered Nanomaterials

One approach to this challenge is to use a set of principles, rather than definitions, to identify engineered nanomaterials for which new research is needed to ensure their safe and responsible development and use. Three possible principles that might be of use here are principles encapsulating emergent risk, plausibility, and impact (Maynard et al., 2011).

1.4.1 Emergent Risk

Emergent risk in this context captures the likelihood of a new material causing harm in a manner that is not apparent, assessable, or manageable based on current approaches to risk assessment and management. This might include the ability of small particles to penetrate to normally inaccessible places, the failure of certain established toxicology assays to respond in expected ways to some materials, scalable material behavior that is not addressed by conventional approaches to assessing hazard (such as surface-area mediated responses where mass is the exposure metric of choice), or the possibility of abrupt scale-dependent changes in material interactions with biological systems. This understanding of "emergence" depends on the potential of a material to cause harm in unanticipated or poorly understood ways, rather than its physical structure or properties *per se*. As such, it is not subject to rigid definitions of nanotechnology or nanomaterials. Instead, it allows engineered nanomaterials that potentially present unanticipated risks to human health and the environment to be distinguished from those that probably do not.

Many of the engineered nanomaterials that have been raising concerns in recent years have shown potential to lead to emergent risks, and would be classified as requiring further investigation under these criteria. But the concept also embraces more complex nanomaterials that are either in the early stages of development or have yet to be developed; this includes active nanomaterials and self-assembling nanomaterials.

1.4.2 Plausibility

"Plausibility" provides an indication of the likelihood of a new material, product, or process presenting a risk to humans or the environment. It is dependent on the possible hazard of a material *and* the potential for exposure or release to occur. But it also addresses the likelihood of a new material being developed and commercialized, which may lead to emergent risks. For example, the "gray goo" of self-replicating nanobots envisaged by Bill Joy in the 2000 *Wired* article (Joy, 2000) might legitimately be considered an emergent risk, but it is far from being a plausible risk. In this way, plausibility acts as a crude filter to distinguish between speculative risks—which are plentiful—and credible risks—which are not.

1.4.3 Impact

"Impact" in this context is an indicator of the extent of the harm a poorly managed engineered nanomaterial might cause. It provides a qualitative "reality check" to guard against extensive efforts to address risks that are unlikely to have a significant impact on human health while ensuring that research and actions having the potential to make a significant difference is identified and supported. Of course, evaluating the impact of a material or product before it has been fully developed or commercialized is not a trivial process, and there is a significant chance that the predictions will not pan out. However, this is an area where scenario-planning methodologies may help explore impacts that are more and less likely from different engineered nanomaterials.

The three principles discussed above provide a basis for developing an informed approach to addressing potential risks from engineered nanomaterials. These are tools that allow, in principle, new materials that raise safety concerns to be differentiated from those that may be novel from an applications perspective but do not present undetected, unanticipated, or enhanced risks. In particular, they are technology independent and, therefore, can be used as long-term drivers of research into the risks of potential nanoscale materials. Whether dealing with early or late generations of nanotechnology-based products, they provide a means of identifying products that require closer scrutiny from a risk perspective. These principles are not a substitute for clear definitions of materials and products that are needed to underpin regulatory decision making, but they do provide a framework within which specific classes of materials and products might be better identified and defined for the purpose of regulation. More significantly, they enable the potential human health risks of engineered nanomaterials to be approached from a position that is informed by relevant and scientifically plausible concerns, rather than being constrained by material definitions that emphasize physical and chemical function rather than potential to cause harm.

1.5 Applying the Three Principles to Engineered Nanomaterials

The three principles described above can be applied across the life cycle of materials and products to identify where context-specific risks that need further research may arise in order to assess and manage them. Here, the concepts of plausibility, emergence, and impact can help distinguish what may be more or less significant in addressing risk. For instance, generating and handling multiwalled carbon nanotubes in a workplace may present a plausible and emergent risk to workers. Given that the production and use of this material is a relatively new area, there are indications that some forms of the material are more hazardous than their chemical makeup alone might indicate, and the potential exists for human exposure to occur through inhalation and possibly ingestion. However, handling a baseball bat made of a composite material that contains multiwalled nanotubes or driving an electric car powered by a nanotube-enabled battery presents a very different scenario. Although the emergent

risk associated with the raw material might exist in each scenario, the plausible risk—the likelihood of people or the environment being exposed during product use to sufficient quantities of material in a form that can cause substantial harm—is significantly low. Finally, when products containing multiwalled carbon nanotubes are disposed of or prepared for recycling, a plausible and potentially high-impact risk may re-emerge, depending on the volume of material in circulation, as the material once again becomes potentially dispersible and biologically available.

In this example, the principles of plausible emergent risk and impact allow potentially significant risk "hot spots" to be identified over the life cycle of a material. This provides a systematic basis for identifying and prioritizing areas where further research is needed to address risks appropriately. It is an approach that has been explored further in the context of developing "prospective" case studies around speculative, yet highly plausible, applications of engineered nanomaterials (Maynard, 2014). Here and elsewhere, using principles, rather than definitions, to determine "action points" when addressing the safety of engineered nanomaterials is similar to the approach previously proposed in the Nano Risk Framework developed by DuPont and the Environmental Defense Fund (DuPont and Environmental Defense, 2007).

When these three principles are applied to existing and emerging engineered nanomaterials, a number of groupings of materials begin to emerge that may require deeper study (Maynard et al., 2011). These are discussed below.

1.5.1 Materials Demonstrating Abrupt Scale-Specific Changes in Biological or Environmental Behavior

These materials undergo abrupt size-dependent changes in their physical and chemical properties, which, in turn, affect their biological behavior, and this may present a hazard that is not predictable from larger-scale materials of the same composition. In this case, size and form at the nanoscale may increase or decrease hazard in a way that is currently not well understood.

1.5.2 Materials Capable of Penetrating Normally Inaccessible Places

Based on current understanding, these materials, by nature of their size, surface chemistry, or both, are able to persist in or penetrate places in the environment or the human body not usually accessible and may present emergent risks. Where there is a credible possibility of accumulation of, exposure to, or organ/system-specific dose associated with a nanoscale material that is *not* expected from how either the dissolved material or the larger particles of the material behave, a plausible and emergent risk potentially arises.

1.5.3 Active Materials

These materials undergo a significant change in their biological behavior in response to their local environment or an external stimulus (Subramanian et al., 2010) and potentially present dynamic risks that are currently not well understood within the context of quantitative and risk assessment based on chemical identity.

1.5.4 Materials Exhibiting Scalable Hazard That Is Not Captured by Conventional Risk Assessments

Where hazard is scaled according to parameters other than those normally associated with a conventional risk assessment, emergent risks may arise when dose-response relationships are inappropriately quantified. For instance, if the hazard presented by an inhaled material is scaled with the surface area of the material and yet the risk assessment is based on mass, the true hazard may not be identified. In this case, the material has the potential to cause unanticipated harm. Where a material's chemical composition and physical form combine to determine biological behavior, there is an increasing likelihood of response scaling with nonstandard measures of dose. In each of these examples (which are not exclusive), there are key research questions that need to be addressed if emergent and plausible risks are to be identified, characterized, assessed, and managed.

Used in this and similar ways, the principles of emergent risk, plausibility, and impact can help underpin a science-based approach to addressing the environmental, health, and safety implications of engineered nanomaterials through strategic research.

1.6 Responsible Research and Innovation

In June 2004, experts from 25 countries convened in Alexandria, Virginia, to discuss responsible research and development of nanotechnology (Tomellini, 2004). Driving them was a shared concern that its promise could be jeopardized if the potential environmental, health, and social impacts of nanotechnology are not proactively taken into account. This early global interest in responsible development led, in part, to the Organization for Economic Cooperation and Development (OECD) efforts to coordinate activities on nanomaterial safety testing and evaluation internationally. It also stimulated work in Europe on developing a "code of conduct" for responsible nanosciences and nanotechnologies research (EC, 2013) and similar work by businesses and other stakeholders on a "responsible nano code" (NIA, 2008).

This early interest in responsibility and innovation has evolved into the broader field of Responsible Innovation (or Responsible Research and Innovation). In Europe, for instance, there is now a growing emphasis on Responsible Research and Innovation within the

European Commission (EC, 2012), and in 2014, the new *Journal of Responsible Innovation* was launched (Taylor-Francis, 2015). Internationally, the Virtual Institute for Responsible Innovation is coordinating activities across 11 countries (VIRI, 2015).

In 2011, René von Schomberg defined responsible innovation as: "A transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products (in order to allow a proper embedding of scientific and technological advances in our society)" (von Schomberg, 2011). The ideas encapsulated here were clarified further by Stilgoe, Owen, and McNaughten in their seminal 2012 paper on Responsible Innovation, in which they defined responsible innovation as "taking care of the future through collective stewardship of science and innovation in the present" (Owen et al., 2012).

Although no longer being anchored specifically in nanotechnology, Responsible Innovation begins to lay the philosophical and ethical foundations for making practical decisions within nanomaterial production and use. It challenges researchers and businesses alike to think through the future consequences of their actions and to make early-on decisions that have the potential to avoid significant risk-liabilities further down the line. It also provides tools that help guide informed decisions that lead to more sustainable products by factoring in societal and environmental factors early in the development process, which reduces the chances of innovations becoming locked into potentially detrimental trajectories.

In 2008, the European Commission made recommendations on a "code of conduct for responsible nanosciences and nanotechnologies research" (EC, 2008). These recommendations foreshadowed current interests around responsible research and innovation and began to flesh out ideas on what responsibility means for researchers engaged in nanoscale science and engineering (Jones, 2009). They did, however, stop short of providing a framework for responsible innovation for business. In this context, there was some resistance to the idea that businesses need an explicit set of guidelines that define "responsibility"—partly under the assumption that few businesses set out to be "irresponsible"—that is, they do aim to be responsible by default. At the same time, the business community has long been aware of the potential impact of societal concerns on economic success and the need to ensure responsible behavior (and to be seen to be responsible) through formal initiatives. Corporate social responsibility, responsible care, and, more recently, sustainable business practices, all reflect this understanding. With growing uncertainty over the governance and impacts (both real and perceived) of technologies such as nanotechnology (Hodge et al., 2010), emerging ideas around responsible innovation are a natural extension of this trend.

In 2006, the Nanotechnologies Industries Association partnered with Insight Investment and the U.K. Royal Society to convene a workshop focusing on the technical, social, and commercial uncertainties associated with nanotechnology within a business context. The

Responsible Nano Code emerged out of the multi-stakeholder dialogue that followed (NIA, 2008). This code is built around seven foundational principles, which, together, create a sound framework for understanding what "responsibility" means from the perspective of nanotech businesses. The principles cover the bases of accountability and stakeholder engagement, environmental health and safety, wider societal and ethical impacts, and transparency and disclosure. They create the basis of a framework for responsibility in nanotechnology innovation that complements other initiatives.

Yet in spite of the creation of frameworks such as the Responsible Nano Code and Code of Conduct for Responsible Nanosciences and Nanotechnologies Research, there remains a need to translate the ideas behind Responsible Innovation to a growing community of entrepreneurs (Maynard, 2015). With continuing progress toward designing, producing, and using increasingly sophisticated engineered nanoparticles, it will become increasingly necessary to understand how the concepts of Responsible Innovation can be embedded within this community.

1.7 Looking Forward

Engineered nanomaterials clearly present a new set of challenges to evaluating and avoiding potential human health impacts and to developing safe, beneficial, and sustainable products. However, defining problems in ways that render these challenges tractable from a scientifically sound and societally responsive basis is not a simple task. The nearly two-decade-long emphasis on nanotechnology—and more recently the environmental, safety, and health implications of nanotechnology—has opened up new discussions on identifying and addressing emergent risks as, and even before, new materials and products come to market. Yet it is clearer now than ever that we need to be increasingly sophisticated in how we characterize the problems than need to be solved. The principles outlined above, together with relevant applications of Responsible Innovation, represent the first step toward this. But more is needed. Even at the basic level, there is a need to establish terminology for the risks of engineered nanomaterials, which clarifies rather than obfuscates the challenges being faced (Maynard et al., 2010), starting with distinguishing the terms *nanotechnology*, *nanomaterial*, and *nanoparticle*, which are too often used interchangeably and inappropriately. Beyond this, new approaches are needed to address the human health impacts of materials, where biologically relevant behavior is mediated by physical form as well as chemistry, relevant material characteristics are dynamic and context specific, and uncertainty over risk abounds. This is where the greatest challenges presented by nanoparticles and engineered nanomaterials lie, and they are not ones that are easily overcome by narrow definitions of what "nano" means or what "responsibility" entails.

As mentioned earlier in this chapter, a growing number of analyses have grappled with this challenge, with varying degrees of success. In 2006, a group of researchers published five

high-level research "grand challenges" to ensuring the safety of engineered nanomaterials in the journal *Nature* (Maynard et al., 2006). These included the following:

- Developing instruments to assess exposure to engineered nanomaterials in air and water
- Developing and validating methods to evaluate the toxicity of engineered nanomaterials
- Developing models for predicting the potential impact of engineered nanomaterials on the environment and to human health
- Developing robust systems for evaluating the health and environmental impact of engineered nanomaterials over their entire lifetime
- Developing strategic programs that enable relevant risk-focused research

These five challenges still stand as markers of where we need to be, rather than where we are, in ensuring the safe use of engineered nanomaterials. Progress continues to be made toward overcoming each challenge. But there is still a long way to go before the potential health impacts of new nanomaterials can be predicted and assessed effectively. At the same time, understanding of the knowledge gaps, which need to be addressed if safer uses of nanomaterials are to result, continues to evolve. A 2010 review of where we are and where we need to be on environmental, safety and health impacts of nanomaterials highlighted many of the issues raised in the 2006 *Nature* commentary (Nel et al., 2011). But it also placed a strong emphasis on innovative and multidisciplinary approaches to predicting, assessing, and managing potential impacts that go beyond the 2006 "grand challenges." In effect, the field of addressing potential risks associated with engineered nanomaterials is developing, along with the generation, production, and use of the materials themselves. This, in turn, places a metachallenge with regard to problem characterization, ensuring that the process of identifying the challenges that need to be met and the data gaps that need to be filled is grounded in science and precedent, and yet remains sufficiently flexible to respond to new information, and does not get bogged down in misconceptions, preconceived ideas, and outmoded understanding.

In other words, addressing the human health impacts of engineered nanomaterials is a complex challenge. But it is, nevertheless, an important one. Without a doubt, the next one to two decades will see the introduction of increasingly complex materials to the workplace, other areas of people's lives, and the environment, which can cause harm in unexpected ways and which potentially slip through the net of established management and governance frameworks. Addressing this challenge is vital for the continued health of people exposed to these new materials. But it is also essential to the long-term sustainability of new technologies that could prove vital to addressing global issues such as treatment of diseases, production of plentiful and nutritious foods, access to clean water and energy, and so on. In moving forward, a delicate balance will be needed between addressing emerging challenges and reassessing the framework within which those challenges are defined. Within this complexity, there are five themes that are likely to underpin the course of future research and action:

- Synergisms between the physical form and chemical composition of materials will continue to influence hazard, exposure, and risk.

- Human health and environmental impacts of engineered nanomaterials will be both time dependent and context dependent.
- Risk management approaches will have to deal increasingly with decision making in the face of uncertainty.
- Integrative approaches to risk assessment and management will become increasingly necessary as materials become increasingly complex.
- Responsible Innovation will need to be applied in practical ways to the challenges of designing and engineering new materials, translating innovations into entrepreneurial ventures, growing nano-enabled businesses, and ensuring the long-term sustainability of commercial applications of nanotechnology.

Irrespective of whether the current buzz-word is "nanotechnology," "nanomaterial," "nanoparticle," or something else, increasing control over matter at the level of atoms, molecules, and small clusters of molecules is leading to the generation of new and sophisticated materials that lie outside our current understanding of how materials potentially impact on human health. Rising to the challenge of ensuring that these sophisticated new materials are as safe and as useful as possible will depend on new thinking and new research on how potential risks are identified, assessed, and addressed. And in this endeavor, perhaps the two biggest dangers are ignoring the past—and the vast wealth of knowledge we already have on potentially harmful materials—and getting bogged down in technology frameworks that do not support science-based problem formulation. If we can avoid the technology hype and build on what is already known, however, there is every chance that new knowledge, tools, and methodologies will be developed, enabling us to assess—and manage—the potential impacts of nanometer-sized particles and nanometer-scale materials on human health.

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CHAPTER 2

Assessing and Managing Exposures to Nanomaterials in the Workplace

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Chapter Outline

Assessing Nanoparticle Risks to Human Health.
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2.1 A General Strategy to Assess Workplace Exposures

Exposure, in general terms, is defined as the intensity of a hazard (e.g., concentration of a gas or particle contaminant) at an appropriate interface between the environment and the individual (e.g., personal breathing zone for respiratory hazards) over a specific time interval that has biological relevance (e.g., 15 min for an acute adverse health outcome). Exposure assessment is the practice of inferring exposures for a group of workers based on a sample from the broader population. The goal of this chapter is to describe an assessment strategy that enables effective and efficient management of exposures to nanomaterials (i.e., a strategy that can identify jobs or tasks that have clearly unacceptable exposures) and requires only a modest level of resources to implement.

The American Industrial Hygiene Association (AIHA) presents a general strategy to assess exposures to hazardous agents in the workplace in this context (Ignacio and Bullock, 2006). This strategy is used by industrial hygienists to protect the health of workers worldwide. A flow diagram of the AIHA strategy is shown in Figure 2.1 as a multistep process.

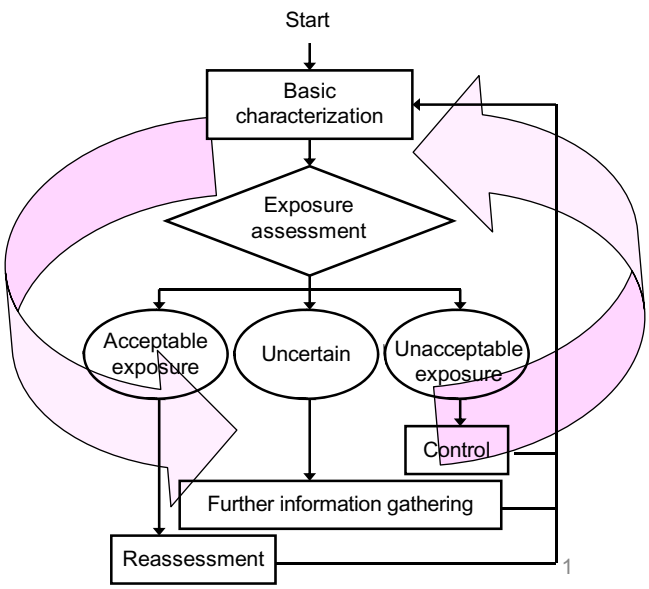

Figure 2.1
The AIHA exposure assessment strategy.

The first step is the *basic characterization* of the workplace, which includes collecting and organizing information on the workplace, workforce, and hazardous agents. The specific hazards (e.g., ergonomic hazards, chemical agents, and physical agents) and any controls (e.g., ventilation characteristics, use of personal protective equipment) are inventoried by workplace process and work task.

Next, this inventory is used to classify workers *a priori* into *similar exposure groups* (SEGs)—groups of workers anticipated to have a similar distribution of exposures. SEGs are defined on the basis of work similarity (similar profiles of job tasks), similarity of hazardous agents (similar chemicals to which they are exposed), and environmental similarity (ventilation characteristics, processes, etc.). The distribution of exposures for each SEG is then measured by using appropriate instruments, and these values are compared with an occupational exposure limit (OEL) with appropriate consideration of measurement uncertainty. On the basis of this comparison, exposures for the SEG are deemed acceptable, unacceptable, or uncertain. SEGs are then prioritized for follow-up and control, with SEGs having unacceptable exposures given high priority for control and those with uncertain exposures high priority for additional measurements. Low priority is given to SEGs with low exposure estimates made with low uncertainty.

This strategy is applied cyclically to achieve continuous improvement in the knowledge and control of exposures in the workplace. The tiered approach of ranking SEGs as having acceptable, uncertain, and unacceptable exposures enables focusing of resources on the most important issues. Available information is evaluated and used to conduct initial assessments of exposures and their associated uncertainties. Those initial assessments are then used to prioritize activities on the basis of the risks posed by the extent of the exposure and the extent of the uncertainty. Properly executing this strategy requires (i) an understanding of the workplace, workforce, and agents in the work environment; (ii) an understanding of potential exposures and at least an initial qualitative judgment on the potential sources likely to contribute to those exposures; (iii) mechanisms for understanding and appropriately resolving or managing uncertainty; (iv) mechanisms for driving appropriate follow-up to ensure that exposures are appropriately controlled; (v) mechanisms for documentation of all aspects of the process, results, and outcomes; and (vi) a structure that provides for prioritization and continuous improvement throughout.

2.2 Uncertainties Introduced by Nanotechnology

Nanotechnology is the manufacturing and application of materials and devices at the nanoscale (1–100 nm) enabled by the unique characteristics in the nanoscale, which are different from those in the macroscale. Engineered nanomaterials are materials with any external dimension in the nanoscale (<100 nm) or having internal structure or surface structure in the nanoscale. Nanomaterials can be classified as nano-objects and

nanostructured materials. Nano-objects are materials with one, two, or three dimensions in the nanoscale and include nanoparticles (all external dimensions <100 nm), nanofibers (two similar external dimensions <100 nm), and nanoplates (one external dimension <100 nm). Nanostuctured materials are materials having internal nanostructure or surface nanostructure. Airborne nanoparticles are divided into two groups: (i) incidentally formed nanoparticles and (ii) engineered nanoparticles. Incidental nanoparticles, sometimes called *ultrafine particles*, are particles unintentionally produced during an intentional operation. Combustion, welding, metal processing, and emissions from diesel engines are examples of major sources of incidental nanoparticles. Engineered nanoparticles are particles designed and produced intentionally to have a certain structure and size, usually smaller than 100 nm.

Industrial hygienists face many uncertainties when the general exposure assessment strategy from the AIHA is applied to nanotechnology and nanomaterials. The first uncertainty is that nanotechnology processes are relatively new and not well documented like those in many traditional workplaces. A second uncertainty is that the same properties that make nanomaterials desirable from a manufacturing standpoint sometimes also make them more biologically active and toxic. Particles smaller than 50 nm may obey quantum physics laws instead of those of classic physics and in response may exhibit physicochemically unique optical, magnetic, and electrical characteristics. As the diameters of particles decrease to the nanoscale, the proportion of atoms or molecules on the surface increases rapidly. The increase in surface area often increases surface reactivity, with chemical bonds on the surfaces of particles being more unstable and reactive than those in the center. Thus, a higher proportion of atoms on the surface can allow a greater likelihood of interactions with biologically reactive groups that may cause further toxicity (Kreyling et al., 2006).

The understanding of health risks posed by most nanomaterials is, at best, limited. Key mechanisms for exposure processes and toxic effects of manufactured and incidental nanomaterials on humans remain poorly understood. Mechanistic uncertainties include those related to the following questions: (i) How long do manufactured nanomaterials persist in the atmosphere? (ii) How stable are nanomaterials over time, given specific occupational conditions? (iii) What is the effect of particle shape on their fate and transport? (iv) What are likely routes of exposure (e.g., inhalation, dermal, ingestion, and ocular)? (v) What are the metrics by which exposure should be measured (e.g., particle mass or number or surface area concentration)? (vi) What are the key mechanisms of translocation to different parts of the body after nanomaterials enter the body? (vii) What are the possible mechanisms of toxicity, including oxidative stress due to surface reactivity, presence of transition metals leading to intracellular calcium and gene activation, and intracellular transport of nanomaterials to the mitochondria? (Kandlikar et al., 2007).

Much of what we do know from toxicologic studies suggests that many of the OELs developed for traditional exposures primarily consisting of fine and coarse particles may not

be appropriate for exposures to the nanoscale form of a material. Most OELs are based on the metrics of mass concentration of particles in the "respirable" or "inhalable" size range. Similarly, the U.S. Environmental Protection Agency regulates atmospheric particulate matter in National Ambient Air Quality Standards as the mass concentration of particles smaller than 2.5 µm ($PM_{2.5}$, fine particles) or smaller than 10 µm (PM_{10}, coarse + fine particles). Other metrics may be more appropriate for assessing nanoparticle exposures. To illustrate this issue, the size distribution of particles emitted from a diesel engine is shown by number and mass concentration in Figure 2.2. Most of the mass concentration of diesel exhaust is associated with particles in "accumulation" (sometimes referred to as the "fine mode") and coarse modes, whereas the ultrafine or nanoparticle mode typically contains the vast majority of the number of particles. Slight changes in operating conditions of a diesel engine can dramatically change the ratio of particle concentrations in different-sized modes. As a consequence, the number concentration of an aerosol is often poorly correlated with its mass. Moreover, the particles in different modes may differ in composition substantially from the fine-mode and coarse-mode particles.

This issue has been observed repeatedly in a variety of settings. For typical atmospheric aerosols, Kreyling et al. (2003) reported that nanoparticles account for less than 10% of the mass concentration of particles smaller than 2.5 µm in diameter ($PM_{2.5}$) but more than 90%

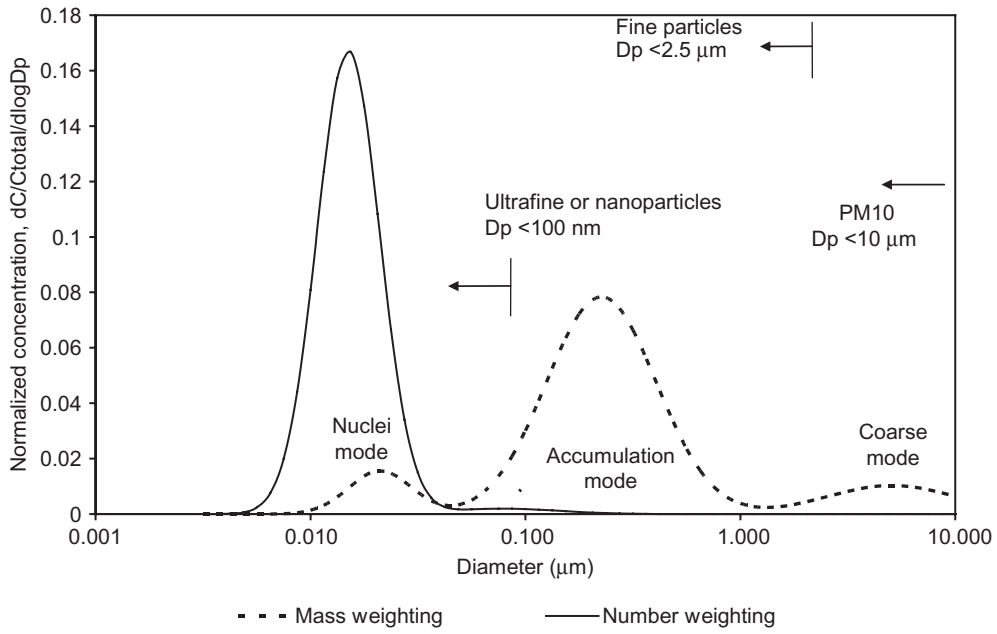

Figure 2.2
Idealized size distribution of diesel exhaust aerosol based on particle number and mass showing different modes. *Adapted from Kittelson (1998).*

of the number concentration. Heitbrink et al. (2009) found similar results for incidental nanoparticles in the automotive industry in the production of engines. For nanomaterials, high particle number concentrations may be present in the air despite very low mass concentrations. For example, a low concentration of 10 μg/m^3 of unit-density, 1-nm particles translates into ~19 × 10^9 particles/cm^3. The same mass concentration of 1-μm particles would amount to only 19 particles/cm^3 (a billion-fold difference). Likewise, the surface area concentration corresponding to 10 μg/m^3 of unit density 1-nm particles is 60,000 μm^2/cm^3, and for 1-μm particles it is 60 μm^2/cm^3 (a thousand-fold difference).

The absence of OELs for nanomaterials presents a problem for implementing the AIHA strategy for exposure assessment. Sampling and analytical procedures for measuring exposures to nanomaterials can be challenging and expensive. The net result is that exposure monitoring in occupational settings for nanomaterials is typically minimal or non-existent. When monitoring efforts are in place, they generally do not follow a consistent strategy but, rather, are executed in an ad hoc fashion. In the remainder of this section, we present what is known about potential routes of exposure and toxicity of nanomaterials. We then discuss OELs that apply to nanotechnology, with an emphasis on several new recommended exposure limits from the National Institute for Occupational Safety and Health (NIOSH) and benchmark exposure limits from Europe. Last, we discuss instruments that can be used to measure airborne personal exposures and area concentrations.

2.3 Exposure Routes

2.3.1 Inhalation

The fraction of particles that deposit in different regions of the respiratory tract depends strongly on particle size as estimated by a deposition model from the International Commission on Radiological Protection (ICRP), as shown in Figure 2.3 (ICRP, 1994). For particles larger than 100 nm, the predictions of the ICRP model have been experimentally validated by numerous studies, as reviewed by Vincent (2005). Although fewer studies are available, deposition measured experimentally for nanoparticles shows reasonable agreement with ICRP model predictions for the tracheobronchial and alveolar regions (Jaques and Kim, 2000) and in the extrathoracic (nasal) region (Cheng et al., 1996).

For particles larger than 300 nm, inertial forces and gravity settling dominate as the primary mechanism of deposition. Most >300-nm particles deposit in the head airways because inertial forces cause them to deviate from rapidly moving air and hit the mucus-laden walls. Inertial forces are, however, sufficient to cause some deposition of these particles in the tracheobronchial region. If particles in this size range pass to the alveolar region, they are often deposited due to gravity settling because the airflow is relatively slow and the residence time is long in the deep lung.

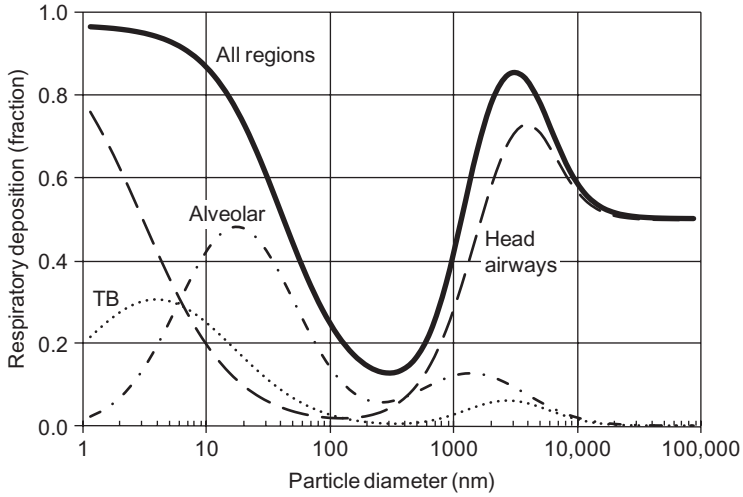

Figure 2.3
The fraction of particles depositing in the respiratory tract from 1 nm to 100,000 nm (100 μm) calculated using the regional deposition model from the ICRP (ICRP, 1994).

For particles smaller than 300 nm, deposition is dominated by the physical process known as *diffusion*—the net movement of a particle caused by Brownian motion. Superimposed on a particle's movement with flowing air, Brownian motion is an irregular wiggling motion imparted to the particle by the constant bombardment of air molecules, which increases with decreasing particle size. The fraction of particles that are deposited by diffusion can be expressed as the distance a particle moves due to diffusion divided by the airway dimension. Only the smallest particles have sufficient movement for deposition by diffusion in the relatively large airways and fast-moving air of the head airways (>20% for particles <10 nm) and the tracheobronchial region. The greatest deposition fraction for particles from 10 nm to 100 nm occurs in the alveolar region because air is slow moving and the alveoli are small (~200 μm in diameter). Particle deposition in the alveolar region peaks at approximately 20 nm because smaller particles are deposited in the upper airways before reaching this region and larger particles experience less movement by diffusion.

The respiratory system is able to clear particles, depending on where they are deposited. Particles that are deposited in the head airways are cleared by the mucociliary epithelium, which moves mucus and deposited particles toward the glottis, where they are swallowed (ingested). The tracheobronchial region is also covered with mucociliary epithelia that move the particles deposited in mucus upward toward the oropharynx (mucociliary escalator), where they are swallowed. Particles depositing in the alveolar region trigger an immune reaction in which alveolar macrophages engulf the particle and move it to the tracheobronchial region.

2.3.2 Dermal Exposure

There is considerable uncertainty about whether dermal exposure is a significant route of exposure for nanomaterials, as reviewed by Labouta and Schneider (2013). Cuts and lacerations can facilitate dermal penetration, many researchers such as Schulz et al. (2002), who studied the penetration of nanoparticles used in sunscreens, found little penetration of particles through an intact stratum corneum. However, penetration through the skin is influenced by nanoparticle characteristics (composition, surface coating, and geometry), skin characteristics, and situation (e.g., flexing of the skin). Monteiro-Riviere and Riviere (2009) showed that skin was permeable to some nanoparticles, especially quantum dot nanoparticles. The formulation of the nanoparticles that contact the skin can also influence the skin's permeability by altering its barrier properties. For example, dimethyl sulfoxide facilitates absorption of substances through the skin by removing much of the lipid matrix of the stratum corneum, leaving holes and shunts. Dermal absorption of nanoparticles does not appear to occur readily but can take place under certain conditions, and the factors dictating the extent to which absorption occurs are varied and complex. Researchers also caution that leaching of selected components of the particles through the skin and into the bloodstream is possible. Confounding these limited findings is the fact that different studies used different experimental protocols, making cross-study comparisons difficult.

2.3.3 Ingestion

Oral ingestion is likely to be an important exposure route. Studies have shown that nanoparticles are efficiently absorbed through the gastrointestinal tract (Jani et al., 1994) and that the particles then translocate through the mucosal tissue into the lymphatic and circulatory systems (Moghimi et al., 2001). Researchers have also found uptake of nanoparticles from ingestion of consumer products such as toothpaste and food additives (Fröhlich and Roblegg, 2012). The risk from accidental exposures to nanoparticles via this route, however, has not been not clearly demonstrated.

2.4 Occupational Exposure Limits

A generic exposure profile of concentrations measured every 15 min in the breathing zone of a worker over a work shift is depicted in Figure 2.4. These measurements are typically compared with OELs, which are based on prevention of the development of adverse health effects. The arithmetic mean exposure over the entire work shift (time-weighted average (TWA)) is compared with an OEL for contaminants with chronic adverse health effects, whereas individual 15-min measurements are compared with short-term exposure limits (STELs) for contaminants with acute adverse health effects. Several agencies and groups establish OELs: the Occupational Safety and

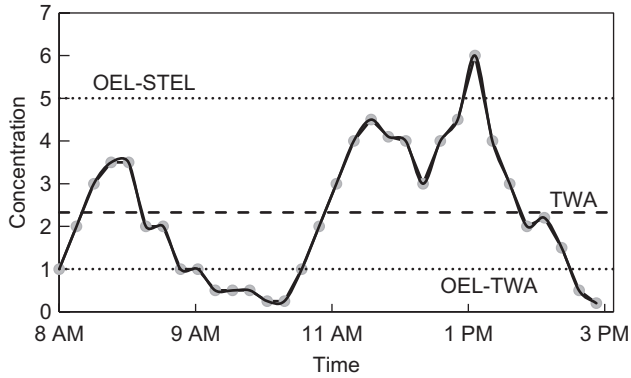

Figure 2.4
Generic exposure profile depicting concentrations measured every 15 min in the breathing zone of a worker over a work shift. The arithmetic average of all concentrations is the time-weighted average (TWA) exposure, which is compared with time-weighted average occupational exposure limits (OEL-TWA). Individual 15-min measurements are compared with short-term exposure limits (STELs).

Table 2.1 Example time-weighted average (TWA) occupational exposure limits (OELs) relevant to nanotechnology

Substance	Nanotech Application	OSHAPEL, mg/m^3	NIOSHREL, mg/m^3	ACGIHTLV, mg/m^3
Particles not otherwise regulated (PNOR) or specified (PNOS)	Many	15 (Total) 5 (Resp)	—	10 (Inhalable) 3 (Resp)
Barium, soluble	Batteries	0.5	0.5	0.5
Copper	Many	0.1 (Fume) 1 (Dust/mist)	0.1 (Fume) 1 (Dust/mist)	0.2 (Fume) 1 (Dust/mist)
Silver	Biocide	0.01	0.01	0.01
Platinum, soluble	Many	0.002	0.002	0.002
Titanium dioxide	Whitener, sun block	—	2.4 (Fine) 0.3 (Ultrafine)	—
Carbon nanotubes and fibers	Strength and electrical	—	0.001	—

Health Administration (OSHA) establishes permissible exposure limits (PELs), which are enforceable by law; the NIOSH establishes recommended exposure limits (RELs); and the American Conference of Governmental Industrial Hygienists (ACGIH) establishes threshold limit values (TLVs). Some TWA-OELs applicable to the nanotechnology industry are summarized in Table 2.1.

2.4.1 Permissible Exposure Limits from the OSHA

Although there are no enforceable PELs specific to engineered nanomaterials, the OSHA has established generic mass-based PELs that apply to airborne exposures in workplaces where nanomaterials are handled and produced. A PEL of 15 mg m^{-3} for total and 5 mg m^{-3} for respirable dust applies to particles not otherwise regulated (PNOR), based on the fact that the physical presence of biologically inert, insoluble, or poorly soluble, low-toxicity particles can overload the clearance mechanisms of the respiratory system. However, these PELs for PNOR are very high and of little practical value for most workplaces. Composition-specific PELs apply to some nanomaterials such as silver metal (0.01 mg m^{-3} for total particles). Workplaces establish compliance with these limits through filter-based sampling with gravimetric and/or chemical analysis.

2.4.2 Recommended Exposure Limits from the NIOSH

The NIOSH develops a current intelligence bulletin (CIB) to address limitations in PELs and the sampling methods that are used to show compliance to them. The CIB presents a quantitative risk assessment that includes dose-response relationships derived from available animal and human data. These relationships are used to establish RELs and assessment strategies to demonstrate that exposures are below these levels. RELs typically represent levels that over a working lifetime are estimated to reduce risks of adverse health outcomes to below 1 in 1000.

In the published CIB for titanium dioxide (TiO_2) (NIOSH, 2011), the NIOSH describes that an unknown number of U.S. workers produce and handle an estimated 1.5 million metric tons of TiO_2, which is incorporated into a wide variety of commercial products, including paints, cosmetics, and food. Exposures to TiO_2 in the workplace fall into the category of general dust (i.e., PNOR) with a PEL of 15 mg/m^3. Some of this material is unintentionally or intentionally produced in fine or ultrafine (nanoparticle) size fractions to achieve characteristics favorable to manufacturing or product performance. Scientific evidence suggests that persistent pulmonary inflammation and lung tumors scale with the particle size and surface area concentration of TiO_2 exposures. The NIOSH therefore proposed RELs for TiO_2 on the basis of the size of the particles in the air: 2.4 mg m^{-3} for fine TiO_2 and 0.3 mg m^{-3} for ultrafine (including engineered nanoscale) TiO_2. These RELs are for time-weighted average concentrations for up to 10 h per day during a 40-h work week. The NIOSH further recommends that exposures be controlled to as low a level as possible below these RELs. In the CIB, the NIOSH further suggests that these adverse health effects may not be material specific but result from a generic effect of poorly soluble, low-toxicity particles in the lung.

The NIOSH also published a CIB for carbon nanotubes and nanofibers in the workplace (NIOSH, 2013). An REL of 1 μg m^{-3} (8-h time-weighted average work shift exposure during a 40-h work week) for carbon nanotubes and nanofibers measured as elemental carbon by NIOSH Method 5040 to prevent excess risk of pulmonary inflammation and fibrosis.

The risk assessment presented in the CIB suggests that workers may have >10% excess risk of developing early-stage pulmonary fibrosis if exposed at the REL for a full working lifetime. However, the REL was set as the limit of quantification of NIOSH Method 5040, which the NIOSH has selected as the best available method to assess exposures. This method is nonspecific for carbon nanotubes and nanofibers, as other sources of elemental carbon are possible in workplace settings. Consequently, the NIOSH encourages the development of more suitable sampling and analytical methods, which may include microscopic methods such as those used to assess exposure to asbestos.

2.4.3 Benchmark Limits

Groups worldwide have used a categorical approach to establish benchmark OELs for nanomaterials without adequate toxicologic information as summarized by (Pietroiusti and Magrini, 2014). Nanomaterials are placed into groups with similar properties (e.g., particle size, surface chemistry) and modes of action (e.g., overburden of respiratory clearance mechanisms, fibrotic development). Limits for the group are based on materials with similar properties and modes of action for which there is toxicologic information. In Table 2.2, a summary of benchmark OELs established by the German Institute for Occupational Safety

Table 2.2 Benchmark exposure limits for nanoparticles from the German Institute for Occupational Safety and Health (referred to as the IFA) in Germany and the British Standards Institute (BSI) in the United Kingdom

Nanoparticle Category	BSI (UK)	IFA (Germany)
Fiber-like		
• Rigid, biopersistent CNT	10^4 f/m^3	10^4 f/m^3
• Metal oxides	10^4 f/m^3	
• CNTs without asbestos-like effects		4×10^4 f/m^3
Biopersistent granular (density <6000 kg/m^3)		
• Titanium dioxide	0.066× WEL	4×10^4 p/m^3
• Carbon black, silica, fullerene, zinc oxide, dendimers, polystyrene, nanoclay	0.066 × WEL or 2×10^7 p/m^3	4×10^4 p/m^3
Biopersistent granular (density >6000 kg/m^3)		
• Cerium oxide, gold, iron, iron oxide, silver, cobalt, lanthane, lead, antimony oxide, tin oxide	0.066 × WEL or 2×10^7 p/m^3	2×10^7 p/m^3
With carcinogenic, mutagenic, asthmagenic, reproduction effects		
• Nickel, cadmium containing quantum dots, chromium VI	0.1 × WEL	2×10^7 p/m^3
• Beryllium, arsenic, zinc chromate	0.1 × WEL	4×10^7 p/m^3
Liquid and soluble	0.5 × WEL	WEL

CNT stands for carbon nanotube; WEL is the work exposure limit established as a regulatory limit based for non-nano material; f stands for fiber; p stands for particle.

and Health (referred to as the IFA) and the British Standards Institute (BSI). In many cases, the benchmark exposure limits are expressed in terms of number concentration (fibers or particles per unit volume of air). In others, the benchmark OEL is expressed as a fraction of the existing exposure limit for a compound.

2.5 Instruments Available to Assess Exposures

In traditional methods for measuring personal exposure to airborne particles, air within a worker's breathing zone is pulled through a filter mounted in a 37-mm cassette (open or closed faced), respirable sampler, or inhalable sampler. The mass concentration is then computed as the mass collected on the filter (determined gravimetrically or by chemical analysis). A variety of samplers and instruments have been developed or applied to assess workplace exposures to particles, including nanoparticles, by metrics other than total, respirable, or inhalable mass concentration. These commercially available instruments are affordable for many organizations, portable, and easily used by industrial hygienists in exposure management.

2.5.1 Direct-Reading Instruments

Number concentration

As summarized in Table 2.3, a variety of direct-reading instruments are available for measuring particle exposures by various metrics. The total number concentration of an aerosol can be measured with a condensation particle counter (CPC). In a CPC, workplace air is saturated with a working fluid (e.g., water, isopropyl alcohol) by drawing it through a wetted tube. The molecules of working fluid then condense onto the particles and cause them to grow by condensation. The particles are then counted individually as they pass through a

Table 2.3 Direct-reading instruments for measuring particle concentrations

Instrument Category	Output	Example Instruments
Condensation particle counter, CPC	Total number concentration from ~15 nm to ~1 μm	Hand-held: CPC 3007 and P-Trak (TSI Inc.); CPC 3800 (Kanomax) Personal: PUFP C100 (Enmont, LLC)
Optical particle counter, OPC	Number concentration by size from ~300 nm to ~10 μm	Hand-held: HHPC6 (Met One); PDM 1.108 (Grimm Technologies, Inc.)
Photometer	Mass concentration from ~300 nm to ~10 μm	Hand-held: DustTrak II 8532 (TSI Inc.) Personal: pDR-1500 (Thermo Sci)
Diffusion chargers	Varies by instrument, but generally surface area concentration of submicrometer particles	Benchtop: NSAM 3550 (TSI Inc.); Aerotrak 9000 (TSI Inc.) Hand-held: DC2000CE (Ecochem Analytics) Personal: Discmini (Matter Engineering)

laser-based optical detector. Hand-held CPCs vary by model but typically measure particles from 10 or 20 nm to >1.0 µm over a concentration range of 0 to ~250,000 particles/cm^3. Newer models have been introduced for personal measurement (Ryan et al., 2015).

Hand-held optical particle counters (OPCs) provide particle number concentration by size typically from ~300 nm to ~10 µm in multiple-sized channels. OPCs use light scattering to count and size particles. Sizing is accomplished on the basis of the fact that larger particles scatter proportionally more light in the forward direction than smaller particles. OPCs are able to detect only those particles that scatter a sufficient amount of light (typically >300 nm).

Mass concentration

Hand-held and personal aerosol photometers are available to measure particle mass concentration. Sampled workplace air passes into a "sensing volume," which is illuminated by light from a laser. The light scattered by the assembly of particles in the sensing volume is measured with a photometer at a discrete angle from the incident light (typically 90°). The intensity of the scattered light is directly related to particle mass concentration but is influenced by aerosol size distribution, shape, and composition. Photometers provide a direct readout of mass concentration and can be operated with a size separator on the inlet to provide respirable mass concentration, PM_{10}, $PM_{2.5}$ or other size fractions. Many photometers provide a built-in filter holder downstream of the detection region. The gravimetrically measured mass concentration measured with this filter over a time-integrated sample period is often used to adjust the highly resolved data from light scattering. This practice improves estimates of mass concentration from a photometer by accounting for effects of site-specific aerosol size, shape, and composition.

Surface area concentration

Hand-held and personal instruments based on diffusion charging are available to directly measure particle surface area concentration. In a diffusion charger, positive ions produced with an electrical corona attach to the surface of particles, and the charged particles are collected on a grounded filter. The electrical current draining from the filter and measured with a highly sensitive electrometer is related to the particle surface area concentration. Diffusion chargers can be operated in different configurations to provide estimates of the surface area concentration that would deposit in various areas of the respiratory tract. A bench-top nanoparticle surface area monitor (NSAM, TSI, Shoreview, MN, USA) can be configured to estimate the surface area concentration that would deposit in different regions of the lung (Asbach et al., 2009). A hand-held model (DC2000CE, EcoChem Analytics, League City, TX, USA) outputs total surface area concentration and has been evaluated for use in workplace environments (Vosburgh et al., 2014). A personal model (DiSCMini) outputs for surface area concentration and particle number concentration of deposits in the lungs (Mills et al., 2013).

2.5.2 Time-Integrated Measurements

Detailed characterization

Several types of devices can be used collect workplace particles for subsequent analysis of size, morphology, and composition. Such information can help distinguish engineered nanomaterials from incidental nanoparticles or larger particles that are in the environment. With this information, the industrial hygienist is in a better position to devise routine measurement strategies and to interpret data from direct-reading instruments. For example, morphology can be analyzed using transmission electron microscopy (TEM) and scanning electron microscopy (SEM), size classification can be achieved using TEM, and chemical composition of the particles can be assessed using TEM with energy dispersive spectrometry (EDS) (Peters et al., 2009).

Several instruments, both personal and hand-held, are available to collect particles directly onto substrates suitable for SEM or TEM. Particles can be collected onto filters amenable for SEM (polycarbonate or mixed cellulose ester) using traditional samplers (e.g., open-faced cassettes, respirable, inhalable samplers), although the filter material makes analysis of nanoparticles challenging by TEM. Electrostatic (Miller et al., 2010) and thermophoretic (Thayer et al., 2011; Azong-Wara et al., 2013) precipitators are available to collect particles onto TEM grids that can then be easily analyzed by either TEM or SEM. When employing electron microscopy methods, representative bulk source nanomaterials should be collected to confirm the identity of engineered materials apart from other particles in the workplace. Electron microscopy is part of the assessment strategy recommended by the NIOSH to distinguish TiO_2 nanoparticles from larger TiO_2 particles and background particles collected with a respirable sampler.

The Nano-Micro-Orifice-Uniform-Deposition Impactor (NanoMOUDI) (Model 125, MSP Corporation, Shoreview, MN, USA) collects particles onto aluminum or polycarbonate substrates in 13 stages from 10 nm to >18 μm. The advantage of this instrument is that the substrates with collected particles can be analyzed gravimetrically, by bulk chemistry methods (e.g., ICP-MS), or by electron microscopy. Operation of the NanoMOUDI, however, requires considerable expertise in selection and proper handling of substrates, assembly and disassembly of impactor plates, and microscopic and chemical analyses.

Routine monitoring

Several researchers have developed personal samplers to collect nanoparticles apart from larger particles. Bulk chemical analysis (e.g., inductively coupled plasma mass spectrometry (ICP-MS)) of the collected nanoparticles can then be performed to directly measure engineered nanoparticle exposure. The continuity with traditional industrial hygiene sampling practices and dramatically lower cost of bulk chemical analysis compared with electron microscopy make these samplers amenable to routine monitoring of exposures to engineered nanoparticles.

The Personal Nanoparticle Sampler (PENS) simultaneously obtains samples for the respirable size fraction and nanoparticles (Tsai et al., 2012). In the PENS, respirable particles passing through a cyclone encounter a micro-orifice impactor that collects particles >100 nm. Nanoparticles are then collected on a Teflon filter. Similar to the PENS, the Nanoparticle Respiratory Deposition (NRD) Sampler (ZNRD001, Zefon International, Ocala, FL, USA) uses a respirable cyclone to sample workplace aerosol from within the breathing zone (Cena et al., 2011). A three-jet impactor removes particles larger than 300 nm, and smaller particles collect to eight nylon meshes, which collect the particles with an efficiency mimicking total deposition in the respiratory tract.

2.6 Specific "Best Practices" for Exposure Assessment Strategy in Nanotechnology

2.6.1 Basic Characterization

Workplace and workforce

Basic characterization by industrial hygienists includes the collection of information on the workplace, workforce, and environmental agents. For any workplace, this process includes an observational walkthrough to gather information on processes, tasks, and controls; a review of Safety Data Sheets (SDSs), previous sampling data, and process flow information; and interviews with supervisors and workers. The process flow patterns must be identified with an accounting of material transfer (e.g., raw material storage, dumping, conveying, and bagging), process output (e.g., intermediate or final products), and byproducts (e.g., cleanup operations, nanomaterials collected through ventilation controls, and waste streams). Process flow diagrams, facility schematics, and descriptions of the process with chemical reactions and standard operating procedures aid in carrying out this step. Information on the workforce, including the division of labor, the frequency of occurrence for tasks required of workers, and personal protective equipment (PPE) use, should be collected in this process. Sources of information include plant rosters and organizational charts, job and task descriptions, current job safety analysis, interviews with supervisors and workers, and detailed workplace observations.

Specific processes leading to direct airborne nanomaterial releases are important to consider in the context of nanotechnology facilities. These processes include vapor-phase synthesis reactors, heavy conveying or bagging operations, and shaping and grinding steps. Even for processes that are closed systems, these operations may require high levels of emission control (Swihart, 2003). In closed systems, unless there are unintentional leaks, the probability for exposure may be low. Exposure potential can be higher when products are being conveyed or dried, during reactor maintenance and cleaning operations, and other material handling tasks (e.g., bagging) when nanomaterials can become resuspended

(e.g., Evans et al., 2010). In the case of airborne releases, nanomaterials may occur as agglomerates in the coarse size range (e.g., Peters et al., 2009). Ignoring these larger-sized particles in favor of nonagglomerates may sometimes lead to incorrect estimates of the true health risk levels because of the potential for some agglomerates to disaggregate into smaller components once deposited in the lungs or onto the skin. An aggregate may also have a biologically relevant nanostructure.

Workplaces in the production category often have regular work, materials handling, and processing schedules and minimal changes in nanomaterial characteristics, whereas research laboratories often feature irregular and less predictable work schedules. In research laboratories, the quantities of nanomaterials handled are typically smaller than in a manufacturing or production environment, but the numerous processing conditions as well as the subtle variations in nanomaterial characteristics can make a proper assessment of exposure potential challenging, time intensive, and costly. For example, Johnson et al. (2010) found that sonicating hydrophobic carbon-based nanomaterials (CNMs) in deionized water suspensions results in airborne particle number concentrations lower than when handling dry CNMs. In contrast, sonicating hydrophilic CNMs in a moderately hard reconstituted water suspension containing natural surfactants dramatically increases airborne CNM particles compared with handling of dry CNMs. Similarly, the presence of functionalized nanoparticles, the type of process, and the surfactants used may also affect the potential for CNM particles to become airborne.

Traditionally, industrial hygienists use professional judgment developed through experience and training to predict potential exposures. However, subtle differences in nanomaterial characteristics can potentially change their exposure potential, rendering such decisions based on professional judgement erroneous. For example, relying on an obvious visible dust source to recognize the potential for exposures may not be appropriate in the case of such small particles.

Initial characterization of the workplace should include identification of any potential background or occupational sources of incidental nanoparticles. The location and an estimate of emissions should be made for each potential source. Combustion and high-temperature sources, whether process or nonprocess related, are particularly noteworthy. The incidental nanomaterials typically are not the focus of the exposure assessment. However, in sufficiently high concentrations, these incidental particles may also be considered a mixed exposure because they may not be without their own adverse health risks.

Characterizing nanomaterials

The industrial hygienist must obtain accurate information on nanomaterial characteristics. Frequently, information provided by the manufacturer can be limited or misleading. On SDSs, many manufacturers do not distinguish nanoparticles from the bulk form of the same substance, listing the Chemical Abstracts Services (CAS) number and OEL for the bulk form. Moreover, the

processing and handling steps can significantly alter nanomaterial characteristics. For example, the size distribution of a nanomaterial powder will often be altered when dispersed in a liquid compared with when dry. Thus, the industrial hygienist must understand the process flow and anticipate the characteristics of the engineered nanomaterial in this process through communication with scientists, engineers, and workers. It is advisable to analyze by electron microscopy samples of the nanomaterial at different stages in the manufacturing process. Images of particles from various processes can then be compared with those from analyses of airborne samples.

2.6.2 Construction of Similar Exposure Groups Combined with Exposure Assessment

SEGs are formed primarily on the basis of professional judgement of the industrial hygienist to increase efficiency of the exposure assessment and management strategy. A critical assumption in such a classification is that the workers within each SEG have similar exposure distributions. However, the professional judgment of most industrial hygienists is calibrated to visual cues related to particle mass concentrations that are often not reliable for number or surface area concentrations, especially for nanomaterials. As an interim strategy, concentration mapping and job-task-related measurements by number and mass concentration are recommended. These measurements can then be used to establish SEGs and strategies for routine monitoring.

Concentration mapping

Concentration mapping involves the measurement of particle concentrations by different metrics at many locations throughout a workplace with direct-reading instruments. The first step is to divide the workplace into a sampling grid based on its size. To minimize uncertainty introduced from temporal variability, an entire set of mapping measurements should be completed within a short period (e.g., 1–2 h) with a nominally 1-min sample obtained at each grid point. The monitoring instruments, placed on a portable cart, can then be moved to the next location in the next minute. Thus, around 60 grid points could be measured in 2 h. The spacing between sampling points can be determined as follows:

$$\frac{\text{Total area of a workplace } (\text{m}^2)}{60 \text{ data points}} = \text{Basic measurement unit } (\text{m}^2/\text{point}) \qquad (2.1)$$

The grid resolution should be tailored to the situation to obtain finer resolution near suspected sources of generation and areas of high occupational activity and a coarser grid for areas farther away.

From the many instruments available (see Section 2.3), we recommend a CPC to measure total particle number concentration from ~15 nm to ~1 μm and an OPC to measure particles by size from 300 nm to ~10 μm. For each measurement point, an estimate of the sub-300-nm number concentration (usually a good indicator of nanoparticle concentrations) is made by

subtracting the number concentration measured with the CPC by that measured with the OPC for bins ranging in size from 300 nm to 1 µm. An estimate of mass concentration can then be made by assuming a particle density by following Peters et al. (2006) or Park et al. (2010). Mapping measurements should be obtained several times to assess temporal variability. Arithmetic average concentrations can be used to construct the final particle maps. Color-coded contour plots can be generated and used to construct an easy-to-read concentration map and to visualize the nanomaterial concentrations by different metrics with the use of mapping software (e.g., Surfer 8.0, Golden, CO, USA). This information can be used to visualize the spatial and temporal variability of aerosol concentrations in a workplace as a function of work processes. This technique can be applied to identify contaminant sources or as a presurvey tool to determine sampling locations for routine aerosol concentration measurements.

For example, Park et al. (2010) used concentration mapping to assess aerosol concentrations by various metrics in a die casting facility (see Figure 2.5 for schematic of facility and Figure 2.6 for hazard maps). Two light-scattering laser aerosol photometers (DustTrak Model 8520, TSI Inc., Shoreview, MN, USA) were used with size-selective inlets to measure the PM1.0 and respirable particle mass concentrations. A real-time CPC that counted single particles with diameters ranging from 0.02 to 1.0 µm was utilized for number concentration (P-Trak Model 8525, TSI Inc., Shoreview, MN, USA). A hand-held OPC (AeroTrak Model 8220, TSI Inc., Shoreview, MN, USA; or HHPC-6, Hach Ultra, Grants Pass, OR, USA) was used to simultaneously count particles >0.3 µm in diameter into six size bins (0.3–0.5 µm, 0.5–1.0 µm, 1.0–2.5 µm, 2.5–4.0 µm, 4.0–0.0 µm, and >10.0 µm). A surface area monitor (AeroTrak Model 9000, TSI Inc., Shoreview, MN, USA) was used for determining alveolar surface area concentration of deposited particles. Spatial distributions and of particle concentrations in different areas (loosely corresponding to SEGs) were different, depending on the concentration metrics chosen.

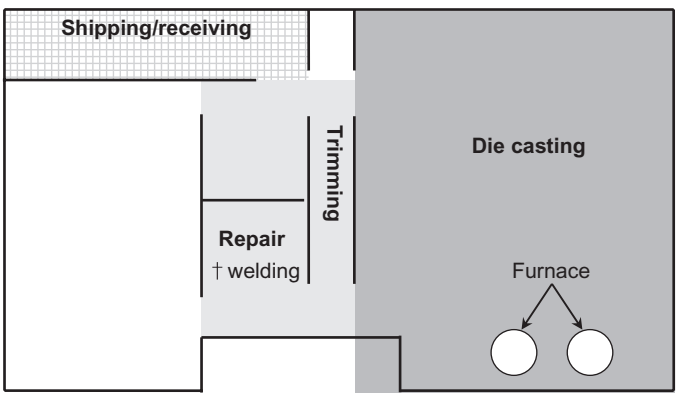

Figure 2.5
Schematic of die casting facility. *From Park et al. (2010).*

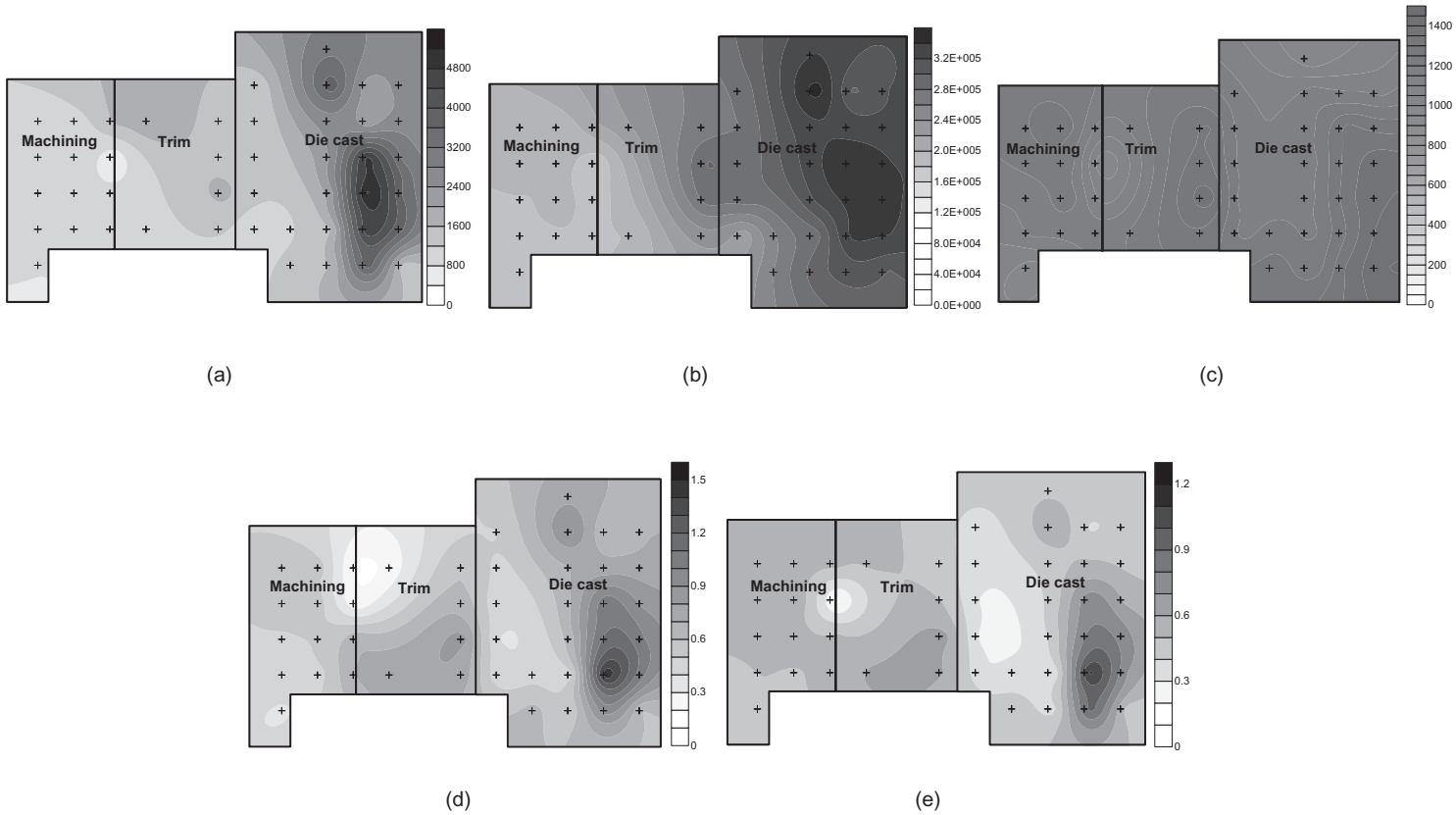

Figure 2.6

Particle concentration maps in the die casting factory (+: sampling location). (a) SA ($\mu m^2/cm^3$). (b) Fine particle number (particles/cm^3). (c) Coarse particle number (particles/cm^3). (d) Respirable matter (mg/cm^3). (e) PM 1.0 (mg/cm^3). *From Park et al. (2010).*

Job-task-related measurements

The same direct-reading instruments used in concentration mapping can be useful in characterizing exposures by tasks within a job. Here, breathing zone measurements are made during specific tasks, and relative particle measurements are used to identify potential sources or work methods that release higher levels of nanomaterials. This technique can be applied to identify short-duration contaminant sources and compare the relative effectiveness of work process control techniques in reducing exposure potential. It is also effective in identifying processes in need of exposure control activities based on comparative readings.

Background particles and incidental nanoparticles

Accounting for background and incidental nanoparticles is important and can be done in several ways, depending on the workplace. This process can be difficult when using only direct-reading instruments because incidental nanoparticles may be in the same size range as the engineered nanomaterial of interest. Sometimes, incidental nanoparticle concentrations also drift substantially for some sources (e.g., exhaust from propane or diesel forklift driving by heating units, cleaning processes, or outside particle sources such as vehicular exhaust that penetrates indoors). In such instances, correcting for incidental nanomaterials by simple before, during, and after subtraction may be more challenging.

Options include measuring airborne particle concentrations with a process on and off, outdoors, and at air supplies. Methner et al. (2010) described a nanomaterial emission assessment technique (NEAT) to evaluate exposure potential to engineered nanomaterials, which is a qualitative approach that uses several direct-reading instruments. In the NEAT, the background aerosol is measured with the process (or task) on and off.

2.6.3 Interpretation of Exposure Assessment Results

Selecting occupational exposure limits

An appropriate occupational exposure limit (OEL) is needed to decide whether exposures are uncertain and require more measurement or are excessive and require control. There are well-developed methodologies by which formal OELs can be established (Schulte et al., 2010). Before an OEL can be established, several conditions must be met:

1. The criteria for exposure assessment need to be established (e.g., what aerosol fraction and what exposure metric is most health-relevant).
2. The exposure assessment strategy should specify if one needs to measure short-term or long-term exposures.
3. The instrumentation and analytical methods for measuring these metrics should be available.
4. A dose-response relationship should be established by means of toxicity data and quantitative risk assessment.

Of these four needs, only the instrumentation and analytical methods (Condition 3) are generally available for most nanomaterials. Consequently, few nanomaterials have specific OELs except those mentioned in Section 2.4.

One option is to adopt conservative "benchmark levels" that have been developed for nanomaterials (see Table 2.2). Alternatively, many companies and chemical manufacturers develop internal ad hoc exposure limits for nanomaterials in the absence of legal exposure limits. Sufficient toxicologic information must be available, with inputs from toxicologists, occupational physicians, and epidemiologists. However, this process requires close attention to the current literature on nanomaterial toxicity and reasoning by analogy. There is a high degree of uncertainty in ad hoc OELs. If the uncertainty in the OEL is high, the industrial hygienist can use large safety factors to ensure that risk is not underestimated.

Defining the exposure profile

The final steps in the exposure assessment process are the characterization of exposure for the SEG and a comparison of the exposure to the appropriately selected OEL taking into account the uncertainty of both. Within each SEG, the workers have a distribution of exposures (i.e., the exposure profile of the SEG) that needs to be characterized. Characterizing an exposure profile requires an understanding of the statistics of sampling and the underlying exposure distribution, estimates of the exposure central tendency and variability, and some measure of the uncertainty in those estimates. A thorough knowledge of exposure variability and its characterization is critical for developing a proper sampling strategy and interpreting the results of sampling.

In addition to an estimate of exposure and its uncertainty for the SEG, outputs from the exposure assessment process include a decision as to whether or not the exposure is acceptable. Here again, it is useful and efficient to define exposure categories. Occupational exposure distributions are typically skewed to the right and are described quite well by the *lognormal probability distribution.* Acceptability is commonly evaluated by comparing an upper percentile such as the true group 95th percentile to the OEL. In the AIHA strategy, the 95th percentile of the exposure profile is estimated along with its upper confidence limit (UCL). Based on the magnitude of the group 95th percentile and its UCL relative to the OEL, the exposure is classified into one of four categories: "highly-controlled," "well-controlled," "controlled," or "poorly controlled" (Table 2.4). In the AIHA strategy, four categories are described, but there is no reason for not using other numbers of categories to better match the specific goals of the organization's exposure assessment strategy.

For conventional chemicals, the vast majority of exposure assessments are based primarily on professional judgment, with formal or informal input from associated exposure models. Even exposure assessments based on a wealth of monitoring data require professional

Table 2.4 Exposure category rating scheme. Exposure rating is assigned by comparing the 95th percentile exposure, $X_{95\%}$, of the exposure distribution to the full shift time-weighted average (TWA), occupational exposure limit (OEL), or short term exposure limit (STEL)

Exposure Rating	Control Zone Description	Qualitative Description	Recommended Statistical Interpretation
1	Highly controlled	Exposures infrequently exceed 10% of limit	$X_{95\%} < 0.10 \times \text{OEL}$
2	Well controlled	Exposures infrequently exceed 50% of limit and rarely exceed the limit	$0.10 \times \text{OEL} < X_{95\%} < 0.5 \times \text{OEL}$
3	Controlled	Exposures infrequently exceed the limit	$0.5 \times \text{OEL} < X_{95\%} < \text{OEL}$
4	Poorly controlled	Exposures frequently exceed the limit	OEL < 95th percentile

judgment to determine how the monitoring data are most appropriately used to assess exposure and to interpret any data analysis. In the case of exposure to nanomaterials, professional judgment may not serve us well because of the limited experience of industrial hygienists in assessing exposures using new and unfamiliar metrics. Therefore, it is recommended that monitoring data be the mainstay of exposure assessment for nanomaterials. Monitoring data should be used to determine the 95th percentile of the exposure distribution relative to the OEL and thus determine which of the four categories an exposure profile falls into.

The AIHA strategy suggests that six to ten measurements be collected for most SEGs that are to be evaluated using exposure monitoring (Ignacio and Bullock, 2006). Each measurement is taken over an averaging time interval relevant to the OEL. For example, if the OEL has an 8-h averaging time, then six to ten 8-h average measurements should be obtained for analysis. For nanomaterial measurements made using direct-reading instruments, it is advisable to make the measurements over the period of the task or process or the entire shift, if needed, in intervals of ~5 s, and then use the data from these short intervals to obtain averages over larger time intervals. For statistical analysis, the measurements should be obtained as randomly as feasible from workers, work shifts, and tasks. An underlying assumption is that the population of exposures does not change during the measurement period. Readings can be plotted as a time series as a subjective test of the stability of the exposure profile. The data can also be used to calculate simple descriptive statistics (i.e., mean, median, minimum, maximum, geometric mean, geometric standard deviation, and percentage of data above the OEL). Measurements can then be ranked and plotted as a cumulative distribution on log-probability axes. If the data fall on a straight line, then the underlying population of exposures is log-normally distributed. A W-test can be used as a more rigorous test of log-normality. The 95th percentile of the exposure distribution can then be calculated along with its upper confidence limit. At this point, a judgment about the acceptability or unacceptability of the exposure can be made.

2.6.4 Follow-Up and Control

As was illustrated in Figure 2.1, SEGs are prioritized for follow-up and control based on the estimates of their exposures, and the acceptability and uncertainty associated with those estimates. Of course, poorly controlled exposures are given priority for control (low uncertainty) or further information gathering (high uncertainty) with possible addition of short-term controls. Lowest priority is given to SEGs with low exposure estimates made with low uncertainty. Different institutions or companies may have different control steps in place, depending on the location of the 95th percentile in terms of the four exposure categories.

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CHAPTER 3

Hazard and Risk Assessment of Workplace Exposure to Engineered Nanoparticles: Methods, Issues, and Carbon Nanotube Case Study*

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Chapter Outline

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3.1 Introduction

Toxicology data from experimental studies in animals are frequently used in risk assessment when human dose-response data are not available. Collaborations among industrial hygienists, toxicologists, risk assessors, and other disciplines provide an opportunity to obtain scientific data and develop an improved basis for assessing the risk of exposure to nanomaterials. In this chapter, the components of the risk assessment process are described, with a focus on assessment of occupational risk of inhaled particles and potential adverse lung effects. A case study using rat subchronic inhalation data of carbon nanotubes (CNTs) and carbon nanofibers (CNFs) is presented, highlighting two studies that were the primary basis for the exposure limit recommended by the National Institute for Occupational Safety and Health (NIOSH) (NIOSH, 2013)—that is, the Ma-Hock et al. (2009) and Pauluhn (2010a) studies of multiwalled carbon nanotubes (MWCNTs). In addition, more recent studies of MWCNTs (Kasai et al., 2014) and of CNFs (DeLorme et al., 2012) are evaluated in conjunction with the case study. These examples illustrate the application of risk assessment methods to currently available toxicology data for estimating the risk of adverse lung effects from occupational exposure to engineered nanoparticles. Challenges in using such data in quantitative risk estimation are discussed, and research needs are suggested to reduce uncertainties in risk estimates.

The data used in various risk assessments of CNTs to date are based on rat studies of pulmonary inflammation and fibrosis (Pauluhn, 2010a; Aschberger et al., 2010, 2011; Kuempel, 2011; Nakanishi, 2011; NIOSH, 2013). Additional *in vivo* studies have reported cardiovascular responses, as well as genotoxicity and cancer, in rodents (Tables 3.1 and 3.2). A large number of *in vitro* studies have also been published, but these studies are not discussed here because they have not yet been used in risk assessment. Studies in humans are extremely limited at this time. One health surveillance study with only nine subjects reported no adverse health effects (Lee et al., 2014).

3.1.1 Risk Assessment Paradigm

Risk assessment is a process to systematically characterize the scientific evidence of potential adverse health effects from human exposures to hazardous agents (NRC, 1983). The traditional risk assessment framework developed in the United States and used in

Table 3.1 Hazard data examples: rodent studies of single-walled carbon nanotubes (SWCNTs)

Response	Dose & Duration[a]	Species & Exposure Route[b]	Reference
Pulmonary inflammation Granulomas	0.1 or 0.5 mg per mouse (7 & 90 d pe)	Mouse ($B6C3F_1$, male); IT	Lam et al. (2004)
Cell proliferation—lung epithelial cells	0.4 mg per rat (1 and 21 d pe)	Rat (F344, female); PA	Mangum et al. (2006)
Pulmonary fibrosis (early onset and persistent)	5, 10, 20, 40 µg per mouse (1, 3, 7, 28 & 56 d pe)	Mouse (C57BL/6, female); PA	Shvedova et al. (2005)
K-ras oncogene mutations in lung tissue; pulmonary fibrosis	5 mg/m^3 (5 h/d, 4 d); 1, 7, & 28 d pe	Mouse (C57BL/6), female; inhalation (whole body)	Shvedova et al. (2008)
Cardiovascular—oxidative stress and plaque formation	20 µg per mouse every 2 weeks for 10 weeks (7, 28 & 56 d pe)	Mouse (C57BL/6, male); PA	Li et al. (2007)
Pulmonary fibrosis; transforming growth factor beta (TGF-β), greater bioactivity than asbestos	40 µg per mouse (1, 7 & 28 d pe)	Mouse (C57BL/6, female); PA	Murray et al. (2012)
Pulmonary fibrosis, greater bioactivity than asbestos	40 µg per mouse (up to 1 yr pe)	Mouse (C57BL/6, female); PA	Shvedova et al. (2014)

[a]In addition to 0 dose (control); pe: post-exposure.
[b]IT: intratracheal instillation; PA: pharyngeal aspiration; IP: intraperitoneal injection.

various forms worldwide includes four main steps: (i) hazard assessment, (ii) dose-response assessment, (iii) exposure assessment, and (iv) risk characterization (NRC, 1983). Research studies in various fields, including toxicology, exposure measurement, and computational methods, are needed to provide data for risk assessment in order to inform risk management decision making. Risk communication and processes to obtain stakeholder input are integral components of the risk assessment process. In many cases, sufficient data are not available for a full risk characterization, and risk management decisions may need to be made on the basis of the limited data available. A higher level of precaution in controlling exposures is prudent when the extent of the hazard is not well known, as with many nanomaterials (Schulte and Salamanca-Buentello, 2007).

This classic risk assessment paradigm was recently re-evaluated by the National Research Council (NRC) in response to a charge from the U.S. Environmental Protection Agency (EPA) to recommend improvements to the risk assessment process as practiced (NRC, 2009). In its report, the NRC recommended retaining the four basic steps of the risk assessment process and recommended additional steps to improve the utility of risk assessment and the technical analyses supporting risk assessment. Among these, the NRC proposed adding an

Table 3.2 Hazard data examples: rodent studies of multiwalled carbon nanotubes (MWCNTs)

Response	Dose & Duration[a]	Species & Exposure Route[b]	Reference
Granulomatous inflammation Lipoproteinosis	0.1, 0.5, 2.5 mg/m^3 (6 h/d, 5 d/wk, for 13 wk)	Rat (Wistar, male); inhalation (head & nose)	Ma-Hock et al. (2009)
Pulmonary inflammation and fibrosis	0.1, 0.45, 1.68, 5.98 mg/m^3 (6 h/d, 5 d/wk, for 13 wk)	Rat (Wistar, male); inhalation (nose-only)	Pauluhn (2010a)
Pulmonary inflammation, fibrosis, mesothelial hyperplasia	0.2, 1, 5 mg/m^3 (6 h/d, 1 d, 5 d/wk, for 13 wk)	Rat (F344, male & female); inhalation (whole body)	Kasai et al. (2014)
Pulmonary inflammation, fibrosis, pleural migration	5 mg/m^3 (5 h/day, 5 d/wk, 12 d)	Mouse (C57BL/6, male); inhalation (whole body)	Mercer et al. (2013a,b)
Pulmonary inflammation and fibrosis	0.5, 2, 5 mg per rat (28 & 60 d pe)	Rat (Sprague-Dawley, Wistar, female); IT	Muller et al. (2005, 2008)
Bronchiolitis obliterans Peribronchial fibrosis	12.5 mg per guinea pig (3 month pe)	Guinea pig (three-color, male); IT	Grubek-Jaworska et al. (2006)
Granulomatous inflammation Pulmonary fibrosis	10, 20, 40, 80 ug per mouse (1, 7, 28, 56 d pe)	Mouse (C57BL/6, male); PA	Porter et al. (2010)
Cardiovascular (loss of coronary artery dilution)	26 mg/m^3, 5 h	Rat (Sprague-Dawley, male); inhalation (whole body)	Stapleton et al. (2012)
Inflammation in peritoneal cavity, associated with carbon nanotube length	50 µg (1, 7 d pe)	Mouse (C57B1/6, f)—all IP	Poland et al. (2008)
Mesothelioma	0.003–3 mg IP (25 to 52 wk pe)	Mouse (p53(+/−, m))	Takagi et al. (2008, 2012)
No mesothelioma (ground MWCNTs)	2, 20 mg (2 yr pe)	Rat (Wistar, m)	Muller et al. (2009)
Mesothelioma (rigid MWCNTs); no mesothelioma (tangled MWCNTs)	1 and/or 10 mg each of four types of MWCNTs (1 yr pe; up to 3 yr pe for tangled MWCNTs exposure group)	Rat (F344/Brown Norway F1 hybrid, m, f)	Nagai et al. (2011, 2013)
Mesothelioma	0.05 to 3.0 mg of one of four types of rigid MWCNTs (2 yr pe)	Rat (Wistar, m)	Rittinghausen et al. (2014)

[a]In addition to 0 dose (control); pe: post-exposure.
[b]IT: intratracheal instillation; PA: pharyngeal aspiration; IP: intraperitoneal injection.

initial step in problem formulation and scoping, as well as revisions to the risk management phase to evaluate both risk and nonrisk information (e.g., technical feasibility) in a systematic evaluation of potential options. Toward the goal of improving the utility of risk assessment, the revised NRC framework explicitly requires reporting of what options are available to

reduce the hazards or exposures that have been identified and how risk assessment can be used to evaluate the merits of the various options (NRC, 2009).

In the absence of epidemiology data on workers exposed to engineered nanoparticles, much of the current focus in risk assessment involves toxicology studies in animals to assess the hazard, determine dose-response and time course relationships, and identify modes of action. The design of toxicology research studies for use in risk assessment necessitates an interface between toxicology and risk assessment to develop adequate data for qualitative and quantitative analyses. Evaluating the key information needs in this process provides an opportunity to focus additional research efforts on generation of data necessary to reduce uncertainties in estimating the hazard and risk of exposure to nanoparticles. As with workers exposed to other chemicals or particles, nanotechnology workers are likely to have the highest exposures and greatest potential for adverse health effects associated with the production of nanoparticles and their use in commercial applications. The hazard and dose-response assessment steps are discussed further in the following sections, as these steps are used in the quantitative risk assessment. The exposure assessment step (which is beyond the scope of this chapter) is needed to characterize the risk in a given population.

3.1.2 Hazard Assessment

The hazard assessment seeks to identify the nature of any hazardous effects and the evidence regarding the biological mode of action. Many of the same adverse lung responses previously reported following inhalation of fibers or fine particles are being found with exposure to nanoparticles, although often at lower mass doses due to the increased total particle surface area (Oberdörster and Yu, 1990; Driscoll, 1996; Sager et al., 2008; Sager and Castranova, 2009) or volume (Bellmann et al., 1991; Oberdörster et al., 1992; Pauluhn, 2010a) per unit mass for nanoparticles compared with their fine-sized analogues. Recent results suggest that the surface area of nanomaterial agglomerates may be more predictive of biological response than the surface area of primary nanoparticles within the agglomerate (Murray et al., 2012; Sager et al., 2015). This suggests that the biologically effective surface area of the particle is that of the outer "envelope" that is in contact with the cell surface. The Sager et al. (2015) results also point to the importance of evaluating the size distribution of the nanoparticles to which humans, animals, or cells are exposed. Poorly soluble nanoparticles (e.g., metal oxides such as titanium dioxide [TiO_2] and aluminum oxide [Al_2O_2]) have been shown to cause greater inflammation response in rodent lungs compared with the same mass of larger-sized respirable particles of the same chemical composition (Bermudez et al., 2002, 2004; Oberdörster and Ferin, 1992; Sager et al., 2008) and in *in vitro* cell assays (Rushton et al., 2010). Common pathways for the pulmonary pathogenicity of inhaled particles of varying sizes and shapes include direct cytotoxicity (e.g., due to reactive surfaces), activation of oxidant release from phagocytes, and secretion of inflammatory cytokines and/or proliferative factors (Donaldson et al., 1996;

Castranova, 1998, 2000; Oberdörster et al., 2005). These pathogenic pathways have been linked to interstitial fibrosis in rodent models and to rat lung tumorigenesis associated with chronic exposures to various types and sizes of poorly soluble particles, apparently by a mode of action involving indirect (secondary) genotoxicity due to the earlier inflammatory and proliferative events (ILSI, 2000; Castranova, 2000; Schins and Knaapen, 2007; Baan, 2007).

Persistent granulomatous inflammation and interstitial fibrosis are also among the responses observed in rodents exposed to MWCNTs or single-wall carbon nanotubes (SWCNTs) by various routes of exposure (intratracheal instillation, pharyngeal aspiration, or inhalation) (Tables 3.1 and 3.2). On a mass-dose basis, SWCNTs appear to be more fibrogenic than MWCNTs due to the enhanced ability of SWCNTs to avoid uptake by alveolar macrophages and to enter the alveolar interstitium (Mercer et al., 2011). In addition, pulmonary exposure to SWCNTs has been associated with oxidative stress and enhanced plaque formation in the aorta, and intraperitoneal exposure to MWCNTs has been linked to mesothelioma in some studies (Tables 3.1 and 3.2). MWCNTs and SWCNTs have been shown in several studies to be more potent on a mass basis (i.e., a lower dose associated with a given adverse lung response, or a greater adverse response at a given dose) compared with ultrafine carbon black (Table 3.3) and other poorly soluble particles, including silica and asbestos (Elder et al., 2006; Lam et al., 2004; Muller et al., 2005; Murray et al., 2012; Shvedova et al., 2005, 2014). In contrast to the metal oxides, cellular responses to CNTs are not well predicted by the reactive oxygen species generation; rather, the nanostructured CNTs appear to act as a basement membrane substrate that enhances fibroblast proliferation and collagen production *in vitro*

Table 3.3 Adverse effect levels in rats after subchronic (13-week) inhalation exposure to carbon particles and carbon nanotubes

Study	Compound	Effect Level in Rats		Effect
		NOAEL (mg/m^3)	LOAEL (mg/m^3)	
Elder et al. (2006)	Ultrafine carbon black (Printex 90)	1	7	Pulmonary inflammation
Ma-Hock et al. (2009)	Multiwalled carbon nanotubes (BASF, Nanocyl)	n.d.	0.1	Granulomatous inflammation
		0.1	0.5	Alveolar proteinosis
Pauluhn (2010a)	Multi-walled carbon nanotubes (Baytubes) (Bayer)			Pulmonary inflammation
		0.1	0.45	Alveolar septal thickening
Kasai et al. (2014)	Multiwalled carbon nanotubes (Mitsui-7)	–	0.2	Pulmonary inflammation, Interstitial hyperplasia

NOAEL: No observed adverse effect level.
LOAEL: Lowest observed adverse effect level.

(Wang et al., 2010). *In vivo*, this would result in thickening of the alveolar septal air–blood barrier and a decrease in gas exchange between the lung and blood (Mercer et al., 2011).

Some types of MWCNTs and SWCNTs have also been shown to elicit similar biological effects as fibers in that the longer, thinner structures are more inflammogenic (Poland et al., 2008) and can penetrate from the lung subpleural tissue to the intrapleural space (Mercer et al., 2010). SWCNTs and MWCNTs have been shown to interfere with normal cell division in cell culture systems (Muller et al., 2008; Sargent et al., 2009) and *in vivo* (mice) (Sargent et al., 2014). MWCNTs can cause the two normal centrosomes to cluster, forming a single pole. The resulting mitotic spindles are monopolar rather than bipolar (Sargent et al., 2011). In addition, MWCNTs have been reported to form cross-bridges between multiple cell nuclei after pulmonary exposure (Muller et al., 2008). In contrast, SWCNTs appear to fragment centrosomes, causing multipolar mitotic spindle formation, abnormal chromosome division, and aneuploidy (Sargent et al., 2009). In comparison, chrysotile asbestos also interferes with the normal mitotic process but not by binding to centrosomes. Rather, asbestos fibers interact with mitotic spindles and interfere with cytokinesis by forming bridges to prevent normal separation of daughter nuclei (Asakura et al., 2010). MWCNTs have also been shown to translocate from the lungs to the mesothelial tissue lining the lung (Ryman-Rasmussen et al., 2009; Mercer et al., 2010, 2013b; Xu et al., 2012; Kasai et al., 2014), to lung-associated lymph nodes (as do other inhaled particles), and to other organs, including the liver and kidneys, with tissue damage observed in those organs (Reddy et al., 2010; Mercer et al., 2013b). Other nanoparticles (e.g., silver, iridium) have also been shown to translocate from the lungs via the systemic circulation to other organs and tissues (Takenaka et al., 2001; Semmler et al., 2004; Semmler-Behnke et al., 2007).

Compared with larger particles, nanoparticles have the unique ability to enter and interact with cells and cell organelles. Individual nanoparticles of TiO_2 have been observed inside cell organelles, including in the cell nucleus (Geiser et al., 2005) and in mitochondria, which can disrupt mitochondrial and cellular functions (Li et al., 2003). In addition, Mercer et al. (2010) have published electron micrographs showing individual MWCNTs within alveolar macrophages and epithelial cells. Spherical nanoparticles that are deposited in the nasal region have been shown to enter the brain via neuronal transport in the rat and cause inflammation in the olfactory bulb (Elder et al., 2006; Oberdörster et al., 2002, 2009).

The nature of the hazard and mode of action influence the extent to which information on larger particles of the same chemical composition or surface reactivity can be reliably extrapolated to nanoparticles. In the case of poorly soluble particles, a relationship between the particle surface area dose of nanoscale or larger particles and pulmonary inflammation or other adverse lung effects (including rat lung tumors in chronic studies) has been reported (Oberdörster and Yu, 1990; Driscoll, 1996; Sager et al., 2008; Sager and Castranova, 2009). Therefore, utilizing the available data for other particles and fibers may facilitate hazard

and risk characterization for classes of materials with common modes of action. However, additional data are needed to link the potential biological effects of the vast number of nanomaterials to given physicochemical properties (Rushton et al., 2010) in order to develop predictive hazard/risk grouping strategies.

3.1.3 Dose-Response Assessment

The basis for quantitative risk assessment is the data on dose-response relationship. Studies that provide epidemiologic data are generally preferred for risk assessment, since there is no uncertainty about extrapolation across species or about the species-relevance of the response endpoint. However, quantitative exposure data are often not available in epidemiologic studies, and in the case of nanoparticles no epidemiologic studies have been reported. Thus, experimental data in animals are used to examine dose-response relationships. Standard methods of risk assessment involve determination of either an adverse effect level (no observed or lowest observed) or a benchmark dose estimate. In either case, the animal dose must be extrapolated to humans, either by allometric scaling (i.e., based on body weight) or other data available on the factors that influence dose to the target tissue in each species (i.e., adsorption, distribution, metabolism, elimination). A potentially useful metric to scale human versus animal dose when evaluating pulmonary exposure–response is deposited dose per surface area of alveolar epithelium (Sections 3.2.3 and 3.3.1).

No observed or lowest observed adverse effect levels

A lowest observed adverse effect level (LOAEL) or no observed adverse effect level (NOAEL) approach has often been used as the point of departure (POD) in risk assessment of noncarcinogenic agents. The NOAEL is defined as the highest dose at which no adverse effects have been detected; and the LOAEL is the lowest dose at which adverse effects have been detected (EPA, 2012). A POD is the external exposure or internal dose to which uncertainty factors or low dose extrapolation methods are applied to derive an exposure limit that is considered acceptable (i.e., associated with no risk or low risk) in humans. Statistical evaluations are usually performed to determine an NOAEL, that is, the dose at which no statistically significant increase in adverse effects is observed. An important area of uncertainty in NOAEL estimation is that it is dependent on the limit of detection within a given study.

For noncancer endpoints, a common assumption in risk assessment is that low doses (e.g., where detoxification and clearance mechanisms are effective and any damage to cells is effectively repaired) would not be associated with any appreciable risk of adverse effects. The NOAEL is thus considered a threshold dose below which adverse effects would not be expected. The NOAEL (or LOAEL) is typically divided by “uncertainty factors” (otherwise known as “safety factors” or “adjustment factors”) to account for uncertainty in the use of these estimates as PODs for risk assessment. Standard uncertainty factors typically include

the following four factors: (i) extrapolating the animal data to humans (both toxicokinetic and toxicodynamic factors), interindividual variability in the distribution of human responses (including most of the sensitive individuals in a population), uncertainty in estimating a chronic response from subchronic data, and/or the use of an LOAEL in the absences of an NOAEL. Factors of 10 for each have typically been used in the absence of other data (WHO, 2005; EPA, 2012). These uncertainty factors are intended to provide a sufficient margin of safety such that no "appreciable risk of deleterious effects in humans" (EPA, 2012) would be expected at exposures below the calculated exposure limits.

The assumption of a threshold dose for noncarcinogens may not be applicable in all cases (e.g., if exposure to a hazardous agent adds to a response associated with another environmental exposure or to background disease processes or incidence) and may not adequately account for interindividual variation in a population (NRC, 2009; White et al., 2009). Benchmark dose (BMD) estimates are generally preferred, if feasible, as a POD for either cancer or noncancer endpoints (NRC, 2009), as discussed in the next section.

Benchmark dose methods

A BMD estimate has several advantages over an NOAEL or LOAEL as a POD in risk assessment when sufficient dose-response data are available (Crump, 1984, 1995; NRC, 2009; EPA, 2012). A BMD is a risk-associated dose estimated by model curve fitting to the dose-response data. BMD estimates have been used in both cancer and noncancer risk assessments. Some examples of using BMD estimates in risk assessment of engineered nanomaterials include those using dose-response data in rodents for pulmonary responses to inhaled fine and nanoscale (ultrafine) particles (Kuempel et al., 2006; Dankovic et al., 2007; NIOSH, 2011) or to CNTs (Kuempel, 2011; NIOSH, 2013).

The term "benchmark dose" is defined as "…a statistical lower confidence limit for the dose corresponding to a specified small increase in level of [adverse] health effect over the background level" (Crump, 1984). In practice, the term "benchmark dose" is often used for the maximum likelihood estimate, whereas the BMD limit (BMDL) is the lower 95% confidence limit. The benchmark response (BMR) is the adverse response level associated with the BMD (BMDL). A BMR is typically in the low region of the dose-response data for example, a 10% response, which is near the statistical lower limit of detection in an animal bioassay. For dichotomous (yes/no) response data, a BMD can be defined as the dose associated with either an extra risk (relative to the background probability of having a normal response) or an excess risk (additional probability above background) (Crump, 2002). Excess risk is used in the example in this chapter because it provides an estimate of the exposure-attributable risk. The BMD is calculated as the dose, d, corresponding to the specified excess risk in the proportion of animals with a given adverse lung response (BMR):

$$BMR = P(d) - P(0)$$

where $P(d)$ is the probability of an adverse response at the BMD, and $P(0)$ is the probability of that adverse response in an unexposed population (Crump, 2002; EPA, 2006).

BMD methods and models are also available for continuous response data (Crump, 1995, 2002; EPA, 2010), although a detailed discussion is beyond the scope of the chapter. Briefly, BMD estimation using continuous data requires specifying a BMR level along a continuum of responses. Continuous response measures may be associated with normal biological structure or function, which can be perturbed in response to a toxicant and eventually result in a functional impairment. Toxicology studies can provide dose-response data for quantitative risk assessment based on continuous responses, as well as information on the biologically relevant level of response in animals and humans.

The BMD method is often preferred to obtain quantitative risk estimates for either cancer or noncancer endpoints (NRC, 2009). BMD estimates are also more useful in estimating the health benefits of reducing exposures, for example, in the context of developing recommended exposure limits, including for regulatory decision making (U.S. Supreme Court, 1980).

Comparison of BMD and NOAEL/LOAEL estimates

There are several advantages of BMD methods over the NOAEL/LOAEL approach: (i) The BMD curve fitting uses all of the data in the dose-response relationship, not just a single data point; (ii) whereas the NOAEL and LOAEL doses are dependent on the particular dose groups and spacing selected for the study (and tend to be higher in studies with fewer observations), the BMD method can provide dose estimates at a constant level of risk (e.g., 10%) for better comparison across studies; (iii) the BMD method takes appropriate statistical account of the sample size and provides estimates of the confidence limits on the BMD estimates; (iv) whereas an NOAEL or LOAEL approach assumes a threshold response regardless of the shape of the dose-response relationship, BMDLs are risk estimates derived from a statistical model fit to the dose-response data. A comparison of NOAELs and BMDs showed that the estimated risk associated with NOAELs were not negligible but ranged from 3% to 21% (Leisenring and Ryan, 1992). Finally, BMD methods provide a consistent framework for comparing the potency (severity of response at a given dose) of various substances and for extrapolating to doses associated with lower risks. As such, BMD methods may facilitate risk comparisons across an array of nanoscale and larger particles.

BMD methods require sufficient data to characterize the dose-response relationship. Dose-response relationships may show an increasing or decreasing trend, depending on the endpoint (e.g., an increase in an adverse effect or a decrease in a normal function associated with increasing dose). At least two dose groups in addition to the control group are generally needed for BMD modeling, although a reasonable BMD estimate may be obtained if the elevated response in the one exposed group is near the BMR (EPA, 2012). More dose

groups may be needed to adequately describe highly nonlinear relationships. If adequate dose-response data are not available for BMD estimation, an NOAEL or LOAEL may be used as the POD for low dose extrapolation or application of uncertainty factors (EPA, 2012). Toxicology study designs that take into consideration the BMD data requirements can greatly facilitate the study utility for quantitative risk assessment.

3.1.4 Interspecies and Temporal Extrapolation

As for most chemicals, data on the potential adverse health effects of nanomaterials on workers are limited. Thus, shorter-term (13-week) studies in rodents (e.g., on subchronic inhalation) often are used to estimate potential health hazards to workers. The LOAELs and NOAELs in studies of humans suffering particle exposures (presumably airborne) were reported to be generally lower than those in animals, suggesting that humans may be generally more sensitive (i.e., 53%, 21%, or 27%, respectively, of higher, similar, or lower sensitivity in humans than animals) (Kalberlah et al., 2002). Similar results were reported for exposures to gases.

Temporal evaluations in animals showed that the NOAELs and LOAELs following chronic exposures were often lower than those from shorter-term studies (Kalberlah et al., 2002). In an analysis of the U.S. National Toxicology Program of 46 subacute, subchronic, and chronic studies in rodents, Kalberlah et al. (2002) estimated that the effect concentrations (NOAELs or LOAELs) in subchronic (13-week) studies underestimated the chronic response by a factor of approximately 2.7 (geometric mean) (1.0–20, 10th and 90th percentiles). Most of those substances were reported to be respiratory irritants acting in the extrathoracic region (with a few acting in the tracheobronchial or pulmonary regions), On the basis of that analysis, the standard uncertainty factor of 10 to extrapolate from subchronic to chronic dose and response (EPA, 2012) would thus seem to be reasonable on average, although it may not be sufficiently protective in the case of some substances. For example, the limited data on substances acting in the tracheobronchial and pulmonary regions prevented a separate statistical evaluation of those substances (Kalberlah et al., 2002); such region-specific information would be useful in assessing the risk of adverse respiratory effects from exposure to airborne particles (including nanodiameter and microdiameter particles) that could deposit in these regions.

In the current example for respirable MWCNTs, the adverse lung responses are assumed to relate to the total estimated lung dose (deposited or retained), which are dose metrics that have been associated with fibrotic and other adverse lung effects from exposure to various other types of poorly soluble particles in animals and humans (e.g., Muhle et al., 1991; Kuempel et al., 2001a; Dankovic et al., 2007). In this case study example, instead of applying an exposure duration uncertainty factor, the total deposited or retained lung doses in rats (over the 13-week subchronic exposure), the total deposited or retained lung doses in rats (over the 13-week subchronic exposure) are converted to equivalent lung doses in workers assuming

exposures up to a 45-year working lifetime. In the absence of a validated lung model for CNT clearance in humans, the deposited or retained lung (alveolar) dose estimates provide bounds on the possible lung burdens in workers, that is, upper and lower, respectively, since some of the CNTs deposited maybe cleared by alveolar macrophages, although at a potentially lower rate than in the case of spherical particles (Pauluhn, 2010a; Mercer et al., 2013a; NIOSH, 2013). The pulmonary region is the focus of these case studies, based on the data available in the rodent studies; however, CNTs deposited in the tracheobronchial region could be a risk factor for diseases of the airways, including cancer (Schulte et al., 2012).

3.2 Case Study Example: Carbon Nanotubes

Three recent subchronic inhalation studies in rats of MWCNTs (Ma-Hock et al., 2009; Pauluhn, 2010a; Kasai et al., 2014) provide examples of dose-response data currently available for quantitative risk assessment of some engineered nanomaterials. These studies are relevant to occupational risk assessment, given that the target organ (lungs), exposure route (inhalation) and pattern (5 day/wk, 6 h/day), and lung responses in the rats were similar to those observed in humans with occupational exposures to other poorly soluble respirable particles (Attfield and Seixas, 1995; Kuempel et al., 2001a; Gardiner et al., 2001).

3.2.1 Data Description

The three MWCNT subchronic studies in rats had similar study designs, although the MWCNT material varied somewhat in their physicochemical properties. In Ma-Hock et al. (2009), the MWCNTs (produced by a vapor deposition technique) had a primary particle diameter of 5–15 nm and length of 1–10 μm; contained 9.6% Al_2O_3 and traces of iron and cobalt; and the specific surface area was 250–300 mg^2/g based on the Brunauer, Emmett, and Teller (BET) method (Brunauer et al., 1938). The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were approximately 1.2 and 2.7, respectively (median value reported). In Pauluhn (2010a), the MWCNTs (Baytubes, a proprietary product of Bayer MaterialScience, Leverkusen, Germany; production method not reported) had a primary particle diameter of ~10 nm and a median length of 200–300 nm; contained 0.5% Co; and the specific surface area (BET method) was 253 m^2/g (bulk). The MMAD and GSD were approximately 2.7 and 2.1, respectively (median value reported). In Kasai et al. (2014), the MWCNTs (produced by floating chemical vapor deposition) had a primary mean diameter of 90.7 nm and a mean length of 5.7 μm; the carbon content was >99.6% (with trace iron contaminant); and the specific surface area was 24–28 m^2/g. The MMAD and GSD range was 1.4–1.6 μm and 2.3–3.0, respectively. In a study of CNFs (vapor grown), by DeLorme et al. (2012), the diameter was 158 nm (range of 40–350 nm), length was 5.8 μm (range of 1–14 μm); content >99.5% carbon (with <0.003% iron); specific surface area (BET method): 13.8 m^2/g. Across the exposure groups, the MMAD was 1.9 to 3.3 μm

and the GSD was 2.0 to 3.1 (DeLorme et al., 2012). Estimated alveolar deposition fractions of MWCNTs or CNFs in rats were approximately 0.05 to 0.07 but may have been as low as 0.02 (NIOSH, 2013, Table A.2 and A.9; Section A.7.6). In each of these subchronic studies, rats were exposed by inhalation 6 h/day, 5 day/week, for 13 weeks. Lung responses were examined at the end of exposure in each study; postexposure follow-up was 3 months in the DeLorme et al. (2012) study (0 and 25 mg/m^3 groups) and up to 6 months for all groups in the Pauluhn (2010a) study.

The exposure concentrations in the Ma-Hock et al. (2009) study were 0, 0.1, 0.5, and 2.5 mg/m^3 (male and female Wistar rats); an LOAEL of 0.1 mg/m^3 was identified for granulomatous inflammation, in which 30% of rats had developed minimal or higher-grade inflammation based on histopathology. At 0.5 mg/m^3, 85% of the rats had developed lipoproteinosis. The exposure concentrations in the Pauluhn (2010a) study were 0, 0.1, 0.45, 1.62, and 5.98 mg/m^3 (male and female Wistar rats). The NOAEL was identified at 0.1 mg/m^3, and the LOAEL was 0.45 mg/m^3 for pulmonary inflammation, based on elevated polymorphonuclear leukocytes (PMNs) in bronchoalveolar lavage fluid (BALF), and on alveolar interstitial (septal) thickening, of which 90% of rats had developed minimal or higher-grade inflammation based on histopathology (Pauluhn, 2010a). The exposure concentrations in Kasai et al. (2014) were 0, 0.2, 1, and 5 mg/m^3 (male and female F344/DuCrlCrlj rats). The LOAEL for granulomatous lesions and changes in BALF was 0.2 mg/m^3. The LOAEL for interstitial fibrosis was 1 mg/m^3. In the DeLorme et al. (2012) study, the exposure concentrations were 0.54, 2.5, and 25 mg/m^3 (male and female Crl:CD Sprague Dawley rats). The NOAEL was 0.54 mg/m^3; and the LOAEL for minimal inflammation in the terminal bronchiole and alveolar duct areas was 2.5 mg/m^3.

3.2.2 Severity of Effects

Quantitative risk assessment involves estimation of the severity and likelihood of an adverse response associated with exposure to a hazardous agent (Piegorsch and Bailer, 2005; NRC, 2009). Although pulmonary fibrosis has not been studied in those working with CNTs, it has been associated with occupational exposure to various types of respirable particles and fibers, including carbon black (Gardiner et al., 2001), coal dust (Attfield and Seixas, 1995), silica (Park et al., 2002), and asbestos (Stayner et al., 2008). Chest radiography or computed tomography is used in medical examinations to identify the occurrence and severity of fibrosis. In animal studies, a more sensitive measure of pulmonary fibrosis is the amount of alveolar interstitial thickening. Since gas exchange occurs across the alveolar septal air–blood barrier, such thickening of the alveolar septum due to fibrosis can interfere with normal lung function.

The rat subchronic lung responses to inhaled MWCNT effects were relatively in the early stage (minimal or mild histopathology severity grades) for either pulmonary septal

thickening, including fibrosis (Pauluhn, 2010a; Kasai et al., 2014) or granulomatous inflammation (Ma-Hock et al., 2009; Kasai et al., 2014). In the Pauluhn (2010a) study, the alveolar septal thickening observed in response to CNT exposure persisted for at least 26 weeks after the end of the 13-week exposure (i.e., at week 39). Several toxicology studies in which mice were exposed to SWCNTs or MWCNTs via pharyngeal aspiration have also shown dose-dependent alveolar septal thickening, and this response persisted or progressed with longer postexposure time (Shvedova et al., 2005, 2008; Mercer et al., 2008; Porter et al., 2010). This progressive alveolar interstitial fibrotic response was verified in a 12-day inhalation study of mice with as long as a 336-day postexposure evaluation (Mercer et al., 2013a). Although limited information is available to evaluate whether the lung responses in animals exposed to CNTs are associated with functional impairment, changes in breathing pattern in SWCNT-exposed mice have been noted (Shvedova et al., 2005). In addition, alveolar septal thickening has been considered relevant to humans and indicates "fundamental structural remodeling" (e.g., in response to ozone exposure) (EPA, 1996; Stockstill et al., 1995). In the Ma-Hock et al. (2009) study, fibrosis was not evaluated, but a subsequent study of the rat lung tissue from the Ma-Hock et al. (2009) study reported no observed fibrosis (Treumann et al., 2013). The findings of granulomatous inflammation and lipoproteinosis observed in that study are also consistent with the development of pulmonary fibrosis in rodents and humans (e.g., from silica exposure) (Porter et al., 2004; Heppleston, 1975; Hoffmann et al., 1973). Therefore, these rat subchronic lung effects in response to CNT exposure may be considered to be in the range of early biological responses associated with altered structure and function (Schulte, 1989) (Figure 3.1).

A more detailed and quantitative scale of adverse effects has been developed for use in deriving inhalation reference concentrations (EPA, 1994). On the basis of that scale (from 0 to 10), these pulmonary changes observed in rats with subchronic exposure to MWCNTs may

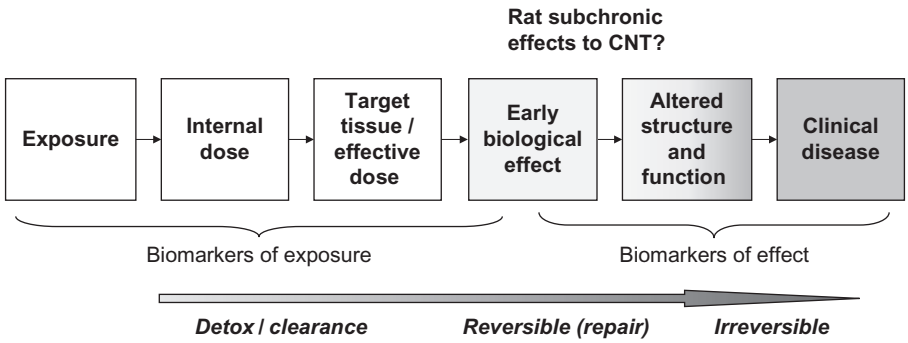

Figure 3.1
Biological continuum from dose to disease with consideration of the lung responses to CNT (carbon nanotubes) observed in the rat subchronic inhalation studies (Ma-Hock et al., 2009; Pauluhn, 2010a; Kasai et al., 2014). *Adapted from NRC (1987) and Schulte (1989).*

correspond somewhere in the range of levels 6–8, although the observed effects may not align exactly with one level:

- Level 6 (LOAEL): Degenerative or necrotic tissue changes with no apparent decrement in organ function
- Level 7 (LOAEL): Reversible slight changes in organ function
- Level 8 (LOAEL/FEL (defined below)): Pathologic changes with definite organ dysfunction that are unlikely to be fully reversible

These levels are consistent with the more qualitative evaluation depicted in Figure 3.1. Effect levels 6 and 7 are considered LOAELs, whereas level 8 is considered an LOAEL/FEL (EPA, 1994). An FEL is a "frank effect level," defined as an "exposure level that produces frankly apparent and unmistakable adverse effects, such as irreversible functional impairment or mortality, at a statistically and biologically significant increase in frequency or severity between an exposed population and its appropriate control" (EPA, 1994). Clearly, a goal in risk assessment is to estimate levels of exposure that are not likely to be associated with any material impairment of health or functional capacity, even if exposures occur over a person's full working lifetime (OSH Act, 1970).

3.2.3 Quantitative Risk Assessment Procedures

The risk assessment process based on animal data, focusing on rodent dose-response data of inhaled particles, is shown in Figure 3.2. An example of the steps in this process, as applied to rat subchronic inhalation studies of MWCNTs, is described in this section.

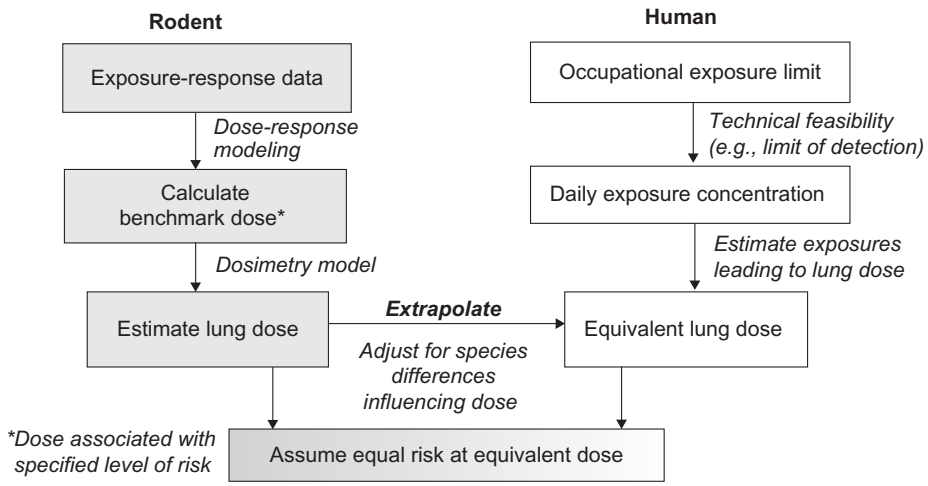

Figure 3.2
Risk assessment steps using animal data of airborne particles, e.g., carbon nanotubes, to develop occupational exposure limits. *Adapted from Oberdörster (1989) and Kuempel (2011).*

Step 1. Evaluation of the exposure (or dose) and response data

The exposure-response data from the three published subchronic inhalation studies of MWCNTs (Ma-Hock et al., 2009; Pauluhn, 2010a; Kasai et al., 2014) are evaluated for possible use in risk assessment because they provide data of relevance to workers (inhalation route of exposure, daily exposures), well-characterized materials (particle size data and chemical composition), and quantitative measures of dose and response. The rat lung responses to respirable MWCNTs are compared with those for CNFs (DeLorme et al., 2012).

The rat lung responses of granulomatous inflammation (Ma-Hock et al., 2009), pulmonary septal thickening (Pauluhn, 2010a), or both granulomatous inflammation and trichrome straining for collagen (Kasai et al., 2014) at minimal or higher severity (grade 1) based on histopathology are selected because they are sensitive, early-stage adverse lung responses to CNT exposure and are relevant to lung disease development in humans. When internal dose data are reported (e.g., lung tissue burden of CNTs), the dose-response data can be used in the estimate of BMD levels and extrapolated to humans based on the estimated equivalent dose in the lungs (e.g., NIOSH, 2013).

Step 2. Estimation of a point of departure

As described earlier (Section 3.1.3), a POD based on a BMDL is estimated by fitting statistical models (e.g., using the BMD software, BMDS (EPA, 2010, 2012)) to rat dose-response data, which, in this case, are the data from each study of CNTs in rats (Ma-Hock et al., 2009; Pauluhn, 2010a; Kasai et al., 2014). A subchronic inhalation study of CNFs in rats (DeLorme et al., 2012) is not included in these case study estimates because the comparable dose-response data for adverse interstitial responses of fibrosis or granulomatous inflammation by histopathologic evaluation were not reported. Other endpoints (e.g., percent PMNs or cell proliferation) might be used in other modeling comparisons; those endpoints (PMNs in male rats and cell proliferation in female rats) remained significantly elevated at the 25 mg/m^3 dose at 90 d after exposure (DeLorme et al., 2012). When estimated deposited lung doses were compared, the adverse lung responses to CNFs in rats (DeLorme et al., 2012) were similar to those observed in mice (Murray et al., 2012; NIOSH, 2013).

In this example, the "dose" is the airborne exposure concentration, resulting in the estimation of a benchmark concentration (BMC) (maximum likelihood estimate) and a lower 95% confidence limit (BMCL) estimate. A challenge in using these data in risk assessment, as shown in the NIOSH (2013) risk assessment, is that the multistage model was the only one in the BMD model suite (EPA, 2010) that converged to a unique solution, or provided adequate fit to the data ($p > 0.1$ in a goodness of fit test) (EPA, 2012) in the Ma-Hock et al. (2009) and Pauluhn (2010a) studies. This is due to the steep dose-response relationship and the sparse data near the 10% BMR, which provided little information for the curve fitting and resulted in multiple solutions in several models. The dose-response data for granulomatous changes in Kasai et al. (2014, Table 2) revealed similar behavior, suggesting similar model-fitting issues.

Table 3.4 Benchmark dose estimates[a] and associated human working lifetime airborne concentrations—based on subchronic inhalation of MWCNTs in rats and estimated deposited lung dose[b] (NIOSH, 2013)

Rodent Study and Response[c]	Rat BMC (BMCL)[d] (mg/m^3)	Rat BMD (BMDL)[e] (μg/lung)	Human-equivalent BMD (BMDL) (mg/lung)	Human-equivalent BMC (BMCL): 8-h TWA & 45 work-years ($\mu g/m^3$)
Granulomatous inflammation (Ma-Hock et al., 2009)	0.060 (0.023)	21 (8.1)	5.4 (2.1)	0.51 (0.19)
Focal alveolar septal thickening (Pauluhn, 2010a)	0.10 (0.051)	28 (14)	7.2 (3.5)	0.77 (0.38)

[a]Benchmark response level: 10% excess (added) risk in exposed animal (EPA, 2010).
[b]Estimated deposited lung dose in rats and humans estimated using MPPD 2.0 model (CIIT and RIVM, 2006); aerodynamic particle sizes (MMAD, GSD): 2.74 (2.11).
[c]Responses are histopathology severity grade 1 or higher.
[d]BMC (BMCL)s; BMC: maximum likelihood estimate of the benchmark concentration; 95% LCL: 95% lower confidence limit of the BMC; dose-response data fit with multistage model (polynomial degree 2) (EPA, 2010). *P*-values for the rodent dose-response models: 0.99 for Ma-Hock et al. (2009) and 0.88 for Pauluhn (2010a) (deposited dose); 1.0 for Ma-Hock et al. (2009) and 0.93 for Pauluhn (2010a) (retained dose), respectively.
[e]BMD: estimated benchmark dose (maximum likelihood estimate): BMDL: estimated 95% lower confidence limit of the BMD.

The rat BMC (BMCL) estimates, as shown in Tables 3.4 and 3.5, Figures 3.3 and 3.4, are 0.060 (0.023) mg/m^3 for granulomatous inflammation (minimal or greater severity) in Ma-Hock et al. (2009) and 0.10 (0.051) mg/m^3 for focal septal thickening in Pauluhn (2010a). Similar BMC (BMCL) estimates were obtained based on the rat pulmonary response of granulomatous changes reported in Kasai et al. (2014, Table 2), i.e., 0.20 (0.056) mg/m^3 in the male rat data, or 0.31 (0.12) mg/m^3 in male and female (combined), also based on a multistage, polynomial degree 2, model. These BMC (BMCL) estimates are all based on the exposure (airborne concentration) and response (lung histopathology results) in each study.

Both Kasai et al. (2014) and Pauluhn (2010b) report BMC (BMCL) estimates. Kasai et al. (2014) reports a "benchmark exposure concentration" of 0.056 mg/m^3 MWCNT for granulomatous changes; although the specific BMDS model or data (male and/or female) are not mentioned, it is the same estimate as the BMCL estimated here based on the male rat data and the multistage (polynomial degree 2) model (gamma model provided identical estimates). Combining the male and female rat data, as done in this example, increases the sample size may increase the confidence (both statistical and biological) in the BMD estimates, assuming similar dose-response relationships in male and female rats. A more rigorous evaluation may be needed to verify that assumption. The pulmonary response of focal fibrosis in Kasai et al. (2014, Table 2) is considered inadequate for BMD modeling since the only responses in the exposed groups were 0 or 100%.

Table 3.5 Benchmark dose estimates[a] and associated human working lifetime airborne concentrations—based on subchronic inhalation of MWCNT in rats and estimated retained lung dose[b] (NIOSH, 2013)

Rodent Study and Response[c]	Rat BMC (BMCL)[d] (mg/m^3)	Rat BMD (BMDL)[e] (μg/lung)	Human-equivalent BMD (BMDL) (mg/lung)	Human-equivalent BMC (BMCL): 8-h TWA & 45 work-years ($\mu g/m^3$)
Granulomatous inflammation (Ma-Hock et al., 2009)	0.060 (0.023)	11 (3.8)	2.7 (0.97)	2.7 (1.0)
Focal alveolar septal thickening (Pauluhn, 2010a)	0.10 (0.051)	14 (6.5)	3.6 (1.7)	4.2 (1.9)

[a]Benchmark response level: 10% excess (added) risk in exposed animal (EPA, 2010).
[b]Retained lung doses in rats and humans estimated using MPPD 2.0 model (CIIT and RIVM, 2006); aerodynamic particle sizes (MMAD, GSD): 2.74 (2.11).
[c]Responses are histopathology severity grade 1 or higher.
[d]BMC (BMCL); BMC: maximum likelihood estimate of the benchmark concentration; 95% LCL: 95% lower confidence limit of the BMC; dose-response data fit with multistage model (polynomial degree 2) (EPA, 2010). P-values for the rodent dose-response models: 1.0 for Ma-Hock et al. (2009) and 0.93 for Pauluhn (2010a), respectively.
[e]BMD: estimated benchmark dose (maximum likelihood estimate): BMDL: estimated 95% lower confidence limit of the BMD.

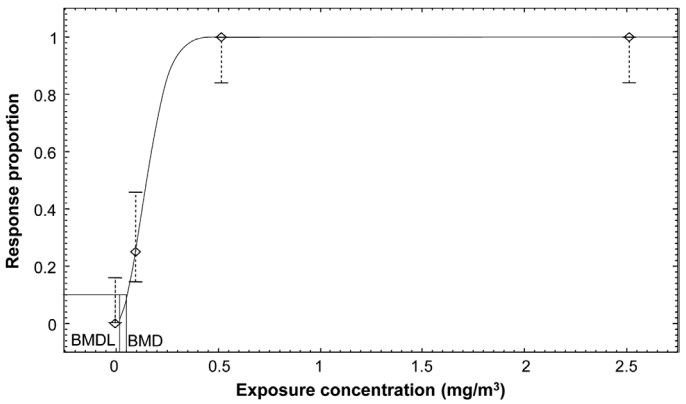

Figure 3.3
Benchmark dose estimation (Kuempel, 2011): Granulomatous inflammation (Ma-Hock et al., 2009). Multistage model, polynomial degree 2, $p = 0.99$. Rat subchronic BMC (BMCL), 10% excess risk: 0.06 (0.02) mg/m^3. (Note: BMD is a general term for a benchmark dose (maximum likelihood estimate) and BMDL is the 95% lower confidence limit estimate of the BMD. In this chapter, the term BMD is used to refer to the lung dose, while the term BMC (benchmark concentration) refers to a BMD based on an airborne exposure concentration).

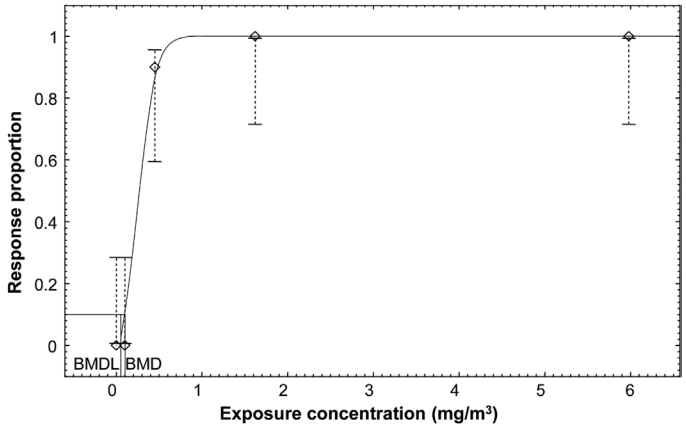

Figure 3.4
Benchmark dose estimation (Kuempel, 2011): Alveolar septal thickening (Pauluhn, 2010a). Multistage model, polynomial degree 2, $p = 0.88$. Rat subchronic BMD (BMDL), 10% excess risk: 0.1 (0.05) mg/m^3. (Note: BMD is a general term for a benchmark dose (maximum likelihood estimate) and BMDL is the 95% lower confidence limit estimate of the BMD. In this chapter, the term BMD is used to refer to the lung dose, while the term BMC (benchmark concentration) refers to a BMD based on an airborne exposure concentration).

Pauluhn (2010b) reports BMC (BMCL) estimates for some pulmonary inflammatory and fibrotic endpoints in BALF, i.e., 0.16, 0.78, and 0.2 mg/m^3 (BMCL) for PMN percent, PMN count, and collagen concentration, respectively (Figure 3 of Pauluhn, 2010b). PMN percent was reported to be significantly increased at the end of the 13-week exposure in rats in the 0.4 mg/m^3 and higher exposure groups (p-values < 0.01); the PMN percent was not significantly increased in rats in the 0.1 mg/m^3 dose group ($p > 0.05$) (Figures 8 and 9 in Pauluhn, 2010a). None of the histopathology responses were significantly increased in male rats (Table 3 in Pauluhn, 2010a); although no histopathology results are reported for female rats. The 0.1 mg/m^3 was regarded as the NOAEL in that study (Pauluhn, 2010a), and is the highest dose that did not have a statistically significant response in male rats. Pauluhn (2010b) uses 0.1 mg/m^3 as the POD for derivation of an OEL for MWCNT (Baytubes®) since that concentration is lower (more protective) than their BMCL estimates for the BALF endpoints. The BMCL estimate of 0.051 mg/m^3 (Tables 3.4 and 3.5) is based on the response of alveolar interstitial (septal) thickening (Table 3 in Pauluhn, 2010a); this BMCL estimate was also used as a POD in the NIOSH (2013) risk assessment. In addition to the POD selected, differences in other factors or assumptions—including those used in extrapolating the animal dose to humans or in accounting for uncertainty in the data—can contribute to differences in the OELs, such as that have been derived for CNTs (Table 3.6).

Table 3.6 Occupational exposure limits (OELs) proposed for carbon nanotubes or nanofibers

Type of Carbon Nanotube or Nanofiber	Occupational Exposure Limit ($\mu g/m^3$)	Reference
MWCNT Baytubes	50	Pauluhn (2010b)
MWCNT (several types)	30	Nakanishi (2011)
MWCNT (based on Pauluhn, 2010b)	2	Aschberger et al. (2010, 2011)
MWCNT (based on Ma-Hock et al., 2009)	1	
CNT and CNF	1	NIOSH (2013)

CNF, Carbon nanofiber; CNT, carbon nanotube; MWCNT, multiwalled carbon nanotube.

In Ma-Hock et al. (2009), rats exposed to the lowest exposure concentration of 0.1 mg/m^3 developed granulomatous inflammation (1/10 in males and 4/10 in females) (Table 2 of Ma-Hock et al., 2009); these response proportions were not reported as being statistically significant (note: it would seem that a 4/10 response proportion in females, compared to 0/10 in controls, would be significant, especially given that the 0.5 mg/m^3 group with 3/10 responders was reported as significant, $p < 0.01$). However, this did not influence the BMD estimates of those data in this example (since all of these dose and response proportion data are included in the model).

In Kasai et al. (2014, Table 2), the granulomatous changes observed in histopathology examination were significant ($p < 0.01$) in male rats exposed at 1 mg/m^3 or higher concentration, while the female rat response was reported as significant only at the 5 mg/m^3 group (although the response proportion was 4/10 at 1 mg/m^3 compared to 0/10 in rats in either the 0.2 mg/m^3 exposure group or the control group). Focal fibrosis was significant ($p < 0.01$) in both male and female rats exposed to 1 mg/m^3, MWCNT but not in rats exposed to 0.2 mg/m^3 ($p > 0.05$). It is not reported whether the PMN responses shown in Figure 2 of Kasai et al. (2014) in female and male rats were significantly increased, although the other BALF parameters are generally significant ($p \leq 0.01$) (Kasai et al., 2014, Figure 2) (the authors only report that "no concentration-related changes were seen in male rats").

Step 3. Estimation of rat lung dose

For the two subchronic studies of CNT available at the time of NIOSH risk assessment (i.e., Ma-Hock et al., 2009 and Pauluhn, 2010a), the BMC (BMCL) estimates provide the basis for estimating an equivalent lung dose (deposited or retained) in rats. The amount of MWCNT deposited in the alveolar (or pulmonary) region of the rat lung at the end of the 13-week study (assuming no clearance) is calculated from data on the ventilation rate (which is related to body mass) (see Appendix), the exposure conditions, and the particle-size

specific deposition fraction in the pulmonary region. In the following example, the BMCL from the Ma-Hock study (Figure 3.3; Table 3.4) is used:

$$\begin{aligned}\text{Deposited Dose} = {} & \text{Airborne concentration} \times \text{duration} \\ & \times \text{ventilation rate} \times \text{deposition fraction} \\ & \text{e.g., } 0.023\ \text{mg/m}^3 \times (6\ \text{h/d} \times 5\ \text{d/wk} \times 13\ \text{wk}) \\ & \times 0.0126\ \text{m}^3\text{/hr} \times 0.072 \\ & = 0.0081\ \text{mg/rat lung}\end{aligned} \tag{3.1}$$

where the ventilation rate in the rat is calculated from: $0.21\,\text{L/min} \times 0.001\,\text{m}^3\text{/L} \times 60\,\text{min/h}$ (Appendix). The ventilation rate is based on species and body weight (EPA, 1994, 2006), assuming 300 g average body weight for male and female rats (since Ma-Hock et al. (2009) did not report the body weights, the values from Pauluhn (2010a) of approximately the same age and rat species/strain were used). The deposition fraction is estimated based on the MMAD and GSD in the rat multiple-path particle dosimetry (MPPD) model (CIIT and RIVM, 2006; NIOSH, 2013, Table A.2).

Although the MPPD model has not yet been validated for CNT, using the measured aerodynamic dynamic diameter should provide a reasonable estimate of the deposition efficiency in the respiratory zone because aerodynamic diameter (which accounts for inertial behavior regardless of density and shape) accurately predicts the particle deposition efficiency in the respiratory tract regions (Hinds, 1999; Kulkarni et al., 2011). Deposited lung burden was used in this example as an estimate of the retained lung burden for CNT over the relatively short exposure period of the subchronic inhalation studies in rats because MWCNT clearance has been shown to be slower than predicted based on clearance data of other poorly-soluble particles (Pauluhn, 2010a,b). Additional comparisons of the MPPD-based model estimates from versions 2.0 and 2.1 as well as with Cobalt-tracer based measurements of retained MWCNT lung burdens reported in Pauluhn (2010b) are reported in NIOSH (2013, Sections A.6.1.1 and A.6.1.2).

Step 4. Estimation of human-equivalent lung dose

The rat lung dose is extrapolated to a human-equivalent dose, in this example, by adjusting for species-specific differences in the surface area of the pulmonary (or gas-exchange) region of the lungs. In making this extrapolation, it is assumed that rats and humans would have equal lung responses to an estimated equivalent dose per unit surface area of alveolar epithelial cells. The basis for this assumption is that the pulmonary region of the lungs (and specifically the alveolar epithelial cell surface) is the primary deposition target which results in interstitial fibrosis that has been observed in both rodents and humans exposed to various

types of airborne particles. Thus, the rat lung dose (0.0081 mg) is extrapolated to humans as follows:

$$\begin{aligned}\text{Human lung dose} &= \text{Rat lung dose} \times \text{Human/rat alveolar surface area } (102\ m^2/0.4\ m^2)\\ &= 2.1\ \text{mg in human lungs}\end{aligned} \tag{3.2}$$

where human and rat alveolar epithelial surface area are taken from morphometric analyses (Stone et al., 1992; Mercer et al., 1994).

Next is to estimate the workplace exposure scenario that would result in the human-equivalent lung dose. The estimated human 8-h time-weighted average (TWA) concentration over a 45-year working lifetime that would result in the human-equivalent lung dose in the pulmonary region of the lungs is calculated as:

$$\begin{aligned}&\text{Human-equiv. lung burden (mg)}/[\text{Air intake} \times \text{exposure duration} \times \text{deposition fraction}]\\ &= 2.1\ \text{mg}/[9.6(\text{m}^3/\text{d}) \times (5\ \text{d/wk} \times 50\ \text{wk/yr} \times 45\ \text{yr}) \times 0.099]\\ &= 0.00019\ \text{mg/m}^3\end{aligned} \tag{3.3}$$

where the human-equivalent lung burden is from Eqn (3.2), the air intake is for the reference worker (ICRP, 1994) and the alveolar deposition fraction is based on the MMAD (GSD) as estimated in MPPD 2.0 (Yeh and Schum human deposition model) (CIIT and RIVM, 2006). As discussed above for the rat lung burden estimate, the aerodynamic diameter should provide a reasonable estimate of the deposited lung dose, while the retained lung dose estimates are more uncertain.

The benchmark dose and exposure concentration estimates shown in this example, based on deposited lung dose estimates (i.e., assuming no CNT clearance from the lungs), are shown in Table 3.4. In addition, Table 3.5 provides benchmark dose and exposure concentration estimates based on estimated retained lung dose in rats (at the end of 13 weeks) and equivalent retained dose estimates in humans (after 45-year working lifetime), assuming spherical particle deposition and clearance kinetics in MPPD 2.0 (CIIT and RIVM, 2006). The steps for deriving BMC (BMCL) estimates based on retained lung dose are similar to those described above for deposited lung dose, except the MPPD model-based estimates of retained dose (which account for time-dependent clearance of the deposited dose) are used instead of the estimated deposited dose in Eqns (3.1) and (3.3). The human-equivalent BMC (BMCL) estimates in Tables 3.4 and 3.5 indicate that working lifetime exposures to 0.2–2 μg/m^3 (as 8-h TWA concentrations, lower 95% confidence limits; based on deposited or retained lung dose estimates) would be associated with a 10% excess risk of early-stage adverse lung effects (pulmonary inflammation and fibrosis) in workers. These airborne mass concentration estimates are quite low relative to estimates for other poorly-soluble fine or ultrafine particles (e.g., Dankovic et al., 2007).

Step 5. Risk characterization

In order to perform risk characterization (step 4 of the risk assessment paradigm) (NRC, 1983, 2009), data are needed on the worker exposures. Because such data are limited (e.g., short-term or task-based area samples of airborne CNT concentration with few personal samples) (Bello et al., 2009; Lee et al., 2010; Johnson et al., 2010), it is not currently feasible to characterize the disease risk in workers producing or using CNT. However, these studies indicate the potential for workplace airborne concentrations of concern and strongly support the need for extra precaution in controlling exposures to CNT (Schulte and Salamanca-Buentello, 2007). NIOSH is currently evaluating exposure levels in ten industrial workplaces producing/using carbon nanotubes. Mean airborne exposures to MWCNT determined by elemental carbon (EC) in the inhalable fraction were approximately 10.6 $\mu g/m^3$ (arithmetic mean) and 4.21 $\mu g/m^3$ (geometric mean), while the respirable fractions were several-fold lower and typically near background EC levels (Dahm et al., 2012; Erdely et al., 2013). The NIOSH REL of 1 $\mu g/m^3$ was set at the limit of quantification (LOQ) for the analytical method (NIOSH Method 5040) (NIOSH, 2013).

3.2.4 Considerations in the Derivation of OELs

In addition to characterizing risk to workers given exposure, risk estimation is also used in developing occupational exposure limit (OELs), the final step in the risk assessment process (Figure 3.2). Details on the development of OELs are beyond the scope of this chapter. However, the specific basis for OELs should be well-documented since differences in the factors and assumptions used in the risk assessment (including those in the derivation of a POD, as discussed in this section) can contribute to differences in the derived OELs. For CNT and CNF, the proposed OELs vary by a factor of up to 50 (Table 3.6), although all of these proposed OELs are low airborne mass concentrations compared to other poorly soluble particles (e.g., OELs for carbon black or graphite are on the order of milligrams per cubic meter of air (NIOSH, 2007), compared to micrograms per cubic meter of air for CNTs) (Table 3.6).

Both hazard and risk-based factors and nonrisk factors (e.g., technological feasibility of measuring and controlling exposures) are typically considered in the development of an OEL. Such factors are also evaluated in conjunction with any exposure measurement data to characterize the risk in a given population and to assess the need for additional protective measures such as personal protective equipment and medical monitoring.

3.3 Discussion

Although the rat subchronic lung responses to MWCNT are early-stage (minimal or higher severity grade of granulomatous inflammation or alveolar septal thickening), a BMR is an

effect level (e.g., 10%) that is considered biologically and statistically significant. In risk assessment practice, a human-equivalent BMD (i.e., the dose associated with the BMR) would not be used directly to develop an OEL. Instead, the BMDL would typically be used as a POD to estimate doses associates with lower risk levels. Alternatively, a BMDL is treated like an NOAEL with the application of uncertainty factors (EPA, 2012).

A health-based OEL is based on an exposure associated with a low risk of disease over a full working lifetime. However, the technologic feasibility of measuring or controlling exposures is also often considered in development of an OEL. For CNTs (as for other materials), there are limitations in the technical feasibility of the method to measure airborne mass concentrations. For example, the limit of quantification (LOQ) of NIOSH method 5040 for elemental carbon, including CNTs, is approximately 1 $\mu g/m^3$ as an 8-hour TWA concentration (NIOSH, 2013). Thus, the risk estimates at this LOQ are greater than 10% for early-stage adverse lung effects (see Section 3.2.3), which indicates the critical need to develop more sensitive measurement methods and to take additional precautionary measures (including engineering controls and use of personal protective equipment) when working with CNTs that may become airborne and inhaled.

3.3.1 Comparison with Other Methods

In addition to the benchmark dose method illustrated here, it is relevant to compare these estimates (Tables 3.4 and 3.5) with those based on other methods. For example, if an NOAEL or LOAEL of 0.1 mg/m^3 (Pauluhn, 2010a; Ma-Hock et al., 2009, respectively) is used as the starting point, the human-equivalent working lifetime 8-h TWA concentration would be <1 or 4 $\mu g/m^3$ based on the methods presented (using deposited or retained lung burden estimates), given that 0.1 mg/m^3 is also the BMC estimate based on the Pauluhn (2010a) study (Tables 3.4 and 3.5). As mentioned, these are human-equivalent concentrations corresponding to 10% excess risk of early-stage adverse lung effects; and no uncertainty factors have been applied to these estimates. The estimates for CNFs, starting with the NOAEL reported in the DeLorme et al. (2012) study, resulted in human-equivalent 45-year working lifetime concentration estimates of 1–4 $\mu g/m^3$ (8-h TWA), depending on the data and assumptions used to estimate the human-equivalent dose (NIOSH, 2013; see Section A.7).

A common method for extrapolating an NOAEL/LOAEL or BMD (BMCL) estimate from animals to humans (e.g., to derive a chronic inhalation reference concentration (RfC)) is the dosimetry adjustment factor (DAF) method for inhaled particles (EPA, 1994). In this method, the animal exposure concentration associated with an adverse effect (NOAEL, LOAEL, or BMC (BMCL)) is adjusted for differences in the animal versus human exposure pattern (hours per day and days per week), then multiplied by the DAF. The DAF for inhaled particles is a series of ratios used to adjust for the interspecies differences that influence the deposited particle dose in the respiratory tract, including the animal versus human ventilation

rate (V_E) (air volume inhaled per unit time); the animal versus human deposition fraction (DF) of particles in the relevant respiratory tract region(s); and a normalizing factor (NF) to adjust the deposited dose across species (e.g., the human versus rat surface area of the respiratory tract region(s) is typically used for insoluble particles, which deposit and clear along the surface of the respiratory tract) (EPA, 1994). Thus, a human-equivalent concentration would be calculated as:

$$\text{Effect Concentration}\left(\text{animal}\right) \times \left[V_E\left(\text{animal}\right)/V_E\left(\text{human}\right)\right] \times \left[\text{DF}\left(\text{animal}\right)/\text{DF}\left(\text{human}\right)\right] \times \left[\text{NF}\left(\text{human}\right)/\text{NF}\left(\text{animal}\right)\right]$$

As seen here, many of the same adjustments are made as in the case study example (Section 3.2). However, the DAF method is based on an average concentration (i.e., the response is assumed to be related to the chronic average exposure concentration rather than to the cumulative dose as in Section 3.2). Appropriate uncertainty factors would be applied to the human-equivalent concentration in deriving an exposure limit (e.g., RfC) (EPA, 1994).

In a recent risk assessment for MWCNTs, Pauluhn (2010b) started with the NOAEL of 0.1 mg/m^3 from a rat subchronic inhalation study (Pauluhn, 2010a) to estimate a human-equivalent concentration as the basis for an OEL, by applying a series of interspecies adjustment factors (AFs) to the rat NOAEL. The first AF was to adjust for rat versus human differences in the ventilation rate, which Pauluhn (2010b) expressed per kilogram of body weight: 0.14 (human)/0.29 (rat) = 0.5. These numbers were derived as follows: human reference worker breathing rate (8-h TWA) and weight: 9.6 m^3/70 kg (ICRP, 1994); and rat ventilation rate: 0.8 L/min/kg × 360 min (in 6-h rat exposure day) × 0.001 m^3/L. The second AF was to adjust for interspecies differences in the percentage of MWCNTs predicted to be deposited in the pulmonary region in each species, based on an MMAD of 3 µm (Pauluhn, 2010b): 11.8% (human)/5.7% (rat) = 2. The third AF was an NF to adjust the deposited lung dose in each species based on the total alveolar macrophage cell volume, assuming a rat-based volumetric overload mode of action (also expressed per kilogram of body weight), which resulted in an AF of 8.7×10^{10} (rat)/5.0×10^{11} (human) = 0.17 (Pauluhn, 2010b). The final AF was to normalize the retained lung dose based on an assumed constant factor of 10 times faster clearance in rats versus humans, based on first-order clearance kinetics. Combining these AFs, Pauluhn (2010b) derived an overall AF of: 0.5 × 2 × 0.17 × 10 = ~2. Dividing the rat NOAEL by this AF, a human-equivalent exposure concentration was calculated as: 0.1 mg/m^3/2 = 0.05 mg/m^3. No uncertainty factors were applied, and the human-equivalent concentration of 0.05 mg/m^3 was suggested as an OEL for MWCNTs (Pauluhn, 2010b). (Note: the ratios used by Pauluhn (2010b) are inverse to those used in the DAF method described above (EPA, 1994); whereas EPA would multiply a NOAEL (or other effect level) by the DAF, Pauluhn (2010b) divided the NOAEL by the AF. In other words, the EPA DAF = 1/AF (Pauluhn, 2010b)).

Extrapolation of an animal effect level to estimate a human-equivalent concentration is, of course, influenced by the various factors and assumptions used, and reasonable alternatives may exist based on the scientific literature. For example, in the Pauluhn (2010b) approach, the expression of the rat and human ventilation rates per body weight has a large effect on the first AF. Since ventilation rates are already derived from a nonlinear allometric relationship to body weight (EPA, 1994) (shown in the Appendix at the end of this chapter), typically these would not be adjusted again by body weight. If the whole animal or human ventilation rates are used instead, the first AF would be: 9.6 m^3 per human 8-h workday/0.085 m^3 per rat 6-h exposure day = 113 (versus 0.5 in Pauluhn (2010b)). The rat ventilation rate of 0.085 m^3 is calculated for a 0.35 kg body weight in a rat (based on equations given in the Appendix) and is similar to an estimate of 0.1 m^3 based on the values reported in Pauluhn (2010b), that is, 0.29 m^3/6-h per kg × 0.35 kg rat = 0.1 m^3/6-h. Thus, the ventilation rates are similar, but are expressed differently in the AF, resulting in a quantitatively different AF. For the second AF, no alternative assumptions would seem reasonable, since the pulmonary deposition percentages are based on the measured aerodynamic diameter of the particles; thus, the same human/rat pulmonary deposition AF of 2 is assumed here. For the third AF, an alternative assumption would be to adjust by the pulmonary surface area (Section 3.2.3; EPA, 1994) instead of using the alveolar macrophage cell volume to normalize the lung dose across species; this would result in an alternative AF of: 0.4 m^2 (rat)/102 m^2 (human) = 0.0039 (versus 0.17 in Pauluhn (2010b)). Regarding the fourth AF, additional issues are discussed below, but for simplicity in this example, the same rat/human AF of 10 is assumed. Thus, using these alternative assumptions, the total AF would be: 113 × 2 × 0.0039 × 10 = ~9. The alternative human-equivalent concentration would be: 0.1 mg/m^3/9 = 0.011 mg/m^3. This estimate is approximately five times lower than that of Pauluhn (2010b). However, this is not a large difference given the uncertainty in the various extrapolation methods. Actually, these estimates are reasonably consistent as low airborne mass concentrations relative to larger size (fine) respirable particles or to other ultrafine (nanoscale) particles (e.g., Dankovic et al., 2007).

In the BMD example in Section 3.2, instead of using an AF of ~10 based on a simple first-order (one compartment) clearance model (as in Pauluhn (2010b)), the interspecies lung dose extrapolation was based on an estimate of the actual lung dose (deposited or retained) for a given exposure scenario. The International Commission on Radiological Protection (ICRP, 1994) human respiratory tract model (which is used in MPPD (CIIT and RIVM, 2006)) includes three pulmonary clearance rate coefficients (three compartments) to estimate particle retention in the alveolar–interstitial region, including a fraction of the deposited dose that is cleared very slowly (approximately 10-year retention half-time). A simple one-compartment model assumed in Pauluhn (2010b) would underestimate the retained human lung burden (Kuempel and Tran, 2002). A higher-order long-term lung retention model that includes an interstitial-sequestration region (Kuempel et al., 2001b) has been shown to better fit several

human data sets, including those on coal miners experiencing high dust exposure (Kuempel, 2000; Tran and Buchanan, 2000) and workers in the nuclear industry exposed to lower nuclear doses (Gregoratto et al., 2010). Revisions to the ICRP model, including the alveolar–interstitial region based on the interstitial-sequestration model have been proposed (Bailey et al., 2008; Gregoratto et al., 2010). None of these models have been evaluated for CNTs, however, and the animal data have shown that MWCNT clearance is slower for a given mass dose than that of spherical poorly soluble particles (Pauluhn, 2010a,b; Muller et al., 2005). Thus, the BMD examples, based on either the deposited or the retained lung dose estimates (Tables 3.4 and 3.5), may represent the upper and lower bounds of the best estimate. That is, the deposited lung dose (assuming no CNT clearance) may overestimate the lung dose over time, whereas the retained lung dose (based on a poorly soluble spherical particle model) may underestimate the lung dose.

Despite these different approaches for dosimetric adjustment of a rodent adverse effect level (NOAEL or BMD) to estimate a human-equivalent dose, these various approaches all provide relatively low mass airborne exposure concentrations. By comparison, in a similar study design (13-week inhalation exposure) in rats exposed to ultrafine carbon black, the NOAEL was 1 mg/m^3 and the LOAEL for pulmonary inflammation and fibrosis was 7 mg/m^3 (Elder et al., 2005). Although dose spacing influences NOAEL and LOAEL values, these findings suggest that MWCNTs are approximately 10 times more potent in causing pulmonary inflammation and fibrosis compared with ultrafine carbon black.

The update of MPPD from version 2.0 to 2.1 (ARA, 2009) included revised rat deposition efficiency prediction equations (Raabe et al., 1988), which have resulted in increased predicted respirable particle deposition fractions in the head/extrathoracic region and, consequently, lower predicted deposition fractions in the rat pulmonary region (Owen Price, ARA, personal communication). For the MWCNT airborne particle sizes, this results in approximately half the estimated deposited dose of MWCNTs in the rat pulmonary region (thus, the rat pulmonary deposition fraction reported by Pauluhn (2010b) would also be about half) (NIOSH, 2013). The lower estimated dose associated with the same response proportion in the rat would result in lower rat BMD (BMDL) and human-equivalent BMC (BMCL) estimates (by a factor of approximately 2) than those shown in Tables 3.4 and 3.5. As additional data become available (e.g., in animal studies) to help evaluate current lung dosimetry models for CNT, the uncertainties in CNT dose and risk estimation may be reduced.

3.3.2 Research Needs

Toxicologic studies in animals and *in vitro* cell systems provide essential data for assessment of the hazards and risks associated with nanoparticles. Additional research needs for nanoparticle risk assessment (which may also apply to risk assessment of other substances)

include: (i) determination of responses not only in the organ of initial exposure but also in distal organs; (ii) identification of the nature of the hazards, including the severity of the effect and mechanism of action in animals and relevance to humans; (iii) determination of a biologically effective dose metric that is associated with these adverse effects; and (iv) generation of quantitative dose-response data in animal studies that are relevant to estimation of equivalent dose and disease in humans. In addition, toxicologic studies can provide more specialized data that are needed to develop mechanistically based risk models, including (v) kinetic data on the dose to the target tissue over time, to measure internal dose and develop dosimetry models; and (vi) time course of the dose and response, to develop biologically based models linking early biological responses and later disease outcomes. For fibrous particles such as CNTs and CNFs, additional dose metrics (e.g., fiber or tube count) may be needed to investigate the dose-response relationships and disease risks in workers (Schulte et al., 2012). Data on workplace exposures to nanomaterials are critically needed in order to characterize the risks and to take appropriate risk management measures to protect workers' health. Improvements in the sensitivity and specificity of measurement and analytical methods are needed for nanomaterials, including CNTs (NIOSH, 2013), in order to detect and quantify low mass concentrations. These low airborne mass concentrations are of concern based on the hazard data from the animal studies and the risk estimates derived from those data (e.g., case study example in this chapter).

3.3.3 Future Directions

Nanotechnology is capable of synthesizing nanoparticles of various sizes, shapes, dissolution rates, surface charge, hydrophobicity, surface functionalization, surface reactivity, chemistry, and so on. Given the vast array of nanoparticles that are being developed, it will be necessary to develop strategies to more efficiently and effectively assess the hazards and risks of nanoparticles to which workers may be exposed. The development of *in vitro* assays that can predict *in vivo* responses would facilitate initial hazard evaluation tests and screening to identify less hazardous nanomaterials (Rotroff et al., 2010). These assays require validation, although some promising studies are emerging. For example, the *in vitro* and *in vivo* dose-response relationships for inflammation-related responses have been shown to correlate well when dose is expressed as particle surface area and the reactivity of the surface is taken into account (Donaldson et al., 2008). More recently, *in vitro* cell assays of oxidative stress were shown to correlate well with *in vivo* acute lung responses in rats based on the particle surface area dose of several spherical metal and metal oxide nanoparticles (Rushton et al., 2010). Zhang et al. (2012) also reported good correlation between *in vitro* and *in vivo* assays of oxidative stress and acute pulmonary responses. Development of a models of the relationships between bioactivity and physicochemical properties (i.e., quantitative structure activity relationships, QSAR) (e.g., Liu et al., 2011, 2013; Gernand and Casman, 2014) may also facilitate comparative potency and hazard ranking strategies.

Future advancements in risk assessment methods may include models to predict disease response based on early biological responses, such as cell signaling and gene expression data (Thomas et al., 2007, 2009). There is also a need to confirm to what degree bolus exposures (intratracheal instillation or pharyngeal aspiration) of biopersistent nanoparticles such as MWCNTs provide similar responses to an equivalent dose by inhalation. Preliminary data suggest that pharyngeal aspiration of a well-dispersed suspension of SWCNTs results in a level of pulmonary inflammation and fibrosis, which is similar to that seen after a 4-day inhalation resulting in the same lung burden of SWCNTs (Shvedova et al., 2008; Mercer et al., 2008). In addition, a one-day (6-h) inhalation exposure in rats showed a similar dose-response relationship for pulmonary septal thickening and fibrosis at 90 days after exposure (Ellinger-Ziegelbauer and Pauluhn, 2009) as the 13-week inhalation study (Pauluhn, 2010a) based on estimated deposited lung dose. Therefore, it appears that shorter-term exposure studies may provide data for comparison with the subchronic studies and expand the database to evaluate the hazard of various types of CNTs.

Chronic exposure studies are needed to evaluate the potential adverse effects that exhibit a long latency, such as lung cancer or mesothelioma. A key area of uncertainty is the carcinogenic potential of the various types of CNTs (Grosse et al., 2014). Recent intraperitoneal studies in rats have reported mesothelioma at similar doses of MWCNTs (as mass or fiber number) to the intraperitoneal doses of asbestos that have been associated with mesothelioma (Takagi et al., 2008, 2012; Nagai et al., 2011, 2013; Rittinghausen et al., 2014). Studies on carcinogenicity of CNTs by inhalation are limited, although a recent study reported that MWCNTs were cancer promotors in mice exposed by inhalation (5 mg/m^3, 5 h/day, 5 day/wk) for 3 weeks (starting 1 week after intraperitoneal injection of the tumor initiator methylcholanthrene) and examined 17 months after exposure for lung tumor formation (Sargent et al., 2014). Cancer bioassay data are still limited or lacking for SWCNTs and for many other types of CNTs or CNFs. More rapid assays are needed for cancer screening (e.g., Wang et al. (2014) biotransformation assay).

Currently, some short-term studies of CNTs have included positive controls, for example, crystalline silica, asbestos, ultrafine carbon black (Lam et al., 2004; Muller et al., 2005; Shvedova et al., 2005, 2014; Murray et al., 2012) for which chronic study data are available in animals and in epidemiologic studies. These data provide a linkage between short-term effects in animals and chronic effects of relevance to humans. Such linkages provide opportunities for comparative potency analyses of these well-studied particles (also known as reference or benchmark particles) and engineered nanoparticles, especially if information is available to indicate the same mode of action (Kuempel et al., 2012a).

In the absence of complete information on the hazards and risks associated with exposure to nanomaterials, a higher level of precaution is needed to control exposures in the workplace (Schulte and Salamanca-Buentello, 2007). Animal studies indicate that inhaled

nanoparticles, including CNTs, may be more hazardous on an equal-mass basis than larger particles of the same chemical composition. Primary prevention through effective control of airborne exposure during production, use, or disposal of nanomaterials is essential to protect workers from developing occupational respiratory diseases (Kuempel et al., 2012b; Schulte et al., 2012).

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Appendix: Pulmonary Ventilation Rate Calculations

Species-specific average ventilation rates can be calculated based on the following allometric scaling equation:

$$\ln(V_E) = b_0 + b_1 \ln(BW) \tag{A.1}$$

where V_E is the minute ventilation (L/min); BW is body weight (kg); and $b_0 + b_1$ are the species-specific parameters; for the rat, $b_0 + b_1$ are -0.578 and 0.821, respectively (in Table 4.6 of EPA (1994)).

Minute ventilation (V_E) (L/min) is itself the product of the tidal volume (V_T) (L) and the breathing frequency (f) (min^{-1}) (EPA, 1994):

$$V_E = V_T \times f \tag{A.2}$$

Rat Ventilation Rate

The default value for minute ventilation in the multiple-path particle dosimetry (MPPD) 2.0 rat model (CIIT and RIVM, 2006) is 0.21 L/min, based on the default values of 2.1 mL (V_T) and 102 min^{-1} (f):

$$0.21\ (L/min) = 2.1\ (ml) \times 102\ (min^{-1}) \times (1/1000)\ (L/ml) \tag{A.3}$$

This minute ventilation corresponds to a rat weighing 300 g, based on Eqn (A.1):

$$0.21\ (L/min) = \text{Exp}\ [-0.578 + 0.821 \times \ln\ (0.3)] \tag{A.4}$$

Minute ventilation values for the rats in the subchronic inhalation studies (Ma-Hock et al., 2009; Pauluhn, 2010a) were also calculated on the basis of body weight. Pauluhn (2010a) reported male and female rat body weights of 369 and 245 g, respectively, in the control (unexposed) group at 13 weeks. Since the alveolar septal thickening response data were reported for 10 male rats per dose group, the male rat body weight (and calculated minute ventilation) was used to estimate deposited and retained lung dose in the Pauluhn (2010a) study. Ma-Hock et al. (2009) did not report the rat body weight, although the rat strain (Wistar) and study duration (13 weeks) were the same as in Pauluhn (2010a). Since the granulomatous inflammation response data in Ma-Hock et al. (2009) were combined for the 10 male and 10 female rats in each dose group (because response proportions were statistically consistent), an average rat body weight in male and female rats of 300 g was assumed, based on the 300 g body weight used in the default minute ventilation in MPPD 2.0 (CIIT and RIVM, 2006) and the male and female average body weight of 307 g reported in Pauluhn (2010a).

Thus, based on Eqn (A.1), a minute ventilation of 0 0.21 L/min is calculated for female and male rats in Ma-Hock et al. (2009) (same as MPPD 2.0 default), and 0.25 L/min for male rats

in Pauluhn (2010a). Assuming the same breathing frequency (102 min^{-1}), a tidal volume of 2.45 mL is calculated (Eqn (A.3)) and used instead of the default value in MPPD 2.0 (CIIT and RIVM, 2006) in estimating the rat lung dose in the Pauluhn (2010a) data.

Human Ventilation Rate

In the human MPPD 2.0 model (CIIT and RIVM, 2006), the default pulmonary ventilation rate is 7.5 L/min, based on default values of 12 min^{-1} breathing frequency and 625 mL tidal volume. The "reference worker" ventilation rate is 20 L/min (ICRP, 1994) or 9.6 m^3/8-hr (given 0.001 m^3/L, and 480 min/8-h). In these estimates, 17.5 min^{-1} breathing frequency and 1143 mL tidal volume were used in MPPD 2.0 to correspond to a 20 L/min reference worker ventilation rate.

CHAPTER 4

Lung Bioassay Methodologies for Assessing Hazards After Exposures to Nanoscale or Fine Particulates

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Chapter Outline

4.1 Introduction and General Background

Approximately 5 years ago, I wrote a chapter for a book in this series, describing some essential topics related to nanotoxicology hazard-testing issues following pulmonary exposures. The brief review was focused on (i) the prevailing view on the potential hazards of pulmonary exposures to nanoparticles; (ii) species differences in lung responses to inhaled fine or nanoscale titanium dioxide (TiO_2) particles; and (iii) examples of pulmonary bioassay studies with both fine and nanoscale TiO_2 particle types as well as fine and nanoscale α-quartz particles.

To this end, pulmonary bioassay studies are extremely useful for comparing the potential hazards of different test materials, for suggesting mechanisms of action, and for generating hypotheses to be tested. Several essential experimental design components are necessary for conducting a pulmonary bioassay that can yield useful conclusions. These include, but are not limited to, the following criteria: (i) robust characterization of the test material; (ii) a realistic (i.e., not excessively high) dose-response paradigms—utilizing relevant dose level settings that could be encountered in occupational or consumer environments; (iii) the importance of time course studies to ascertain the sustainability of any measured responses; and (iv) the inclusion of reference materials to better interpret the experimental findings that are derived

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from a study. The inclusion of reference or benchmark materials may not be possible for some or all longer-term inhalation studies, but certainly are critical for interpreting findings of intratracheal instillation studies. When implemented properly, the results of pulmonary bioassay studies can provide important information for hazard screening purposes and, under certain circumstances, may be utilized for exposure level setting; if the findings are benchmarked or bridged to other longer-term inhalation data from other similar test materials.

An example of the utility of pulmonary bioassay data for developing meaningful occupational exposure limits for engineered nanomaterials was recently published by Gordon et al. (2014). These investigators summarized the findings of a recent workshop on the potential effectiveness of various alternative strategies for setting occupational exposure limits (OELs) for nanomaterials. Clearly, it is unrealistic to assume that the longer-term inhalation toxicity database will be sufficiently advanced or completed in the near term or a future period. In offering an alternative approach, Warheit (2013) utilized a bridging developmental method that benchmarked the results of intratracheal instillation studies with subchronic and chronic inhalation studies to suggest a methodology to better estimate OELs.

When considering the issue of interpreting experimental-type studies versus guideline studies, it seems reasonable to suggest that mechanistically driven, experimental-type study such as a pulmonary bioassay (Warheit et al., 2007a,b) can add significant value to more insightful estimations of time course events related to the development of pathologic outcomes following nanoparticle exposures. Nonetheless, when setting safety standards for workers and consumers, it would be preferable and more dependable for the conduct of inhalation studies to follow the test guidelines (TGs) of the Organization for Economic Cooperation and Development (OECD); which provide the most reliable assessments of the hazards of test materials. These TGs are standardized and developed by the OECD precisely for data generation for the purpose of establishing safe exposure limits for a given form of a chemical substance, including nanoparticles. Moreover, the OECD Good Laboratory Practices (GLPs) principles and the specific TGs serve to advance the quality and validity of test data. The GLP concept represents a structure that mandates a set of prudent practices under which the circumstances for conducting laboratory studies are carefully documented and specified. Moreover, the mutually agreed upon OECD TGs are required to be followed by other testing facilities conducting studies, the results of which will be submitted to national authorities for assessments of chemicals (OECD, 1997).

In the following section, the methodology and results of a subchronic inhalation study in rats with aerosolized carbon nanofibers (CNFs) are described. This subchronic, 90-day study with CNFs was conducted under the OECD Test Guideline (TG) 413. This TG was designed to fully characterize the test article's toxicity by the inhalation route for a subchronic duration (90 days) and to provide robust data for the development of quantitative inhalation risk assessments. According to the TG, groups of at least 10 male and 10 female

rodents are exposed, 6 h per day during a 90-day (13-week) period, to the test article at three or more aerosol concentration levels, utilizing filtered air as negative control. Rats are generally exposed 5 days per week. The results of the study are required to include detailed measurements of hematology and clinical chemistry, gross pathology, organ weights, and histopathology parameters. This TG allows the flexibility to include satellite (reversibility) groups, interim sacrifices, bronchoalveolar lavage (BAL), and additional clinical pathology and histopathologic evaluations in order to better characterize the toxicity of a test article. In a summary of the 90-day study with carbon nanofibers (CNF) described below, we incorporated cell proliferation assessments of various components of the respiratory tract to enhance the evaluation of the effects of inhaled CNF in rats (Delorme et al., 2012).

4.2 Subchronic Inhalation Study in Rats with Carbon Nanofibers—OECD Test Guideline 413

The objective of this study was to evaluate the toxicity of inhaled VGCF-H CNFs in male and female Sprague Dawley rats following 90 days of exposure and to investigate the potential adverse systemic effects, including those on the respiratory tract and cardiovascular systems in these animals. To conduct this study, four groups of rats per sex were exposed nose-only, 6 h/day, 5 days/wk to target concentrations of 0, 0.54, 2.5, or 25 mg/m^3 CNF over a 90-day period. Additional groups of rats exposed to 0 and 25 mg/m^3 CNF for 90 days were evaluated at 3 months postexposure by using conventional clinical and histopathologic methodologies, BAL assessments, and cell proliferation endpoints. Bromodeoxyuridine cell proliferation studies concomitant with morphologic assessments of several anatomical compartments of the respiratory tract were conducted at three selected anatomical compartments of the respiratory tract; namely, the (i) airways—terminal bronchiole; (ii) lung parenchyma—alveolar duct; and (iii) subpleural regions (Figures 4.1–4.3).

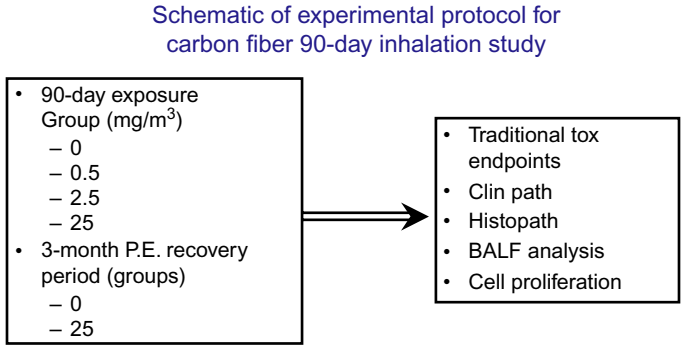

Figure 4.1
Schematic of experimental protocol—OECD Guideline 413 study.

90-day inhalation exposure study with carbon nanofibers

- **Histopathology**
- **BAL fluid endpoints**
  - Total cell counts and cellular differentials
  - BAL fluid LDH (cytotoxicity)
  - BAL fluid microprotein (permeability)
  - BAL fluid alkaline phosphatase (Type II cell cytotoxicity)
- **Cell proliferation studies – BrdU**
  - Terminal bronchiolar (airway)
  - Lung parenchymal cell
  - Subpleural/(mesothelial)

Figure 4.2
Specific BAL fluid and cell proliferation endpoints.

Aerosol sample taken from filter in high-exposure conc. chamber — TEM

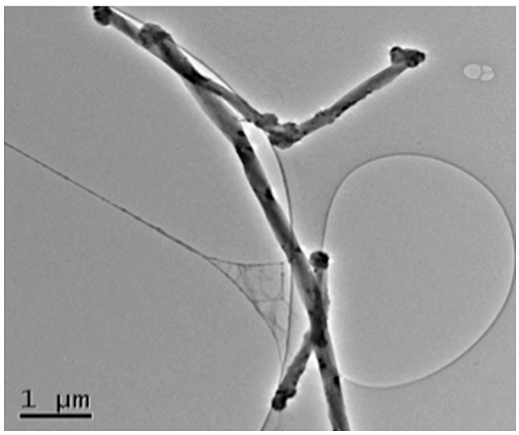

Figure 4.3
Transmission electron micrograph of an aerosol sample of CNF taken from the exposure chamber.

The results demonstrated that aerosol exposures of rats to 0.54, 2.5, and 25 mg/m^3 of CNF produced concentration-related small, identifiable accumulations of CNFs that had translocated to the respiratory tract—with no adverse systemic tissue effects, apart from those measured in the respiratory tract anatomical compartment. Lung morphology observations revealed that at the two highest exposure concentrations, a minimal (2.5 mg/m^3) and slight (25 mg/m^3) inflammation of the terminal bronchiole and alveolar duct areas of the lungs was present, in areas where fiber-laden alveolar macrophages had accumulated. This observation

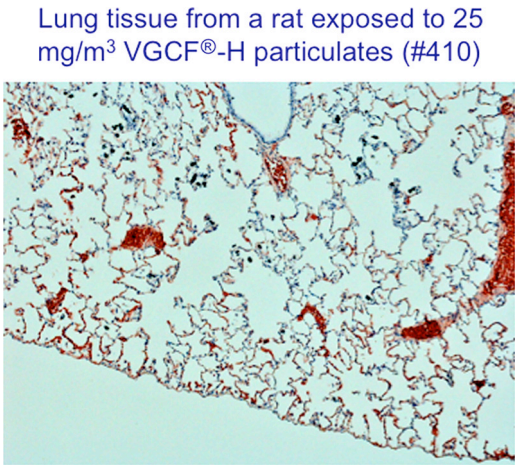

Figure 4.4
Lung tissue from a rat exposed to 25 mg/m^3 CNF after a 90-day exposure.

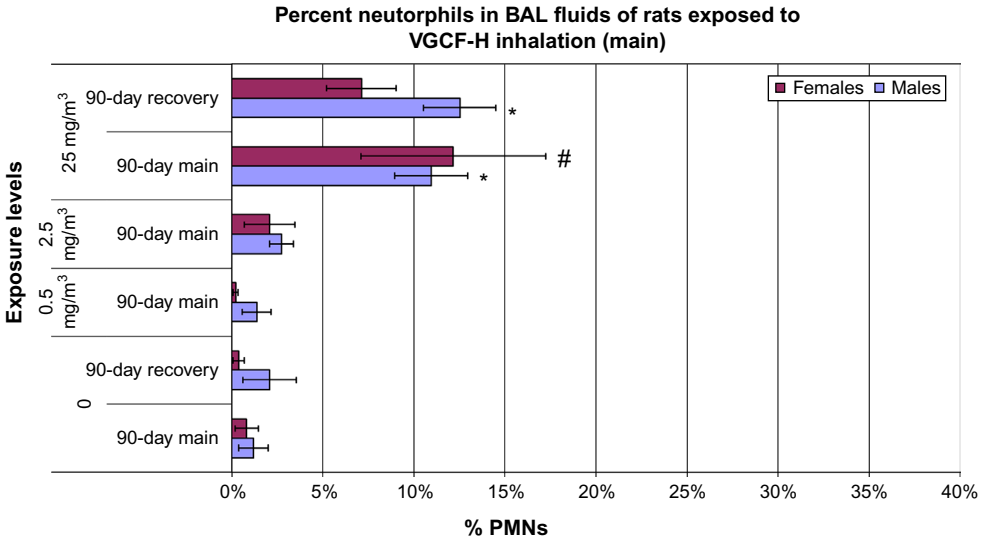

Figure 4.5
Percentages of neutrophils in BAL fluids recovered from rats exposed to carbon nanofibers.

was characterized by the presence of some inflammatory cells and associated thickening of interstitial walls and hypertrophy or hyperplasia of type II epithelial cells and was graded as "slight" for the rats exposed to the 25 mg/m^3 (highest) concentration (Figure 4.4). Increased BAL fluid inflammatory (Figures 4.5 and 4.6) and cell proliferation endpoints relative to air-exposed controls were documented only at 25 mg/m^3 CNF (the highest exposure

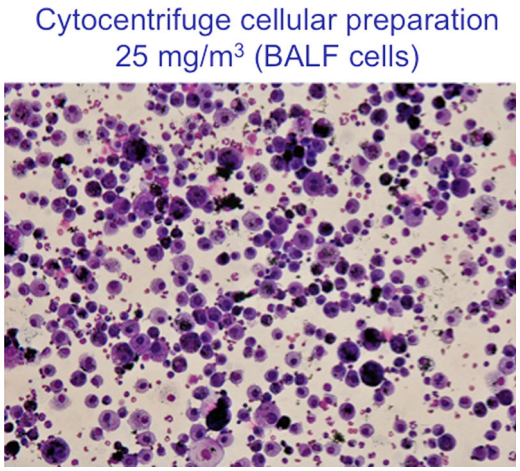

Figure 4.6
Cytocentrifuge cellular preparation from a rat exposed to 25 mg/m^3 CNF after a 90-day exposure.

concentration) but were not different from control values at the 0.54 or 2.5 mg/m^3 exposure concentrations. Of the CNF–exposed, BAL-recovered pulmonary macrophages from the 25 and 2.5 mg/m^3 exposure group, >90% contained nanofibers (>60% for 0.54 mg/m^3). It is likely that migration and macrophage accumulation of particulates in the lung could account, in part, for the histopathologic assessment of minimal inflammation in rats exposed to 2.5 mg/m^3 CNF, as noted by the pathologist. However, these observations of minimal lung tissue alterations at this intermediate exposure concentration (2.5 mg/m^3) should, instead, be considered normal physiological adaptations to subchronic inhalation exposures of particulates. The morphologic, biochemical, and cell labeling results were consistently evident at the high exposure concentration (i.e., 25 mg/m^3); but at the intermediate concentration (2.5 mg/m^3), there was a distinct lack of convergence between the reported histopathologic findings versus the more sensitive and BAL (inflammatory and cytotoxicity) and cell turnover results with copious measured endpoints (Delorme et al., 2012). Therefore, it is recommended that a weight-of-evidence approach be implemented or incorporated as the guidance criteria recommended for interpreting study findings (Warheit et al., 2013).

In a previous chapter, I presented the idea that data generated from a well-conducted pulmonary bioassay study have significant informational benefit for comparing hazard profiles of a variety of nanoparticulate materials. Although the intratracheal instillation method (used in many of these studies) as a route of pulmonary exposure may not be as physiologically relevant when compared with the inhalation route; this type of study has many advantages (as well as some disadvantages). For instance, intratracheal instillation studies can be implemented to monitor a variety of materials in a more expedient fashion.

They are less costly and less time consuming and provide accurate screening data, as a prerequisite for implementing longer-term inhalation studies. Given that the inhalation database for quality and subchronic inhalation studies on nanomaterials is extremely limited, this route of exposure and this type of pulmonary bioassay could serve an important function. However, the experimental design of these studies should have important requirements for developing meaningful data: (i) The nanomaterial must be robustly characterized; (ii) dose response and appropriate dose metrics for the pulmonary route of exposures are critical; (iii) time course studies—preferably up to 3 months after exposure are highly recommended; and (iv) benchmark control particles or reference particles are necessary for better interpretation of the findings. When competently implemented, a pulmonary bioassay can be a useful means for better understanding potential pulmonary mechanisms of action and, in some cases, can be an integral component for occupational exposure level setting—when the results are bridged to previously conducted inhalation studies with similar materials (e.g., TiO_2 inhalation studies) (Warheit, 2013).

4.3 Conclusions

The current chapter was designed to articulate the strengths and weaknesses of experimental-type studies compared with guideline-type studies. Experimental studies, as evidenced by the pulmonary assay investigations that we have previously published, have great utility in comparing the potential lung hazards of one nanoparticulate with those of another. The information gained from these studies can also be utilized to predict mechanisms of action and to generate testable hypotheses for further investigations. Under certain circumstances, they are useful for bridging functions when benchmarked to data from inhalation studies on similar or identical materials. Alternatively, it is the standardized, guideline inhalation studies that provide the most useful information for determining safety levels and for implementing risk assessments.

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CHAPTER 5

Using Expert Judgment for Risk Assessment

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Chapter Outline

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5.1 Introduction: Uncertainties in Risk Assessment

The fields of synthetic chemistry, biotechnology, and, more recently, nanotechnology have yielded many benefits for society and promise to deliver more as they continue to mature. Accompanying these benefits, however, is the ever-present challenge of understanding and managing the potential for harm to human health and the environment. New technologies are specifically designed to produce societal benefits (and thus their benefits are easy to recognize), but their harmful effects are not so easily understood at the outset. This is not only due to the difficulty of anticipating the uses and misuses of technologies but also because new technologies or materials can interact in environments or the human body in ways that are not well understood. In essence, the "newness" of emerging technologies means that there may be little information that can help risk assessors understand the potential for negative implications.

In addition to the challenges posed for risk assessment, a high degree of uncertainty can make it difficult to mitigate impacts through prescriptions for safe use or through the redesign of materials, products, or technologies. Moreover, uncertainties about the health and environmental effects of emerging technologies can feed directly into the risk–benefit debates that increasingly shape society's response to, and regulation of, new technologies (Kandlikar et al., 2007). Increasingly, the potential and often uncertain risks of new technologies can diminish society's appetite for such technologies if legitimate efforts are not made to understand and manage risks (Stern et al., 1996; Satterfield et al., 2009). Risk assessment is therefore a necessary tool for understanding and mitigating unintentional negative consequences.

Human health impacts of toxic substances and pollutants can be studied by using frameworks of risk assessment that have been developed over the past 30 years. Risk assessment provides a set of tools used to integrate hazard, exposure, and health effect information to characterize the potential for risk to human health (NRC/NAS, 1983; Kandlikar et al., 2007). Such methods typically utilize quantitative predictions of health impacts and explicitly model and incorporate uncertainties. Modern risk assessment aims to present decision makers with risk estimates and uncertainties so they may decide on the protective policies that are warranted

in light of the range of possible future outcomes of alternative policies (Haimes and Lambert, 1999). If there is uncertainty regarding exposures or dose in a population, for example, risk assessors can decide to collect more data, extrapolate values from other similar populations, or use numerical models to estimate missing values. The next section will investigate the use and limitations of these three methods of reducing uncertainty.

5.1.1 Challenges and Uncertainty in Data Collection, Extrapolation, and Modeling

Three standard approaches can be utilized for reducing uncertainty for risk assessment—data collection, extrapolation, and modeling. Data generation and collection can provide relevant information that is specific to the risk assessment at hand, but data are often difficult and costly to produce if not already available (Choi et al., 2009). Data can also be extrapolated from studies performed on similar populations to determine parameters that are not otherwise available. Although it may be difficult, in the case of emerging technologies, to find comparable data from which to estimate parameters, and uncertainty factors are typically required to account for the errors that are introduced during extrapolation (Kuempel et al., 2007). Finally, numerical models include several sources of uncertainty (described below), but they are flexible and can integrate various types of data and utilize subjective expert judgment to estimate parameters that are not otherwise available. Given the limitations of data collection and extrapolation, traditional risk assessment techniques often employ numerical models and subjective expert judgment when uncertainty is high (Fryer et al., 2006).

It is important to characterize the various sources of uncertainty present with numerical models to minimize their impact on risk assessment. Numerical models used in risk analysis inherently contain some degree of *aleatoric* and *epistemic uncertainty.* Aleatoric uncertainty, also known as *stochastic uncertainty*, is defined as randomness or inherent variability of a phenomenon. It is, by nature, irreducible. When sufficient data are available, aleatoric uncertainty can be characterized by using probability distributions. *Epistemic uncertainty* occurs due to incomplete knowledge about a system or phenomenon and, by comparison, is reducible. This category includes uncertainties in values of model parameters (*parametric uncertainty*), as well as uncertainty about proper forms of models (structural or *model uncertainty*). *Subjective judgment* also introduces epistemic uncertainty into analyses, especially when data are scarce. Disagreements may also occur between scientific studies or expert's subjective judgments, thereby increasing uncertainty over what would constitute "proper" or "accurate" models or parameters.

In summary, several main types of aleatoric and epistemic uncertainty are present in numerical models (Morgan et al., 1990; Regan et al., 2002; Dantan et al., 2013):

Aleatoric uncertainty

- *Natural variation* – resulting from changes in systems (with respect to time, space, or other variables) in ways that are difficult to predict

- *Inherent randomness* – occurring because a system is, in principle, irreducible to a deterministic one

Epistemic uncertainty

- *Parametric Uncertainty*
  - *Systematic error* – resulting from bias in measuring equipment or sampling procedure
  - *Measurement error* – manifested as seemingly random error due to imperfections in measuring equipment and observational techniques
- *Model uncertainty* – as a result of our limitations in representing physical and biological systems, uncertainty can arise from approximation of a model to enable the solution of a problem
- *Subjective judgment* – resulting from uncertainties in interpretations of data or in experts' estimations.

Environmental health risk assessment models typically contain a combination of both aleatoric and epistemic uncertainties. Common sources of uncertainty include measurement errors (e.g., errors in measuring emissions from sources), systematic biases (e.g., using centrally located outdoor monitors for air pollutants to estimate exposures for a population that spends most of its time indoors), and non-representativeness (e.g., estimating an exposure–response curve from an epidemiologic study conducted with a sample that does not represent the general population). In these cases, methods such as Monte Carlo analysis and nonlinear optimization methods can be used to effectively characterize uncertainty (Dantan et al., 2013). In contrast, *model uncertainty* arises when the relationships within and among various components of the risk assessment framework are poorly understood. There may be several competing models to explain relationships among variables of interest, or in the worst case, no models may exist at all. Therefore, uncertainty lies not in the choice of values for the parameters of a model but in the choice of model itself. Such extreme uncertainty is inherently difficult to quantify (Risbey and Kandlikar, 2007; Aven et al., 2014). Although many sources of uncertainty may exist, the careful use of numerical models can help risk assessors to better understand potential impacts from materials or technologies. In the case of emerging technologies, scarce data may necessitate the use of both models and expert judgment to make estimations until more scientific data are available. The next section will explore the traditional risk assessment framework for environmental health and the ways in which expert judgment can be utilized to reduce uncertainty.

5.2 Limitations of Existing Methodologies for Risk Assessment and Precedents for Using Expert Judgment

5.2.1 Traditional Risk Assessment

Risk assessment is a complex process that involves the integration of information across a range of domains, including source characterization, fate and transport, hazard assessment,

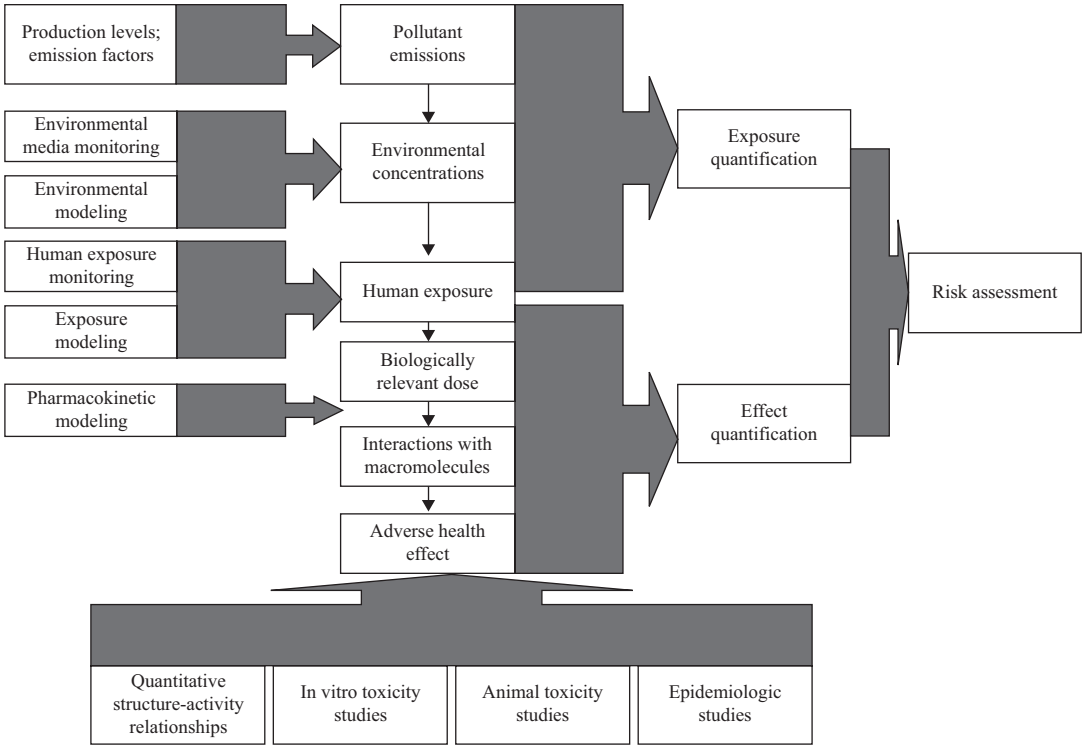

Figure 5.1
General environmental health framework for risk assessment.

exposure assessment, and dose-response analysis. Well-defined quantitative models describe the relationships between various elements of the risk assessment paradigm, as shown in Figure 5.1. Health risks have traditionally been identified and quantified on the basis of measured *hazards*, and information about *exposure* and *dose-response relationships*. The setting of standards or guidelines regarding safe or acceptable levels of exposure for a population is implicit in this process.

Hazards are typically estimated based on information provided by *in vitro* and in vivo toxicologic studies, quantitative structure–activity relationships (QSARs) modeling (Coleman et al., 2003), and epidemiologic studies. These information sources are shown in the lower part of Figure 5.1. Exposure is defined as the intensity of contact between a contaminant and the relevant biological sites of impact over a relevant period of time. Factors involved in exposure are shown on the left side of Figure 5.1 (based on Sexton et al. (1995)). Exposure is determined by assessing sources of pollutants and their strengths, measuring or modeling concentrations in environmental media, measuring or modeling human exposures through various pathways (inhalation, ingestion, dermal), and sometimes through biological monitoring to measure tissue burden to determine dose. The estimation of a biologically

relevant dose from exposure information is, however, often very difficult and requires fairly detailed knowledge of the toxicokinetics of the pollutant in the human body (Kandlikar et al., 2007).

The general environmental health framework (in the center), and its relationship to the risk assessment framework (loosely based on Sexton et al., 1995) is shown (Sexton et al., 1995; Kandlikar et al., 2007).

By quantifying hazards and exposures, risk assessors can determine the extent of risk and can choose appropriate measures for managing risks. For noncancerous toxicants, it is often assumed that there is some level below which there are no adverse effects—the no observed adverse effect level (NOAEL). An acceptable exposure limit—reference dose for ingestion, or reference concentration for inhalation—is established below this threshold. For carcinogens, the standard practice is to assume that no threshold exists below which there is no risk to human health (i.e., the threshold is zero). Exposures exceeding the prescribed threshold are considered to cause adverse effects, and measures should be taken to mitigate or reduce exposures. Health risks can be calculated for different exposures if a "dose-response" curve is well-defined above this exposure threshold. Dose-response curves are typically extrapolated from high to low dose and are assumed to be linear. The excess risk is calculated by multiplying the dose by the dose-response curve slope factor. Although this health risk model assumes no threshold level, for the purpose of risk management and prioritization, risks exceeding some minimum risk probability (e.g., $1/10^3$ for occupational populations, or $1/10^6$ for non-occupational populations) are considered to be of concern (Kandlikar et al., 2007).

5.2.2 Using Expert Judgment in Risk Assessment

Uncertainty can be found in every element of the risk assessment framework, and this uncertainty is often compounded in the case of emerging technologies. In the absence of sufficient empirical data, uncertain parameters and models can be estimated by using subjective expert judgment obtained through careful elicitation processes. Subjective or Bayesian methods for handling uncertainty have a long history originating with the use of the Delphi method in technology forecasting and nuclear deterrence (Helmer et al., 1966; Kahn et al., 1967; Linstone and Turoff, 1975), with subsequent applications in policy analysis, engineering, and risk analysis (Morgan et al., 1990). Expert judgment is most often used to quantify uncertain parameters in a probabilistic form. However, it is not solely limited to assessing model parameters. Often, and especially in the early stages of a scientific issue when uncertainty is high, expert judgment is used to structure problems, to indicate key variables, and to examine relationships between variables by building "influence diagrams" (Morgan et al., 1990). These influence diagrams are useful devices for structuring problems and can be used quantitatively if sufficient data are available about the quantitative relationships between variables (Morgan, 2005).

Subjective uncertainty analyses do, however, require a significant commitment of resources and involve the use of methods that are not typically familiar or comfortable to research scientists or policy analysts. In addition, some scientists are unwilling to provide or accept subjective quantitative estimates of uncertainty based on the conviction that no rigorous scientific basis exists for such estimates (Morgan et al., 1990). These tensions reflect both a prevailing resistance to assessing and characterizing uncertainty, and a historical lack of practice of uncertainty assessment in policy decisions.

However, there are substantial benefits to understanding uncertainty. In the domain of risk assessment, an informed understanding of uncertainty can enhance decisions on complex health or environmental issues and has been used in environmental exposure assessment (Hawkins and Evans, 1989; Ramachandran, 2001; Ramachandran et al., 2003; Ramachandran and Vincent, 1999; Walker et al., 2001), and in assessment of global climate change (Morgan et al., 2001; Morgan and Keith, 1995; Risbey et al., 2001; Risbey and Kandlikar, 2002). Careful expert assessment of uncertainty can provide improvements in choosing explicit and consistent decision criteria and policy strategies, in choosing relevant boundaries for analysis, in improving transparency in the choice of relevant variables, and in understanding further research needs (Burgman, 2005; Morgan et al., 1990). Additionally, uncertainty analysis can help guide the design and refinement of a model, and can explicitly characterize technical uncertainties to clarify issues of value and of fact. The following section looks in detail at the process and challenges of eliciting judgments from experts.

5.3 Eliciting Expert Judgment—Selection of Experts, Elicitation Protocols, and Best Practices

5.3.1 Expert Performance on Elicitation Tasks

Perhaps the most important question to ask when considering the use of expert judgment is: Can experts provide reliable estimates? An expert's performance can be tested by measuring judgment on tasks where actual values are known and then evaluating the discrepancies between elicited values and actual values. However, few studies that compare expert judgments with actual probabilistic outcomes have been conducted (Burgman, 2005; Wright et al., 2002). In two notable studies that tested expert performance, the results were poor. Krinitzsky (1993) and Fischhoff (1982) both found poor performance in geotechnical experts who were asked to predict the height of fill at which an embankment would fail (Burgman, 2005; Fischhoff et al., 1982; Krinitzsky, 1993). In all cases the true value fell outside the expert's confidence intervals.

Calibration and feedback

Although early research into expert performance in elicitation tasks has yielded unimpressive results, several factors that may underlie poor performance have been identified. One factor is

expert "calibration." Some experts may not be "calibrated" well enough to make probability estimates that closely match reality. That is, their judgments may be biased, or they may be "overconfident" (as described in the example above) and provide too narrow a range of estimated values compared with actual ranges (Bazerman and Moore, 1994; Fischhoff et al., 1982; Morgan et al., 1990). Calibration techniques have been found to improve performance and correct for overconfidence (Logan et al., 2009; Morgan et al., 1990; O'Hagan et al., 2006). These techniques involve training experts on elicitation tasks where values are known and providing feedback on performance. The topic of expert calibration is discussed further in the section on elicitation methods.

Domain and "learnability"

In addition to the need for well-calibrated experts, their domain of expertise must be relevant to the required elicitation tasks. Bolger and Wright (1994) and Rowe and Wright (2001) suggested that elicitation performance will be good if the tasks an expert faces have a high degree of ecologic validity and learnability (Bolger and Wright, 1994; Kynn, 2008; Rowe and Wright, 2001; Shanteau, 1992). That is, the ecologic validity of the task is high when it requires experts to make judgments inside their domain of professional experience, and they can express their judgments in familiar metrics. Similarly, the learnability of a task is high when good judgment can be learned because objective data and models exist for the problem and there is adequate and timely feedback. When one of these two elements is lacking, performance suffers.

Substantive versus normative expertise

Elicitation protocols involve asking experts to estimate uncertain physical quantities, odds ratios, probability estimates, or probability distributions for a given problem. In general, however, experts and non-experts alike do not typically estimate probabilities in accordance with statistical principles (although "calibration" techniques may improve this ability to varying degrees) (Tversky and Kahneman, 2000). While experts may be knowledgeable in their field of study, they may not be experienced in making predictions in the form of probabilities. Experts typically possess a high degree of *substantive expertise.* That is, they are knowledgeable in their fields of study. However, an expert may not possess *normative expertise*, or knowledge in the use of a particular response mode (Meyer and Booker, 2001). As such, an expert with substantive expertise that is relevant to the problem at hand may still perform poorly due to a lack of normative expertise in the elicitation task (e.g., estimating probability distributions or model structure). It is not clear whether an expert's substantive knowledge enables them to effectively extrapolate beyond the available data or to make judgments outside the realm of their expertise. It is important, however, that experts recognize and admit their own cognitive limitations (Fischhoff et al., 1982).

Heuristics and biases

Expert judgment is also affected by heuristics—mental "shortcuts" or simplifying strategies—that people utilize when assessing probabilities and predicting values. In general, heuristics can help people to cope with situations in an uncertain world. However, in some instances, they may lead to systematic errors or biases in judgment (cognitive biases). In their seminal 1974 paper published in *Science*, Kahneman and Tversky described three important heuristics: (i) the "representativeness heuristic," (ii) the "availability heuristic," and (iii) the "anchoring and adjustment heuristic" (Tversky and Kahneman, 2000). These three main heuristics have been found to play a large role in judgment under uncertainty.

The "availability heuristic" influences probability judgments based on the ease with which a person can think of previous occurrences of an event, or the ease with which they can imagine an event occurring (Tversky and Kahneman, 1973, 2000; Bazerman and Moore, 1994). The availability heuristic will yield reasonable results when a person's memory of observed events corresponds well with the actual frequency of events. However, it can otherwise lead to erroneous estimations.

When a person is asked to judge the probability that object A belongs to class B, or that event A originates from process B, they will typically rely on what is called the "representativeness heuristic." With this heuristic, people tend to evaluate probability by the degree to which A is representative of, or resembles, B (Tversky and Kahneman, 2000). One possible bias is an insensitivity to sample size, where people may expect a small sample to be representative of the parent population without recognizing that small samples are subject to greater variability (Tversky and Kahneman, 2000). Another bias occurs due to misconceptions of chance, where people may expect a small sample of an event to "look" like its parent process (Morgan et al., 1990). For example, when flipping a coin, a sequence of heads and tails that appears more random (e.g., H-T-H-T-T-H) will be judged as more likely to occur than a sequence that is more ordered (e.g., H-H-H-T-T-T). However, each of these sequences is equally probable (Bazerman and Moore, 1994; Kahneman and Tversky, 1972).

The "anchoring and adjustment heuristic" refers to the tendency, when making an estimate, to start from an initial value (an anchor) and adjust that value up or down. The initial value may be suggested by the formulation of a problem, or may be inferred based on a partial calculation. Unfortunately, people tend to stick close to their initial value and make insufficient adjustments (Kahneman et al., 1982; O'Hagan et al., 2006). Although this strategy enables people to reduce computational effort or processing time when performing the same judgment repeatedly, it can result in judgment bias.

In addition to these heuristics, several studies have demonstrated an "affiliation bias" in judgments among experts who share a similar domain of expertise but practice their research

within different types of institutions (Barke and Jenkins-Smith, 1993; Bostrom, 1997; Kraus et al., 1992; Slovic et al., 1995). In addition, cultural, political, and philosophical contexts can influence judgments (Burgman, 2005; Campbell, 2002), as can variables such as gender (Bostrom, 1997; Kraus et al., 1992; Slovic et al., 1995), trust and technologic optimism (Gaskell et al., 2004), and several psychometric variables of perceived risk, including familiarity of risk, dread, and risk of exposure (Fischhoff et al., 1978; Siegrist et al., 2007). A great deal of research has been conducted over the last several decades to better understand these and other heuristics and biases and their effects on expert judgments in elicitation contexts (Kynn, 2008).

5.3.2 Elicitation Methods and Best Practices

In the process of eliciting expert judgments, it is important to take into account the many ways in which judgments can be biased. Development of a successful elicitation protocol should involve careful consideration of biasing effects due to perceptions, motivations, heuristics, framing, and context and should utilize techniques constructed to minimize their effects. This section contains an overview of accepted expert elicitation techniques and protocols, methods for calibration, evaluation of the reliability of judgments, and techniques for aggregating judgments from multiple experts.

Elicitation processes can involve simple correspondence, questionnaires, personal interviews (by telephone or in person), group meetings aimed at achieving consensus (simple group meetings, Delphi method), and various other combinations of interactions (Burgman, 2004). Each has its own benefits and challenges (Meyer and Booker, 2001). O'Hagan et al. suggested that for single experts, face-to-face interviews are, by far, the best approach, compared with questionnaires, and are preferred to telephone interviews, which can be effective but limit certain kinds of interactions (such as visualizations). For elicitations involving several experts, interviews are also strongly preferred to questionnaires. There are administrative and cost benefits from separate elicitations as opposed to group interviews; however, group elicitation has the benefit of allowing experts to share knowledge and form a consensus, if desired (O'Hagan et al., 2006).

There is great deal of agreement on the necessary elements of an elicitation protocol. O'Hagan et al. described five similar assessment protocols (Clemen and Reilly, 1996; Garthwaite et al., 2005; Phillips et al., 1999; Shephard and Kirkwood, 1994; Walls and Quigley, 2001) and proposed a five-step protocol as follows (O'Hagan et al., 2006):

1. Background and preparation
2. Identifying and recruiting expert(s)
3. Motivating and training the expert(s)
4. Structuring and decomposition
5. Elicitation

This framework is utilized here to investigate the findings and best practices reported in the expert elicitation literature.

Background and preparation

This stage involves the identification and clarification of the variables for which expert assessment is needed, as well as the planning of the elicitation sessions. Depending on the types of information to be elicited during a session, it is important to know how difficult a task may be, and how to structure elicitation practices to minimize difficulty and maximize familiarity to the expert. Elicitation tasks may involve eliciting probabilities and/or probability distributions, parametric distributions, correlation coefficients, regression parameters, model form, or estimating uncertainty or imprecision (Ayyub, 2001; Meyer and Booker, 2001; O'Hagan et al., 2006). Meyer and Booker noted that biases are likely to occur based on the elicitation methods planned and recommended that methods be structured to avoid these biases. Furthermore, the project personnel should become familiar with expected biases so that they can act to avoid them in the elicitation process.

Identification and recruitment of experts

O'Hagan et al. suggested involving experts with alternative points of view, a stance that is supported by others, including Burgman (2004) and Bier et al. (1999). Burgman noted one substantial pitfall that can occur with too narrow a selection of experts: underestimation of uncertainty, or overconfidence. Research by Bier et al. (1999) demonstrated that uncertainty will be underestimated if the experts involved share common values, experiences, professional norms, context, and cultural background so that they stand to gain or lose in similar ways from the outcomes of decisions and hold the same motivational biases (Bier et al., 1999; Burgman, 2004). Both Burgman (2004) and Clemen and Winkler (1999) claimed that multiple experts from various backgrounds increase the knowledge and experience contributing to an assessment (Burgman, 2004; Clemen and Winkler, 1999).

O'Hagen et al. also suggested searching for those who have an adequate level of statistical understanding, particularly with probabilities and distributions (O'Hagan et al., 2006). Further, they suggested utilizing six selection criteria, defined by Hora and Von Winterfeldt (1997) in their work in the field of nuclear waste. Due to the controversial nature of the topic, Hora and Von Winterfeldt suggested a nomination process that is open and seeks out participation from various groups (public interest groups, professional organizations, academics) to obtain a balanced perspective. The six criteria for experts are as follows:

1. Tangible evidence of expertise
2. Reputation

3. Availability and willingness to participate
4. Understanding of the general problem area
5. Impartiality
6. Lack of an economic or personal stake in the potential findings

They argued that (5) and (6) may be difficult to satisfy, in which case it is important to record any potential conflicts of interest. Most important for controlling for cognitive biases are (1) and (4), whereas (2), (3), (5) and (6) are important for both controlling for motivational biases as well as maintaining an open, transparent, and seemingly unbiased process.

As mentioned previously, it is important to find the "right" experts. For managing cognitive biases that may arise, it is important to choose experts whose domain of expertise is relevant for the required elicitation tasks. That is, it is important that their "substantive expertise" match the problem at hand (Meyer and Booker, 2001). The poor performance of experts, in some cases, can be attributed to the subjects not having enough relevant experience to be considered an "expert" (Kynn, 2008).

Motivating and training experts (calibration)

In the words of Morgan et al. (1990), the one consistent finding across all elicitation techniques that have been examined is a strong and consistent tendency to overconfidence (Morgan et al., 1990). There are mixed opinions on how calibration should be conducted and whether attempts at calibration are effective. Reliable estimates are typically demonstrated in people who make frequent, repeated, easily verified, unambiguous predictions so that they learn from feedback. For example, weather forecasters demonstrate good calibration due to experience with forecasting and timely feedback on the accuracy of their judgments. For eliciting judgments from experts who do not benefit from such experience, several methods can be employed for calibrating their judgment.

In general, the key proposed elements of a motivation and training program include (Burgman, 2004; Meyer and Booker, 2001; Morgan et al., 1990; O'Hagan et al., 2006; Wright et al., 2002):

- Familiarization with heuristics, biases, and common errors:
  - Include a brief presentation and discussion of common heuristics, biases and errors, and suggestions for counteracting their effects
- Probability training:
  - Provide a short lesson on the fundamentals of probabilities and distributions
- Feedback on performance:
  - Conduct practice elicitations and comparison with known values to see how well they can predict the outcome

- Ask for reasons to justify their judgments. Morgan et al. suggested that there is evidence that asking assessors to provide reasons justifying their judgments has a significant improvement on calibration. However, asking for reasons may have more impact on judgment tasks for which the expert has limited experience than for tasks with which they are intimately familiar.

In addition to the calibration of experts, the cognitive models' research suggests it is also important to consider the *coherence* of judgments and the *self-consistency* or *reliability* of judgments (Kynn, 2008; O'Hagan et al., 2006). Coherence (also known as *internal consistency*) is a measure of how well judgments fit with the rules of probability. A set of probability statements is considered *coherent* if they are collectively consistent with the laws of probability (O'Hagan et al., 2006). For example, when considering the probability that exactly one of three outcomes—A, B, or C—will occur, the total probability for the three events should sum to 1. A set of judgments would be considered incoherent in the case that the probabilities were assessed as $P(A) = 0.4$, $P(B) = 0.2$, and $P(C) = 0.5$, where $P(A) + P(B) + P(C) = 1.1$ (rather than 1). Coherence is largely dependent on context, framing, and specific details of an elicitation procedure, and effort should be taken to encourage coherent assessments from experts (Kynn, 2008; O'Hagan et al., 2006).

Reliability (also known as *self-consistency*) is a measure of how consistent an expert's judgments are in repeated tests. Kynn suggested that an expert's judgment should only be inconsistent with itself if the expert has changed his or her mind between testing, or if the elicitation techniques did not give an accurate representation in the first place. It is important to provide adequate task information and cognitive feedback to ensure that probability estimates will reflect the expert's internal beliefs (Kynn, 2008).

Structuring and decomposition of tasks

In addition to careful selection and calibration of experts, Morgan et al. recommended that the elicitation problem be broken down into tasks that are familiar and comfortable for the expert (Morgan et al., 1990). Tasks should be "ecologically valid," allowing experts to make judgments within their domain of expertise and experience. Similarly, tasks should have a high "learnability" such that good judgment can be learned because there are objective data and models for the problem, as well as ample and timely feedback (Bolger and Wright, 1994; Rowe and Wright, 2001). O'Hagen et al. also suggested that a significant amount of time be spent with experts to elicit problem structure, such as dependencies and functional relationships. The experts may have insights of their own to contribute, and this process will increase their ownership and a sense that their judgments adequately represent their understanding and beliefs (O'Hagan et al., 2006).

Elicitation process

The elicitation process itself is fairly straightforward, and several studies have suggested an iterative process that involves the following:

1. Elicitation of measures of the expert's distributions (e.g., probability quartiles)
2. Fitting a probability distribution
3. Assessing the adequacy of the distribution, and repeating the process asking experts to make adjustments if the results are not adequate

Each of these steps can be time consuming, so care should be taken to limit the number of tasks required in a sitting to reduce fatigue (Ayyub, 2001; Meyer and Booker, 2001; O'Hagan et al., 2006).

5.4 Arriving at Consensus Risk Estimates

Morgan et al. (1990) suggested that consensus among experts is typically established over time as part of scientific activity. The process of gathering evidence and comparing alternative theories usually generates an eventual consensus about matters such as values of scientifically measurable quantities. However, in cases where data are hard to obtain, such as with measurements of health effects of widely dispersed environmental contaminants, it may take a very long time for consensus to be reached. Disagreement can arise from different technical interpretations of the same scientific evidence, differing perspectives for viewing evidence (e.g., disciplinary paradigms), and direct or indirect stakes in the outcome of an analysis that may influence judgments based on motivational bias (Morgan et al., 1990). When there is consensus among experts, there is a high degree of confidence in a particular theory, physical quantity, or established model. In the absence of consensus, however, it is difficult to interpret the validity of scientific findings. Therefore, in expert elicitation protocols, consensus is often sought or measured through various means of aggregating judgments.

Clemen and Winkler (1999) described two fundamental approaches to aggregating the subjective probability judgments of experts: behavioral aggregation and mathematical (or numerical) aggregation. Mathematical aggregation uses processes or analytical models to calculate a mean or "combined" probability distribution. A common approach involves the weighting of expert's opinions and utilizing sensitivity analysis to examine the effects of each opinion on the conclusions of the analysis. In contrast, behavioral aggregation approaches utilize interaction between experts to get them to agree in some way (Burgman, 2004; Clemen and Reilly, 1996). This approach may involve face-to-face meetings or can be carried out without direct contact (Delphi method). Clemen and Winkler (1999) suggested that mathematical and behavioral aggregation perform similarly, with the mathematical methods providing a slight edge. Meyer et al. suggested that behavioral methods have the

advantage of producing an aggregated result during a session and protecting anonymity; however, the disadvantages include the need for advanced planning, there is potential for group-think situations, and this obscures individual expert's judgments (Meyer and Booker, 2001). Mathematical methods have the advantage of not requiring the same level of planning; however, disadvantages include obscuring of differences between expert's judgments and the production of a single answer that all experts may reject.

Consensus is often not possible, or researchers may want to investigate a wide range of opinions among experts, rather than establishing consensus. In that case, structured elicitation of individual expert's judgments can be performed without seeking consensus, and without iterative communication between experts. Such a protocol provides the advantage of eliciting a range of judgments that are unhampered by social interactions and are open to discussion of extreme views, which may be constrained in group settings (Morgan et al., 2006).

In the case of health risks from emerging nanotechnologies, expert judgment has been valuable for scoping possible scenarios related to hazards and exposures (Fauss et al., 2009; Morgan, 2005). These scoping exercises broaden understanding of potential risks to identify areas of concern. However, expert judgment may be most useful for converging upon concepts and models for understanding nanoparticle behavior (e.g., selection of an appropriate dose metric for nanoparticles). The next section looks at the use of expert judgment with nanoparticle risks to understand some of the main challenges in the field today.

5.5 The Use of Expert Judgment for Nanoparticle Risks

Deep uncertainty pervades every element of the exposure–response–risk paradigm for nanoparticles and exists, in part, due to the wide and disparate forms that nanotechnology can take (e.g., medical nanotechnology, environmental applications, use in consumer products). Given the myriad applications and types of nanomaterials, it is difficult to understand which materials or applications may pose risks and to what extent. Additionally, a tremendous amount of uncertainty arises due to changes in physical and chemical properties that can occur when bulk materials with known properties are manufactured at the nanoscale (Fairbrother and Fairbrother, 2009). Nanomaterials can behave in novel and unpredictable ways, challenging researchers to find an understanding of the parameters that contribute to and help predict these properties. Given this high level of uncertainty, researchers and policy analysts in academia, industry, and government are grappling with the challenge of risk assessment for emerging nanotechnologies (Beaudrie, 2010; Beaudrie et al., 2013). The following section highlights several areas of uncertainty with regard to nanomaterials that must be better understood before risks can be assessed.

5.5.1 Uncertainty in Characterizing Health Risks from Nanoparticles

Model uncertainty, described earlier, is endemic to the problem of calculating nanoparticle risks. Doing risk calculations for nanoparticles leads to an explosion of potential model forms, rendering the uncertainty extreme. Model uncertainties in risk assessments of nanoparticles can be classified into three categories: (i) those resulting from *physical and chemical characterization* of nanoparticles, including the choice of an appropriate exposure metric; (ii) those resulting from *uncertainty in dose and health end-points* from different exposure routes; and (iii) those resulting from a *lack of understanding of toxicity mechanisms*. A few particle characteristics are discussed below in terms of the uncertainty surrounding their effects on fate and transport and toxicity. Nano-silver is used as an example to illustrate that even in a nanomaterial as well studied as this one, substantial uncertainties linger, preventing quantitative risk assessment.

Size and agglomeration

As particle size becomes smaller, a greater fraction of atoms are at the surface, and quantum effects tend to increase surface reactivity. The size distribution of nanoparticles does not necessarily remain constant and depends on the chemical and physical environment surrounding nanoparticles; nanoparticles can agglomerate or aggregate to form larger-sized clusters. Agglomeration can lead to a reduction in the number of atoms at the surface, with a reduction in surface energy. Since coagulation half-lives of nanoparticles are of the order of tens of microseconds to a few milliseconds (Preining, 1998), nanoparticle concentrations can decrease rapidly by agglomeration. How rapidly the particles cluster in an aqueous medium depends on particle collision frequencies (e.g., Brownian motion and particle concentration), the energy of the particle collisions, the attractive–repulsive properties of the particles involved (e.g., repelling surface charges of two positively charged particles), and the interactions with colloidal materials such as natural organic matter present in the water. After collision, particles can remain in aqueous phase as single particles or form particle–particle, particle–cluster, and cluster–cluster aggregates (Aitken et al., 2004; Wiesner et al., 2006). The dispersion state describes the extent to which particles become clustered by interparticle attractive forces. Surface coatings and stabilizing agents can enhance the stability of the dispersion and maintain the original or intended size distribution in order to exploit high surface reactivity for various useful ends. This increases the potential for human inhalation exposures to very small nanoparticles and also affects their disposition in the body and toxicity. For example, nano-silver used in some products can enter the environment as individual nanoparticles or as small clusters. In other cases, the nano-silver incorporated into consumer products as composites or mixtures could be released into the environment in an encapsulated form (Lowry and Casman, 2009). The translocation of particles depends, in part, on their size; hence, clusters of nano-silver behave quite differently compared with single

particles (Ma-Hock et al., 2008). The size of the nano-silver (i.e., an individual particle versus a cluster) can determine the likelihood of release of silver ions, sometimes referred to as Ag^+ ions, from the particle and the particle's behavior in the environment (O'Brien and Cummins, 2009).

Agglomeration properties of various engineered nanoparticles (e.g., single or multiwalled carbon nanotubes, nanoclay particles, zinc oxide nanoparticles, dendrimers, or fullerenes) are not well known, limiting our ability to estimate the size distribution of the airborne nanoparticles and, thus, their fate in the human body after inhalation.

Particle shape

Prior experience with asbestos and other fibrous aerosols indicates that the shape of the particles (i.e., their length and diameter) has a profound effect on toxicity. Smaller diameter fibers penetrate deeper into the respiratory tract, and longer fibers are cleared more slowly (Mossman et al., 1990; The Royal Academy, 2004). Engineered nanoparticles come in various shapes such as spheres (e.g., dendrimers), tubes (e.g., single-walled carbon nanotubes and multiwalled carbon nanotubes), plates (e.g., nanoclay flakes), fullerenes, and needles. For example, nano-silver can be synthesized into various forms, including particles, spheres, rods, cubes, truncated triangles, wires, films, and coatings (Pal et al., 2007; Wijnhoven et al., 2009).

The shape of nano-silver particles can affect the kinetics of their deposition and transport in the environment. Depending on its surface structure and shape, a nano-silver particle might exhibit different reactivity (Oberdorster et al., 2005a,b), as its shape could make it difficult for particles to approach each other. Such shape-related interactions can be controlled in some situations by adding detergents or surface coatings to the particles to change their shape or surface charge.

Pal et al. (2007) studied the antibacterial activity (using *Escherichia coli*) of silver nanoparticles of various shapes. Results indicated that nano-silver particles of various shapes could kill *E. coli*, but the inhibition results differed and could be explained based on the percent of active facets in the crystal structure. Specifically, truncated triangular silver nanoplates with a [1 1 1] lattice plane as the basal plane displayed the strongest biocidal action compared with the spherical and rod-shaped nano-silver particles, indicating that increasing the number of active facets on the surface of a crystalline, or highly ordered, nanoparticle increases its ability to inhibit bacterial growth.

Surface area

Because of their small size, nano-silver particles have greater specific surface area compared with the same mass of material in larger particles and have a greater surface area-to-volume ratio. A 10-nm particle has approximately 35–40% of its atoms on the surface compared with 15–20% of the atoms on a particle larger than 30 nm in diameter. This large surface

area of nanoparticles relative to their mass or volume increases their reactivity and sorption behavior (Auffan et al., 2009; Tiede et al., 2008; U.S. Environmental Protection Agency, 2010). Large specific surface area enhances chemical reactivity, which means that smaller silver nanoparticles have more reaction sites (i.e., sites that can receive electrons) on their surfaces and are more sensitive to oxygen, a natural electron donor, compared with larger particles (Auffan et al., 2009). Therefore, smaller particles could exhibit greater efficacy as biological agents or stressors in ecosystems or on human health. Surface area also affects the ratio of silver ions on the surface of a silver particle to silver ions that are buried inside the same silver particle. This ratio might also increase as particle size decreases. Thus, for larger particles with a smaller ratio of surface area to volume, most of the silver ions might be unable to interact with the environment or biological surfaces.

Chemical composition

Chemical composition of the surface and the bulk of engineered nanoparticles will affect toxicity. For silver, Ag^0 (zero-valent), and Ag^+ are the most commonly occurring oxidation states in the environment. Speciation strongly influences how much silver is available to affect living organisms. To achieve stability, positively charged silver ions will associate with negatively charged ligands (e.g., sulfide in fresh water and chloride in salt water) (Luoma, 2008). The concentrations of these ligands and the bond strength between the silver ions and the ligands influence the distribution of silver as free silver ions (its more bioavailable form) and the less available ligand-bound forms.

Chemical composition also includes the surface coating of the nanoparticle (Sayes and Warheit, 2009). Coatings may be used to stabilize the nanoparticles in solution, to prevent agglomeration, or to add functionality to the nanoparticle, depending on its intended use. Surface coatings that modify the agglomeration properties of nanoparticles will have biological effects (Oberdorster et al., 2005a; Warheit et al., 2005a). Nano-silver is often coated with a surfactant, polymer, or polyelectrolyte (Lowry and Casman, 2009). These coatings can impart charge to the particles (positive or negative) and stabilize them against clustering. Experiments using fullerene soot with different impurities (e.g., metallic endohedral fullerene) indicate that the pulmonary toxicity response depends on the types of nanomaterials and their impurities (Quan and Chen, 2005).

Choice of exposure metric

The appropriateness of the mass concentration metric for nanoparticles has been called into question because nanoparticles feature high particle counts and large surface area per mass. Although mass concentration has traditionally been used as the metric for exposure assessment of airborne particles and the basis for regulation, it may not always be appropriate for nanomaterials. Several studies have suggested that at similar mass concentrations, nanometer-sized particles are more harmful than micron-sized particles (Brown et al., 2000, 2001; Cullen

et al., 2000; Dick et al., 2003; Donaldson et al., 1996; Donaldson, 1999; Donaldson et al., 2000; Lison et al., 1997; MacNee and Donaldson, 2003; Oberdorster et al., 1995; Peters et al., 1997; Renwick et al., 2001; Seaton et al., 1995; Tran et al., 2000; Utell and Frampton, 2000). One possible explanation for this is that since the number of particles and particle surface area per unit mass increases with decreasing particle size and pulmonary deposition increases with decreasing particle size, dose by particle number or surface area will increase as size decreases. Exposure assessments that rely on mass concentration could underestimate ultrafine particle toxicity, since these particles do not contribute significantly to total mass concentration despite their high numbers. Kreyling et al. (2006) reported that the proportion of nanosized particles is less than 10% of PM2.5 concentrations in terms of mass but more than 90% of the fine particle number concentration.

A change of the exposure paradigm for nano-sized particles from a mass basis has been suggested (Kreyling et al., 2006; Maynard and Aitken, 2007). Particle number and surface area concentrations have been proposed as alternative metrics. Lison et al. (1997) and Tran et al. (2000) have demonstrated a close association between aerosol surface area and inflammatory response when using a range of chemically inert materials with low solubility. Oxidative stress has been highlighted in a number of studies as being a significant mechanism underlying an indicated increase in toxicity within ultrafine and highly specific surface-area particles (Dick et al., 2003; Donaldson et al., 2000; Stone et al., 1998). At the same time, some preliminary studies seem to indicate that in some cases, exposures to nanoparticles may be less inflammatory than exposures to microscale particles (Warheit et al., 2005b). McCawley et al. (2001) showed that particle number concentration was the more appropriate metric for chronic beryllium disease and found no correlation between mass and number concentration (McCawley et al., 2001). Peters et al. (1997) found that a decrease of peak expiratory flow among 27 nonsmoking persons with asthma had stronger association with number concentration than mass concentration. Several toxicologic studies have shown that the inflammatory responses in the lung by low-solubility ultrafine particles and fine particles showed a better dose-response relationship with surface area regardless of particle size (Brown et al., 2001; Monteiller et al., 2007; Oberdorster, 2000; Tran et al., 2000). Driscoll (1996) demonstrated that overload tumors were best correlated with surface area and not with number or mass concentration (Driscoll, 1996). The damage of particle clearance was related to lung surface area dose, not to lung mass dose for nontoxic particles like titanium dioxide and barium sulfate (Tran et al., 2000).

Ramachandran et al. (2005) conducted exposure assessments using multiple metrics, including active surface area, particle counts, mass, and elemental carbon mass concentrations (Ramachandran et al., 2005). They characterized three job groups—bus drivers, bus mechanics, and parking garage attendants. Rankings of aerosol concentrations (highest to lowest) were different, depending on the metric chosen. Thus, mass concentration, regarded

in the field of industrial hygiene as a standard aerosol concentration metric, cannot be a substitute or surrogate for surface area or fine particle number concentration. Park et al. (2010) made measurements using several exposure metrics in a die casting plant to compare the spatial distributions of particle surface area, number, and mass concentrations and rank exposures in different areas by those metrics (Park et al., 2010). Spatial distributions and ranking of particle concentrations in different areas (loosely corresponding to similar exposure groups) were different, depending on the concentration metrics chosen. Also, average concentration by job location in these mapping measurements showed different rankings, depending on the selected aerosol characterization metric.

Implications for risk assessment

These findings demonstrate the tremendous potential for variability in nanoparticle properties, given the differences in size, shape, surface area, and surface coating. Furthermore, these properties can change with nanoparticles made with different materials (e.g., metal oxides, silver, carbon, silicon, etc.) and could be impacted by impurities and manufacturing byproducts (Nel et al., 2006). Our understanding of the properties and reactivity of nanoparticles is still in the early stages, which limits any attempt at analyzing risks from emerging nanomaterials. In the presence of such high levels of uncertainty, expert judgment can be utilized to estimate model parameters and model forms to enable risk assessment with the limited data. Expert judgment has been used in many contexts when uncertainty is high and is a suitable means to meet the challenges posed by emerging nanomaterials (Kandlikar et al., 2007). However, the elicitation of expert judgments will likely be challenged by various factors, including the selection of experts from a relatively young field and the need for refinements to existing models for nanomaterials. The next section investigates several challenges that may be encountered when using expert judgment for evaluating emerging nanotechnologies.

5.5.2 Challenges in Using Expert Judgment for Evaluating Emerging Nanotechnologies

Selection of experts

A fundamental challenge for nanomaterial risk assessment is the selection of appropriate experts to participate in elicitation tasks. Given the young and relatively small fields of nano-environmental health and safety (nano-EHS) and nanotoxicology research, specific expertise in nanotechnology risks is limited but growing. A number of modeling exercises have utilized expert judgment (Money et al., 2012; Metcalfe et al., 2009), and elicitation exercises and deliberative workshops have been held to explore uncertainties (Flari et al., 2011), characterize and classify nanoparticles (Berube et al., 2011), facilitate risk ranking (Linkov et al., 2007; Grieger et al., 2014; Hristozov et al., 2014), and develop research priorities (Davis et al., 2010; Powers et al., 2014a,b). In addition to those with in-domain

expertise, experts may also be drawn from outside of nanotechnology for certain risk assessment tasks. Recent research by Fauss et al. (2009) involved experts from various disciplines and institutions, including government, industry, nonprofit organizations, and academia, to understand possible exposure routes for consumer products containing nano-silver particles. Collectively, the experts came up with a much larger set of exposure pathways than any single expert can (Fauss et al., 2009) and demonstrated the value of expertise from areas outside of the nanotechnology domain. Additionally, the similarities between nanoparticle research and the well-established PM2.5 (particulate matter that is <2.5 microns) research mean that PM2.5 scientists may be suitable candidates for expert judgment on a variety of aspects of nanoparticle risk assessment. Specific expertise is expanding in the young fields of nanotoxicology, nano-risk, and nano-EHS research. However, it may be some time before nano-experts have the substantive expertise to make accurate judgments on various aspects of nanoparticle risk.

Absence of objective models

Another challenge for expert judgment in the field of nanotechnology is that objective models that guide judgments may not exist, and reliable feedback on the accuracy of an expert's judgments may not be possible. This can lead to elicitation tasks that are practically "un-learnable" (Bolger and Wright, 1994; Rowe and Wright, 2001). However, depending on the decision context, analogous models may be helpful as a proxy for proper nanospecific models (e.g., PM2.5 research). When existing models are not directly appropriate for the case of nanomaterials, they may serve as a framework for developing new models. For example, the field of chemical risk assessment has developed quantitative structure–activity relationship (QSAR) models to help experts estimate the hazard and exposure potential of chemicals, given the physical and chemical properties of the materials (Kandlikar et al., 2007; Morgan, 2005). Similar nanomaterial-specific QSAR models are currently being developed to help perform the same assessments for nanomaterials (Gajewicz et al., 2014; Puzyn et al., 2011). However, the fundamental relationships between physical or chemical characteristics of nanomaterials and their hazard and exposure potential are quite different from those of nonparticle-based chemicals (Puzyn et al., 2010). Therefore, the QSAR models for chemicals serve more as a guiding framework for the creation of nanomaterial-specific QSARs than as proxy models for estimating risks. Formalized elicitation of expert judgment could be helpful in the creation of a nanomaterial-specific QSAR, and elicitation tasks would require both judgments on model structure and parameters. Considering the complexity in approaching the development of nanomaterial-specific QSAR models, the elicitation protocol would require careful selection of experts with appropriate expertise and breaking down of tasks that are familiar to experts.

Lack of feedback

Finally, considering the limited collective empirical operating experience with nanomaterials and nanotechnologies, the challenge for researchers will be determining whether the estimates

of probabilities of rare events are too high or too low, and they may make errors. Freudenburg (1988) argued that many areas of risk assessment provide enough experience to correct errors; however, with events that are truly rare, or technologies that are still new or untried, there may be too little information to permit the needed corrections (Freudenburg, 1988). As such, it is important to proceed with caution when making estimates that may have a large impact on society, especially when we have little empirical information to gauge and correct errors.

Extreme uncertainty

As described earlier, deep uncertainty pervades every stage of the environmental health risk assessment framework. This could be part of the reason that fewer studies of expert judgment on nanomaterial risks have been conducted than would be expected. However, we believe that careful utilization of expert judgment will enable the formation of nanomaterial-specific models or the modification of existing models to enable the use of this framework. Early attempts at risk assessment may have to focus on risk ranking or other forms of comparison of risks, given that there is too little data to enable us to perform a comprehensive risk assessment. Careful identification of research needs and relevant areas of expertise can help guide research on the fundamentals, which, in turn, could enable nanomaterial-specific risk assessments in the near future.

5.6 Expert Judgment in the Development of a Nanomaterial Risk Screening Tool

In a recent example of the use of expert judgment to enable risk assessment under high uncertainty, a framework for nanomaterial risk screening was developed through a structured expert elicitation process and group dialogue (Beaudrie et al., 2014). Drawing upon expertise in nanotoxicology, human exposure, environmental fate and transport, and structured decision making (Gregory et al., 2012), a decision-support framework was created by using influence diagrams to relate key nanomaterial physicochemical and product characteristics to important hazard and exposure indicators. Through this process, experts were engaged in identification of key model parameters and elicitation of model form.

Although not intended as a *quantitative* framework for risk assessment, the Nanomaterial Risk Screening Tool (NRST) was created to enable decision makers to *qualitatively* "score" nanomaterial risks and uncertainties using available data and expert judgment. The NRST was designed to be an open-source tool such that key parameters and model form can be adapted over time as scientific understanding of nanomaterial toxicity, fate and transport, and exposure improves. An example of an influence diagram for evaluating nanomaterial hazards is shown in Figure 5.2.

The influence diagram–based nanomaterial hazard model used in the NRST relates a number of intrinsic and extrinsic physical chemical parameters to two hazard indicators (reactive

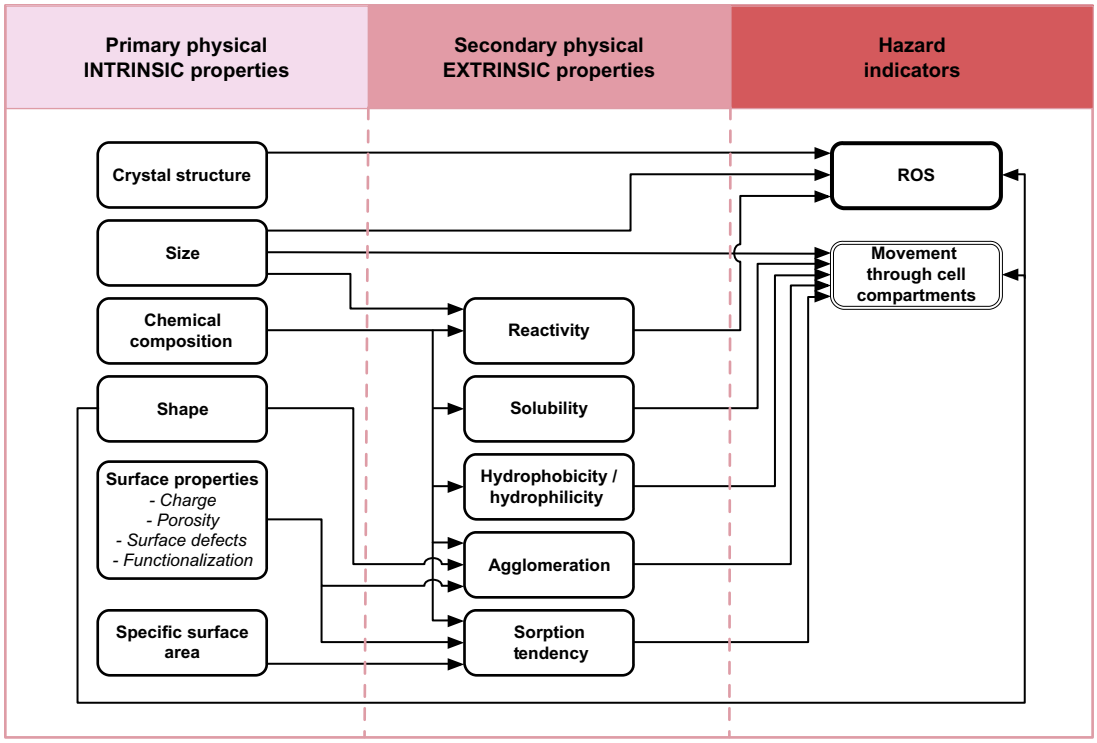

Figure 5.2
NRST Hazard Model.

oxygen species potential, and potential for movement between cell compartments). Using this model, available data and expert judgment can be utilized to qualitatively "score" each nanomaterial property and obtain hazard indicator scores as the output (Beaudrie et al., 2014).

5.7 Conclusions

Expert judgment can be a useful tool for enabling risk assessment for emerging technologies when data are scant and uncertainty is high. Although expert judgment is subject to many biases, methodologic best practices can be employed to minimize their effect. This report has identified several best practices for the selection of experts and the design of elicitation protocols to manage biases and to reduce uncertainty. Furthermore, several considerations have been outlined for employing expert elicitation when performing risk assessments for emerging nanotechnologies. Given the high level of uncertainty surrounding the potential risks of nanomaterials, it is important to understand the ways in which expert judgment can improve assessments, as well as the challenges and limitations of this approach. The use of expert judgment in early nanotechnology risk research has proved to be conceptually valuable, and continued research in nanotechnology utilizing expert judgment is warranted.

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CHAPTER 6

Risk Assessment Using Control Banding

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Chapter Outline

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6.1 Introduction

Control banding (CB) strategies offer simplified solutions for controlling worker exposures to constituents often found in the workplace. Although the original CB model was developed within the pharmaceutical industry, the modern movement of CB involves models developed for non-experts in small and medium enterprises to input information on the hazard and exposure potential in bulk chemical processes, with advice on control as the outcome (Nelson and Zalk, 2010). CB's simplicity can be seen in the fact that it minimizes or eliminates the need for complex quantitative assessments of worker exposure for comparison against occupational exposure standards and instead provides a specific risk band based on a substance's hazard (often based on Safety Data Sheets (SDSs)) and potential exposure (e.g., dispersibility) characteristics. The simplicity afforded by CB can be particularly useful when dealing with nanomaterials (NMs). As stated in previous chapters, NMs present a number of real challenges to industrial hygiene (IH) practitioners. This is, in part, due to the lack of a clear toxicologic basis for setting NM-specific occupational exposure limits, since nanoparticles can affect a broad range of toxicologic endpoints with their high degree of reactivity, their ability to deposit in various regions of the respiratory tract, and their ability

to cross normally impenetrable barriers (e.g., blood–brain barrier, skin). The challenge is, in another part, due to their growing presence in the workplace, since applications for engineered nanoparticles appear endless and both government and private industries are investing substantially into the research and development of nanotechnologies. As products utilizing nanotechnologies are becoming more and more commonplace, and given the general lack of understanding of their toxicologic parameters, caution has been urged because groups of NMs that appear promising in, say, nanomedical applications have themselves been found to be potentially toxic to the patient (Liu et al., 2009; Card et al., 2008). The potential for worker exposures during the handling of NMs is also very real, as evidenced by worker exposures to polyacrylate nanoparticles in a Chinese factory (Song et al., 2009), silicon dioxide NMs playing a major role in the development of cardiovascular diseases (Petrick et al., 2014), and nickel NM powders causing sensitization (Journeay and Goldman, 2014). Based on these and similar incidents, it is becoming increasingly clear that the very properties that make nanoparticles technologically beneficial may also make them hazardous to humans and the environment, and nanoparticle health effects have been reported as major news by the *Forbes* magazine (Bowman, 2014), the British Broadcasting Corporation (BBC, 2010), the Dutch *NRC* (NRC, 2008), and the *San Francisco Chronicle* (Fernholm, 2008). For example, the *Dutch NRC* article refers to the similarity between carbon nanotubes (CNTs) and asbestos, in their shape characteristics as well as their pathogenicity (Poland et al., 2008), the *San Francisco Chronicle* article referred to the potential adverse effects of silver nanoparticles on the environment, the BBC reported on the U.K. House of Lords criticizing the food industry for being too secretive about its use of nanotechnology, and *Forbes* reported that production line work with nanoparticles might be causing serious health effects in workers. Recognizing the power of people to decide which technologies succeed and which do not, whether based on real or perceived risks (Renn, 2005), the role of the IH practitioner cannot be overemphasized in relation to society's ability to reap the full benefits of nanotechnologies. The IH practitioner must establish appropriate means for assessing and controlling the risks posed by NMs, as workers handling them represent the first line of people to face possible risks. Only a proper understanding and acceptance of the risks posed by NMs, by both workers and the public at large, will enable nanotechnologies to develop and thrive. This chapter describes CB as a means for conducting a qualitative risk assessment of nanotechnology operations and utilizing appropriate controls to minimize risks to workers.

6.2 Challenges Related to the Traditional Industrial Hygiene Approach

The traditional IH approach to controlling exposures to harmful particles in the workplace is to measure the air concentrations of the particles of interest from the worker's breathing zone, compare those concentrations to exposure limits determined for those particles, and implement control measures to reduce concentrations below the exposure limits. This assumes the following: (i) The sampled concentrations are representative of what the worker is actually breathing; (ii) the appropriate index of exposure is known; (iii) analytical methods

are available to quantify that index; and (iv) the exposure levels at which those particles produce adverse health effects are known. If any of these is not well characterized, the measurements taken will have limited value because it would be difficult to perform a valid risk assessment. In addressing worker exposures to nanoparticles, the first requirement can be satisfied by obtaining an air sample from the worker's breathing zone with the use of a sampling pump; in such areas, forces such as particle inertia and gravity have minimal impact on the ability of the nanoparticles to follow the sampled air into the sampler, since the sizes of nanoparticles approach molecular size. The second requirement—an appropriate index of exposure—has not yet been satisfied for nanoparticles, with no international scientific community consensus on what the relevant index of exposure is (NIOSH, 2006; ISO, 2007, 2012). For example, a number of studies are suggesting that total surface area concentration may be a better exposure index than mass concentration (Oberdorster et al., 1994; Tran et al., 2000). Particle number concentration has also been suggested as an alternative to mass concentration (NIOSH, 2006, 2009). This lack of consensus directly affects the third requirement, since sampling and analytical methods rely on knowledge of what needs to be measured. Commercially available instruments can measure surface area concentration, number concentration, or mass concentration, but these generally measure larger particles in addition to nanoparticles, introducing potentially large biases (summarized in ISO, 2007 and NIOSH, 2006). For example, both the CPC Model 3007 (TSI, Shoreview, MN, USA), which measures particle number concentration, and the Model 3550 Nanoparticle Surface Area Monitor (TSI, Shoreview, MN, USA), which measures total particle surface area, measure particles up to 1000 nm in diameter, and do not have cut-offs at the upper limit of what is defined as a nanoparticle. The fourth requirement may be the largest barrier to assessing the risk of working with NMs. Very little toxicologic data for determining exposure limits for nanoparticles and virtually no human studies are available (Gordon et al., 2014; Maynard and Kuempel, 2005). This is due to the lack of consensus on the appropriate index of exposure and the relative novelty of nanotechnology and the new materials used in this technology. Therefore, there are numerous barriers to overcome before traditional IH can produce meaningful data in relation to nanoparticle exposures. Although this issue has been well known and researched for over a decade, the barriers remain.

In an attempt to overcome some of these uncertainties, CB was proposed, at least conceptually, as an alternative to the traditional IH approach (Warheit et al., 2007a; Thomas et al., 2006; Maynard, 2007; Schulte et al., 2008). This strategy would facilitate decisions on appropriate levels of control, based on product and process information, without complete information on nanoparticle hazards and exposure scenarios. In the pharmaceutical industry, the limited availability of pharmacologic and toxicologic data of products handled by workers was the main motive to develop control strategies as part of a risk management approach. CB uses categories, or "bands," of health hazards, which are combined with exposure potentials, or exposure scenarios, to determine desired levels of control (Zalk, 2010). The

bands of health hazards for some CB approaches are based on the European Union risk phrases, whereas exposure potentials may include the volume of the chemical used and the likelihood of the chemical becoming airborne, estimated by the dustiness or volatility of the source compound (Maidment, 1998). CB strategies have been further refined through International CB workshops, which explored possibilities of applying the CB approach to other domains such as ergonomics, occupational safety, and environmental hazards, as well as in multidisciplinary formats to the construction industry and as an occupational health and safety management system (Zalk, 2001; Swuste, 2007; NIOSH, 2009; Zalk et al., 2010a, 2011; Coleman and Zalk, 2014). Although CB has received criticism (see, for instance, Kromhout, 2002; Swuste et al., 2003; Jones and Nicas, 2006; ACGIH, 2008), the focus on controls is a strong point of the approach and makes it applicable for operations with many uncertainties in hazard, exposure, and consequence data (ACGIH, 2008; NIOSH, 2009). CB's simplicity is viewed both as a strength and as a weakness, since much of its criticism has focused on issues relating to the simplicity of the CB approach and how this has ignored the experts and their traditional, quantitative methods. With nanoparticle exposure and its many toxicologic and quantitative measurement uncertainties, however, one can argue that the CB qualitative risk assessment approach, at this time, may, in fact, be superior to the traditional quantitative methods (Zalk and Paik, 2010).

The CB concept for nanoparticles was first developed into a usable tool with the creation of the CB Nanotool (Zalk and Paik, 2010; Zalk et al., 2009; Paik et al., 2008). The CB Nanotool has garnered considerable international attention from organizations such as the World Health Organization, the International Labor Organization, and the ISO. CB for work with NMs is now recommended by many countries, including Australia, Canada, The Netherlands, France, Switzerland, Germany, and South Korea, and the CB Nanotool remains a baseline for their evaluation and validation for national regulatory considerations as well as the primary approach for a qualitative decision matrix for risk assessment that leads to commensurate controls (IRSST, 2009; Safe Work Australia, 2009, 2010). A detailed description of the CB Nanotool is provided later in this chapter.

6.3 Control Banding and Risk Prioritization Tools for Nanomaterials

Current research has confirmed that there are consistently identified workplace factors that can increase exposure potential to NMs. These factors include NM-related tasks such as pouring or mixing operations with liquid suspensions, handling powders, open system generation of product, as well as machining, sanding, and drilling of NM (NIOSH, 2009). Available workplace exposure data indicate that potential airborne exposure to NMs can also be minimized during work-related tasks or NM-generating processes that use standard engineering control techniques, such as local exhaust ventilation systems, enclosures, and comparable controls employed in reducing exposures to aerosols and fine dusts. The

characterization and management of the potential risks associated with NMs remains a priority. Potential health risks relating to the development of occupational exposure limits (OELs) are lacking the necessary data for most engineered nanoparticles. The use of CB strategies has become a primary route for the assessment and management of potential health risk prioritization resulting from work-related exposures (Kuempel et al., 2012; Zalk, 2010; Schulte et al., 2008; Maynard, 2007). The number of CB strategies has grown in support of this pragmatic approach to preliminary risk management (Brouwer, 2012). These CB strategies for NMs include: CB Nanotool, Stoffenmanager Nano 1.0, and the French Agency for Food, Environmental and Occupational Safety (ANSES), as well as others, which have not been formally published (Riediker et al., 2012; Paik et al., 2008; Zalk et al., 2009; Van Duuren-Stuurman et al., 2012). Brouwer (2012) reviewed many of these CB tools for NMs relating to their applicability and scope, hazard and exposure banding parameters, and risk classification or control bands. Each strategy appeared to target different users and work area applications, with some focusing on research laboratories and others on medium-size and small-size enterprises. In addition, the extent and detail of preliminary information required differs between these CB tools, which leads to a variety of potential user knowledge necessary for implementing each of the strategies that were reviewed. For those that utilize hazard and exposure bands, there were differences in the parameters that were addressed and the methods necessary to assign the appropriate band. A consistent need for calibration of these tools and some aspect of a performance check on both inputs and outputs of these CB strategies were identified. For many of these CB tools, there was also a consistent need to bring in experts, to fill knowledge gaps and also as a default outcome based on some input parameters. The CB Nanotool does help with this issue, since it has an "unknown" input component on each of its severity and probability input factors. The review concluded that several of the proposed strategies are moving in the right direction to develop controls in the absence of toxicology and exposure data for NMs. This outcome is based on multiple factors, including the emphasis on prevention by weighting to a more conservative outcome, the identification of higher hazard issues in the weighting or flow of the process, and the inclusion of essential severity parameters such as carcinogenicity in the matrix of determining the outcome control band. Regardless of the CB strategy used, the uncertainty of the potential health risks of NMs seems to result in a conservative hazard characterization that results in a high level of risk determination and consequently the need for a high level of exposure control (Brouwer, 2012; Fleury et al., 2013).

Most of the CB and risk prioritization tools for NMs have been developed in line with the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulation within the European Union and includes the Precautionary Principle (Hanson et al., 2007). The REACH requirements include environmental as well as IH considerations, since it applies to chemicals substances with a cradle-to-grave mindset. Therefore, nanoparticle CB tools linked to REACH also apply the Precautionary Principle to their strategy. This

precautionary decision-making concept includes the following common elements: (i) taking preventive action in the face of uncertainty, (ii) shifting the burden of proof to those in favor of potentially harmful activities, (iii) emphasizing exploration of alternatives to potentially harmful actions, and (iv) increasing public participation in decision-making processes (Hanson et al., 2007; Raffensperger and Tickner, 1999). Brouwer (2012) concluded that this precautionary approach is a strength, given the uncertainty associated with NMs. These tools incorporate this concept by assigning higher risk or CBs to higher-concern substances such as fibers; and upon selection of certain single-hazard parameters such as carcinogenicity, the tools produce an outcome that defaults directly to "expert opinion" or the highest control band. The problem with utilizing the Precautionary Principle in this manner, however, is that this concept was initially intended to apply to environmental and public health issues (Raffensperger and Tickner, 1999). Traditional IH works with an acceptable exposure range within its professional construct, and OELs are derived on the basis of this process. IH OELs differ from environmental limits, since they are often 1000 times higher and protect different populations (healthy working-age individuals versus children, older adults, and the immunocompromised) in a different time frame (40 h per work week versus 24 h a day over a lifetime). Therefore, the Precautionary Principle's application to IH is not a common or standardized principle of the profession. In addition, NMs present a unique situation in that there is limited "expert opinion," and this is the primary reason for the development of CB tools in the first place. Defaulting to experts for nanofibers, as an example, does not necessarily yield more information on how to control a given work application. The CB Nanotool differs from tools that incorporate the Precautionary Principle in that it does not default in this manner to experts but rather captures this uncertainty for each of the input parameters with an "unknown" option, which is explained in more detail below (see CB Nanotool description). In addition, an independent evaluation of the CB Nanotool found it useful in overcoming this precautionary approach challenge. It was found that the CB Nanotool provides a factor for understanding uncertainty without using a worst-case approach, even with temporary or highly variable applications (Casuccio et al., 2010). Even within the paradigm of traditional IH methods based on quantitative exposure measurements to establish controls, the uncertainty in work-related health effects relating to NMs render the CB Nanotool an integral component of risk management programs (Casuccio et al., 2009).

6.4 ISO Standard on Use of the Control Banding Approach

In January, 2014, the ISO issued a new technical specification standard on the use of CB for managing inhalation risk from engineered NMs (ISO, 2014). The document proposes guidelines for controlling and managing occupational risk based on a CB approach specifically designed for NOAAs (nano-objects and their aggregates and agglomerates greater than 100 nm). The standard states, in its introduction, that in the absence of relevant regulatory specifications, a CB approach can be used as a first approach to controlling

workplace exposure to NOAAs. The standard provides a description of CB for both proactive and retroactive risk assessment, which is distinguished by whether or not existing controls are used as input variables in determining the control band. The CB Nanotool is described as an example of the proactive approach, and Stoffenmanager Nano is described as an example of the retroactive approach. It is also suggested that the retroactive approach be considered a means for periodic re-evaluation of the proactive approach.

The general structure of the CB process is described as having five steps:

1. Information gathering
2. Hazard banding: Assignment of NOAAs to a hazard band
3. Exposure banding: Description of potential exposure characteristics
4. Control banding: Definition of recommended work environments and handling practices
5. Risk banding: Evaluation of the control strategy

By clearly defining hazard bands, exposure bands, control bands, and risk bands, the standard provides an excellent framework for bringing all these elements together in a comprehensive risk assessment. Specific guidance on how to assign hazard bands and exposure bands are presented in the standard, with several examples of relevant hazard properties of NOAAs and types of activities that present increased potential for exposure.

Annex A of the standard provides a description of the exposure algorithm in the Stoffenmanager Nano risk banding approach, and Annex B provides the different health hazard classes according to the Globally Harmonized System (GHS).

6.5 CB Nanotool

A survey of companies working with engineered NMs found that 65% of them do not perform any kind of risk assessment relating to their product use (Helland et al., 2008). Therefore, the development of a standardized risk decision framework is necessary and has been called for in many of the latest investigative studies (Schulte et al., 2008; Warheit et al., 2008; Hallock et al., 2009). Maynard (2007) presented a conceptual CB model using "impact" and "exposure" indices. This model combines engineered NM composition parameters (shape, size, surface area and surface activity) with their exposure availability (dustiness and amount in use). These indices are linked to bands with four corresponding control approaches. The control approaches are a grouping of three levels of engineering containment, based on sound IH principles; (i) general ventilation, (ii) fume hoods or local exhaust ventilation, and (iii) containment. The fourth level is "seek specialist advice," referring to specialist IH expertise. In the recently published papers on the pilot "CB Nanotool," the feasibility of using CB principles is further developed and has been put into practice at a U.S. national research laboratory (Zalk et al., 2009; Paik et al., 2008). It is important to note that for containment, as a control, there is an optimal flow rate for work with dry NMs within hoods (Geraci, 2008).

It is recommended to avoid higher face velocities when working in hoods with dry powder forms of NMs, with an optimal face velocity range of 100 fpm (feet per minute), since some light-density NMs have been seen to escape at low or high face velocities during transfer operations (Hallock et al., 2009). The control band for a particular operation is based on the overall risk level (RL) determined for that operation. This RL is the result of a combination of a severity score and a probability score for that operation (Figure 6.1), analogous to the impact and exposure indices described by Maynard.

The CB Nanotool's development faced many challenges—chief among these was determination of weightings for the different risk factors. To accomplish this, a group of experts was convened, in over 20 meetings over a 6-month period, to address health, safety, and environmental control of NMs to protect the health of both workers and the public while balancing the needs and requirements of researchers to continue their operations in a safe manner. The expert group over this period included six IHs, four researchers, a safety expert, and an environmental analyst. The outcomes and judgments of the expert group led to how

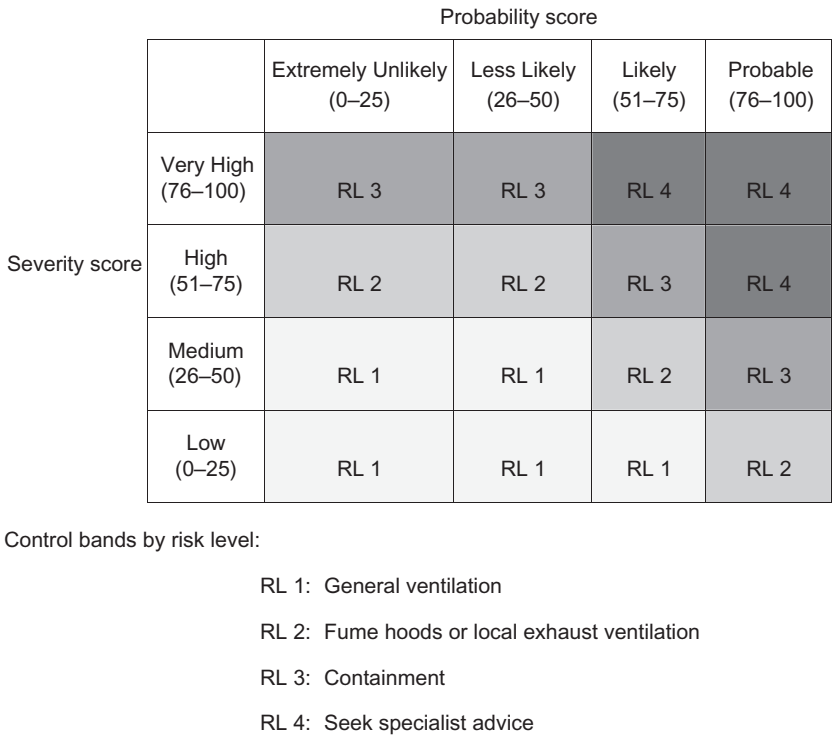

Figure 6.1
Risk level (RL) matrix as a function of severity and probability scores. Control bands are based on overall RLs.

these weightings were determined from ongoing applications of the CB Nanotool. A review of the relevant research in evaluating the basis of the CB Nanotool and its input factors requires an evaluation of the cumulative information on its scoring parameters.

The element of uncertainty and the unknown factors relating to the severity aspects of NMs was an important consideration in the CB Nanotool development (Zalk et al., 2009; Paik et al., 2008). It was recognized that while traditionally an unknown hazard would be treated with the highest level of concern (consistent with the Precautionary Principle), it was also acknowledged that this would more than likely place an unnecessary burden on those managing the risk and limit the tool's usefulness, since largely unknown operations would result in the maximum required control of "seek specialist advice." For that reason, it was decided that 75% of the point value of "high" would be assigned to a given factor with "unknown information." The implication, depicted in Figure 6.1, is that for a nanotechnology operation where nothing is known, RL 3 (containment) would be required. In this particular scenario, if just one rating of any of the factors were changed to "high," the tool would require an RL 4 assignment for the activity, which is the maximum control. Presented below is a summary of the severity factors, probability factors, and the maximum scores attributed to each of these factors. The latest version of the CB Nanotool and additional resources are available at www.controlbanding.net.

6.5.1 Severity Factors

In consideration of the health effects potentially related to NMs and the environmental safety and health protocols necessary to perform appropriate risk assessments, the majority of the physicochemical aspects presented below are strongly supported by the current literature (Warheit et al., 2008; Yang et al., 2008; Hallock et al., 2009; Orthen, 2008). These physicochemical aspects include particle surface chemistry, surface area, solubility, particle number, shape, and biological availability for translocation (Yang et al., 2008; Warheit et al., 2007a). Extrapulmonary translocation varies in degree of toxicologic consequence due to differences in chemical composition, particle size, and surface characteristics, including surface electrostatic charge on inhalation, leading to higher deposition rates (Yang et al., 2008). Additional research has shown that when selected NMs of the same size are held constant, it is the structure (e.g., anatase > rutile) that is the toxic differential and that surface area alone is not enough to address pulmonary exposure (Liao et al., 2009; Warheit et al., 2007b). Based on the literature available to date, the factors listed below are considered to determine the overall severity of exposure to NMs. These factors influence the ability of particles to reach the respiratory tract, their ability to deposit in various regions of the respiratory tract, to penetrate or to be absorbed through the skin, and to elicit biological responses systemically. The division of severity factor points taken cumulatively is 70% for the NM and 30% for the parent material (PM). Current research does not contraindicate the

potential for an engineered NM to be more toxic than its PM. The individual factors that make up NM severity factors are discussed below.

Surface chemistry of NM

Surface chemistry is known to be a key factor influencing the toxicity of inhaled particles (Maynard and Kuempel, 2005). Crystalline silica, for example, elicits a much stronger response than titanium dioxide (TiO_2), even when normalized for surface area or mass. Particle surface free radical activity is the primary factor that influences the material's overall surface reactivity. Research studies should be consulted, when available, to make a judgment on whether the surface reactivity of the NM is high, medium, or low. For example, free radical activity is associated with the generation of reactive oxygen species (ROS) and oxidative stress responses in the lungs. ROS and oxidative stress responses can be quantified by analyzing the bronchoalveolar lavage fluid (BALF) from rats used in toxicologic studies. The BALF may be analyzed for markers of inflammation, levels of pulmonary oxidants, antioxidant status, and markers of lung tissue damage (Albrecht et al., 2006). These types of information need to be consulted in determining the surface reactivity of the NM. Points are given based on a judgment on whether the surface activity of the nanoparticle is high, medium, or low.

High: 10 Medium: 5 Low: 0 Unknown: 7.5

Particle shape of NM

Studies have shown that exposure to fibrous particles such as asbestos have long been associated with increased risk of fibrosis and cancer (Doll, 1955). Tubular structures such as CNTs have also been shown to cause inflammation and lesions in rat lungs (Lam et al., 2004). Based on this information, the highest severity score is given to fibrous or tubular-shaped particles. Particles with irregular shapes (other than tubular or fibrous) are given a medium severity score because they typically have higher surface areas relative to isotropic (e.g., compact or spherical particles) particles. The highest severity score is given to fibrous or tubular-shaped particles. Particles with irregular shapes (anisotropic) have higher surface areas than isotropic or spherical particles.

Tubular, fibrous: 10 Anisotropic: 5 Compact/spherical: 0 Unknown: 7.5

Particle diameter of NM

Based on the particle deposition model developed by the International Commission on Radiological Protection (ICRP, 1994), particles in the 1–10 nm range have >80% chance of being deposited in the respiratory tract. Particles in the 10–40 nm range have a >50% possibility of being deposited in the respiratory tract, and particles in the 41–100 nm range have a >20% possibility of depositing in the respiratory tract. Since deposition is the first step

in producing potential adverse health effects, the severity score was based on the particles' deposition in the respiratory tract, regardless of the region in the respiratory tract.

1–10 nm: 10 11–40 nm: 5 <41–100 nm: 0 Unknown: 7.5

Solubility of NM

A number of studies have shown that poorly soluble inhaled nanoparticles can cause oxidative stress, leading to inflammation, fibrosis, or cancer (Castranova, 1998; Donaldson et al., 1998). Since soluble nanoparticles can also cause adverse effects through dissolution in blood, severity points are assigned to soluble nanoparticles as well, but to a lesser degree than for insoluble particles.

Insoluble: 10 Soluble: 5 Unknown: 7.5

Carcinogenicity of NM

Points are assigned on the basis of whether an NM is carcinogenic or not, regardless of whether the material is a human or animal carcinogen. Very few NMs (e.g., TiO_2) have been identified as potential carcinogens (IARC, 2006).

Yes: 6 No: 0 Unknown: 4.5

Reproductive toxicity of NM

Points are assigned on the basis of whether an NM is a reproductive hazard or not. This information is not readily available for most NMs.

Yes: 6 No: 0 Unknown: 4.5

Mutagenicity of NM

Points are assigned on the basis of whether an NM is a mutagen or not. This information is not readily available for most NMs.

Yes: 6 No: 0 Unknown: 4.5

Dermal toxicity of NM

Points are assigned on the basis of whether an NM is a dermal hazard or not. This is understood to encompass both dermal absorption and cutaneous toxicity. This information is not readily available for most NMs.

Yes: 6 No: 0 Unknown: 4.5

Asthmagen of NM

Points are assigned on the basis of whether an NM is an asthmagen or not. This information is not readily available for most NMs.

Yes: 6 No: 0 Unknown: 4.5

Toxicity of PM

The bulk materials of some nanoparticles have established OELs. Although it is known that the toxicity of particles at the nanoscale can differ significantly from that of their larger counterparts, this provides a good starting point for understanding the toxicity of the material. Points are assigned according to the OEL band of the bulk material. Points are assigned according to the OEL of the bulk material.

$<1\,\mu gm^{-3}$: 10 $1–100\,\mu gm^{-3}$: 5 $101\,\mu gm^{-3}–1.0\,mgm^{-3}$: 2.5 $>1.0\,mgm^{-3}$: 0
Unknown: 7.5

Carcinogenicity of PM

The National Toxicology Program, International Agency for Research on Cancer, and the American Conference of Governmental Industrial Hygienists have provided lists of suspected and confirmed human carcinogens. Points are assigned on the basis of whether the PM is carcinogenic or not.

Yes: 4 No: 0 Unknown: 3

Reproductive toxicity of PM

Points are assigned on the basis of whether the PM is a reproductive hazard or not.

Yes: 4 No: 0 Unknown: 3

Mutagenicity of PM

Points are assigned on the basis of whether the PM is a mutagen or not.

Yes: 4 No: 0 Unknown: 3

Dermal hazard potential of PM

This is understood to encompass both dermal absorption and cutaneous toxicity. Points are assigned on the basis of whether the PM is a dermal hazard or not.

Yes: 4 No: 0 Unknown: 3

Asthmagen of PM

Points are assigned on the basis of whether the PM is an asthmagen or not.

Yes: 4 No: 0 Unknown: 3

A number of studies have shown that the particle surface area is closely associated with lung responses, including tissue damage and inflammation in rat lungs (Oberdorster et al., 1994; Tran et al., 2000). This factor is accounted for by assigning higher severity scores to smaller particles (which would have a higher surface area compared with larger particles at the same mass concentration) and anisotropic particles (which generally would have higher

surface-to-volume ratios). This factor is also accounted for by assigning higher probability scores to operations that have higher "dustiness" levels (see next section), which would invariably have higher overall surface area concentrations relative to operations with lower dustiness levels. The overall severity score is determined on the basis of the sum of all the points from the severity factors. The maximum score is 100. Since nanoparticles usually behave much differently from their PMs because of their small scale, greater consideration was given to the NM characteristics (70 possible points out of 100) than to the PM characteristics (30 possible points out of 100). Since the PM and the NM are both considered in determining the severity score, it should be understood that the PM ratings should not influence the ratings that are given for the same factor at the nanoscale (e.g., carcinogenicity)—that is, each factor should be rated independently of another. An overall severity score of 0–25 was considered low severity; an overall severity score of 26–50 was considered medium severity; an overall severity score of 51–75 was considered high severity; and an overall severity score of 76–100 was considered very high severity.

6.5.2 Probability Factors

In order to obtain the probability score that can be combined with the severity score to determine the overall RL of the operation, the authors believe the following factors should be considered when determining the overall probability score based on research and development activities at a national research laboratory. These factors determine the extent to which employees may be potentially exposed to nanoscale materials. The probability score is based on the potential for nanoparticles to become airborne. This primarily affects exposure by inhalation; however, it also influences the potential for dermal exposure because the likelihood of skin contact with the NM increases with more nanoparticles becoming airborne and depositing on work surfaces.

Estimated amount of NM used during operation

When all else is constant, the amount of the NM used during an operation increases the likelihood of the material being available to interact with the user. For NMs embedded on substrates or suspended in liquids, the amount should be based only on the NM component itself, not to include the substrate or liquid portion. Therefore, points are assigned based on the total amount of NM used during a single operation.

>100 mg: 25 11–100 mg: 12.5 0–10 mg: 6.25 Unknown: 18.75

Dustiness/mistiness

Since employees are potentially exposed to nanoparticles in either the dry or the wet form, this factor encompasses both dustiness and/or mistiness of the NM. For the same mass concentration, however, nonagglomerated dry nanoparticles should be given a higher

dustiness/mistiness rating compared with agglomerated or liquid-suspended nanoparticles. Although not required, quantitative measurement devices would be particularly useful in determining the dustiness/mistiness level. A condensation nuclei counter that provides number concentration, for example, would provide insight into the overall dustiness level. Knowledge of the operation (e.g., handling dry powders versus liquid suspensions of nanoparticles) and observation of work surfaces (e.g., cleanliness of surfaces prehandling and posthandling of NM) would be another means to qualitatively estimate dustiness/mistiness. Because of the size of NMs, visibility may not a reliable means to estimate overall dustiness/mistiness. Until further guidance is provided on the appropriate means to quantify exposure to nanoparticles, points will be assigned based on an estimate of "relative" dustiness/mistiness level. One design feature of the CB Nanotool is that a rating of "none" for dustiness/mistiness level (and only for this factor) automatically causes the overall probability score to be "extremely unlikely," regardless of what the other probability factors are, since the other factors will not be relevant if no dust or mist is being generated. Examples of operations that would result in a "None" rating are handling of CNTs embedded on fixed substrates and working with nonagitated liquid suspensions. This feature was specifically incorporated into the tool for this reason and represents the only departure from the "rules" that govern the tool. The dustiness/mistiness factor is the most important one in determining the overall probability score, and as such, relatively high numbers of points are assigned to the ratings in this category.

High: 30 Medium: 15 Low: 7.5 Unknown: 22.5

Number of employees with similar exposure

For this factor, points are assigned according to the number of employees assigned to this activity. With higher numbers of employees engaged in the activity, there is a higher probability of employees being exposed.

>15: 15 11–15: 10 6–10: 5 Unknown: 11.25

Frequency of operation

Points are assigned on the basis of the frequency of the operation, as more frequent operations are more likely to result in employee exposures.

Daily: 15 Weekly: 10 Monthly: 5 Less than monthly: 0 Unknown: 11.25

Duration of operation

Points are assigned on the basis of the duration of the operation, as longer operations are more likely to result in employee exposures.

>4 h: 15 1–4 h: 10 30–60 min: 5 <30 min: 0 Unknown: 11.25

Table 6.1 Severity and probability factors and maximum points per factor

Severity Factor	Maximum Pts	Maximum Severity Score
Surface chemistry (NM)	10	100
Particle shape (NM)	10	
Particle diameter (NM)	10	
Solubility (NM)	10	
Carcinogenicity (NM)	6	
Reproductive toxicity (NM)	6	
Mutagenicity (NM)	6	
Dermal toxicity (NM)	6	
Asthmagenicity (NM)	6	
Toxicity (PM)	10	
Carcinogenicity (PM)	4	
Reproductive toxicity (PM)	4	
Mutagenicity (PM)	4	
Dermal hazard (PM)	4	
Asthmagenicity (PM)	4	
Probability Factor	**Maximum Pts**	**Maximum Probability Score**
Estimated amount of nanomaterial	25	100
Dustiness/Mistiness	30	
Number of employees with similar exposure	15	
Frequency of operation	15	
Duration of operation	15	

NM, Nanomaterial; PM, parent material.

The overall probability score is based on the sum of all the points from the probability factors. The maximum score is 100. An overall probability score of 0–25 was considered extremely unlikely; an overall probability score of 26–50 was considered less likely; an overall probability score of 51–75 was considered likely; and an overall probability score of 76–100 was considered probable. On the basis of the severity score and probability score for an operation, the overall level of risk and corresponding control band is determined by matching each score to its corresponding axis in the matrix shown previously in Figure 6.1. A summary of input parameters and maximum scoring outcomes is given in Table 6.1.

6.6 Evaluation of the CB Nanotool

A great deal of research and consideration of the collective information available was performed during the development of the CB Nanotool. In concept, as described above, it was easiest to begin with the realization that traditional IH did not provide a comprehensive and accurate quantitative risk assessment of NMs. This realization also provides a validation that CB is gaining legitimate recognition as a viable risk assessment strategy in the eyes of occupational health experts for challenging work-related hazards. It has also led to an

increasing recognition of the CB Nanotool as an integral part of the prevention of NM exposures and a further evaluation of this method around the world. On the macroscale, Safe Work Australia has performed significant research to the applicability of both CB for NMs in general and in the evaluation of the CB Nanotool itself (Safe Work Australia, 2009, 2010). It was determined that CB is the most suitable risk control for managing nanoparticle exposure in the Australian nanotechnology industry (Safe Work Australia, 2010). It was also determined that the CB Nanotool model looks promising in addressing satisfactory control of NM exposures in the workplace, and further evaluation has led to a national validation effort for the CB Nanotool relating to national regulatory considerations (Safe Work Australia, 2009, 2010). In addition, scientific review articles of the latest NM sciences have found that the CB Nanotool's approach is considered by numerous researchers to have the potential to offer the greatest utility to NM producers as well as users, on both local and national scales (Schulte et al., 2010; Savolainen et al., 2010). Others have stated that the CB Nanotool offers an appropriate insight to end users by providing an inherent presentation of potentially unknown health factors as part of a given risk assessment, which, in turn, affords a comprehensive understanding of the each of the input factors that lead to the RL outcome. This offers flexibility to the end user, since it provides its 75% score weighting to address uncertainty while not defaulting to the worse-case RL outcome. This is especially useful for performing risk assessment and obtaining commensurate control outcomes associated with what may be a temporary or highly variable application, as well as with specific changes in a given task's processes (Casuccio et al., 2010).

These collective accolades can be seen as a considerable success for qualitative risk management methods in general; however, the quantitative methods for NM risk management should continue to be evaluated for their role in risk assessment and exposure reduction. In performing evaluations, the use of available quantitative instruments and their utility needs to be considered in line with their potential biases. These biases can include skewing mass concentration, particle number, and surface area results. The expense of the available and more accurate exposure monitoring tools also must be part of the decision-making process because they are seen by many field practitioners as cost prohibitive, especially in the face of so much uncertainty. These considerations were all part of the initial evaluation that led to the creation and implementation of the CB Nanotool. Once the decision was made to build a qualitative approach, it was also easy to decide on using the 4×4 risk model that is utilized in many of the CB strategies. The 4×4 risk matrix has been found over time to balance ease of use with an appropriate level of rigor to develop a binning of established and graded control approaches in a historically acceptable manner (Maidment, 1998; ANSI, 2000; Zalk and Nelson, 2008). The research also presented a relatively consistent set of factors that should be used in the model; however, the weighting of each factor relative to the others was a bit more involved and required a relative risk approach in line with the available research (Robichaud et al., 2005).

6.6.1 Severity

Physicochemical characteristics NM (40 points)

Research showed a strong agreement that the physicochemical aspects of NM structure have a predominant effect on their potential toxicity (Maynard, 2007; Warheit et al., 2007a; Thomas et al., 2006). Therefore, both the physical parameters (particle shape and diameter) and chemical parameters (surface chemistry and solubility) were weighted equally with 20 points attributed to each parameter as research did not indicate that one parameter or the other led to a more elevated risk. This decision was also based on the fact that appropriate standardization of testing did not appear available in the literature, only that both of these considerations were necessary when evaluating the potential toxicity of a given NM (Powers et al., 2006).

Toxicologic characteristics NM (30 points)

Having taken into account the more generic health hazard parameters of NMs, it was also necessary to account for the toxicologic concerns that might be related to research on specific NM effects. As the research on NMs, as a whole, had not delved into these specific toxicologic aspects to date, agreement by experts invariably noted that the more classic toxicologic outcomes for an individual NM product should also be considered (Maynard, 2007; Powers et al., 2006). Therefore, the toxicologic adverse outcomes that would lower any prospective occupational exposure limit were included, and these were carcinogenicity, reproductive toxicity, mutagenicity, and dermal toxicity. From an IH perspective, it is difficult to consider weighting these adverse outcomes as anything other than equally as any one of these toxic effects will lead to an appropriate lowering of its OEL to avoid a health hazard.

Toxicologic characteristics of PM (30 points)

As stated earlier, the properties that make NM unique in their utility also have the potential to create unique toxicologic considerations. Without more specificity of this issue presented in research publications, it is necessary to start with the likelihood that much more of this toxicologic information would be available for the bulk PM. Therefore, equal weight was given for the research-derived toxicologic characteristics for both the NM and the PM, with both at 30 points. This also gave an appropriate greater weighting to the physicochemical aspects of NMs (40%), which are being extensively researched, than for the specific toxicologic outcomes of both the NM (30%) and its PM (30%). A decision was made to use the same toxicologic characteristics for the PM and the NM, dividing their points equally, although greater weighting was given to the NM (30%) than to the PM (20%) to reflect concerns expressed in the research. To make up the additional 10 points to equalize PM toxicity with NM toxicity, the PM's OEL was included in the PM toxicologic outcome determination, since this is more holistic in offering a relative weight to a more broad classification of epidemiology and toxicology issues. Thus, the PM OEL (10%) was given twice the value of any of the individual PM toxicologic characteristics (5%).

6.6.2 Probability

Dustiness/mistiness (30 points)

Research confirms the importance given to the CB Nantool's weighting of both dustiness/mistiness and estimated amount of chemical used. The same logic for offering a higher score relating to the NM's ability to become airborne has been given even greater emphasis in the more recent publications. The physicochemical focus remains on the biologically available surface area and its ability to translocate systemically. The unique properties of a given NM, inherent in its design and aiding its intended utility, also seem to afford an elevated, persistent, and comprehensive risk potential. Therefore, the CB Nanotool's conservative approach to capture and weight the factors that reflect the probability for an NM to become airborne and persist in the work environment relative to a given task's exposure potential appear to remain consistent with the pervasive expert call for a precautionary approach in implementing controls and worker protection (Yang et al., 2008; Warheit et al., 2008; Hallock et al., 2009; Orthen, 2008). In determining the factors that would lead to potential exposure of employees, the primary consideration would be based on the opportunity for the NM in question to become airborne. Experts are in agreement that the most important factor for determining the potential for exposure and, therefore, the potential for bioavailability and translocation systemically is with regard to inhalation (Warheit et al., 2007a; Maynard, 2007; Thomas et al., 2006; Powers et al., 2006; Tsuji et al., 2006; Holsapple et al., 2005). The consideration was therefore a balance between its ability to become airborne, to disperse easily, and the amount of material used. It was determined to give dustiness/mistiness the greatest weight of the probability factors (30%). Consideration has been given to the possibility that many of the CB Nanotool users performing an initial screening of NM activities could default here to "unknown" if no other parameters for airborne potential were readily available (Donaldson et al., 2006). Then, if the RL outcome were too restrictive with the weighting on an "unknown" score, a decision could be made to use quantitative measurements to assist in scoring this category. This focused use of quantitative monitoring tools is considered a more appropriate and cost-efficient application and is not confounded by the biases of using multiple monitoring devices simultaneously. In addition, although dustiness and mistiness are characterized together, mistiness in isolation would likely have a lower score then dustiness as the nanoparticles would be in the form of wet suspensions. This score for mistiness would therefore be more analogous to a lower score for dry, agglomerated particulates compared with non-agglomerated, highly dispersed particulate in a similar operation.

Estimated amount of chemical used (25 points)

The more material that is used, the better chance there is that it will become available as a potential source term for employee exposure. The weighting of the amount of chemical used in a given task was considered to be a slightly lower relative risk (25%) than the consideration

for the airborne potential (30%). The authors also considered the combination of dustiness and amount used as being the primary exposure probability factors, in deference to Maynard's (2007) use of this as the only exposure factors, and therefore wanted this combination to be greater (55%) than the remaining factors that are task specific (45%). This overall weighting is not entirely based on the relative risks presented in research for these factors due to the fact that this information is acknowledged as not being available in sufficient depth to make such a determination (Nasterlack et al., 2008; Tsuji et al., 2006; Holsapple et al., 2005). Therefore, IH expertise was utilized to make this relative risk delineation based on decades of combined field practitioner experience for factors culminating in exposure.

Opportunity for exposure (45 points)

For all of the discussion on the toxicologic aspects of working with nanoparticles, this factor focuses on the more classic nature of traditional IH. Exposures and the potential for employee uptake are typically seen as a function the length of the task at hand and the periodicity of which that task is performed. Taking on aspects of epidemiology and a statistical view of the potential for variance from the mean, the more workers there are that are performing a given task, the higher is the probability of exposure. Therefore, these three aspects relating to exposure opportunity were given an equal weighting with frequency of operation, duration of operation, and the number of employees performing the task, each given 15% of the probability factors scoring.

6.6.3 Addressing Expert Opinion

As the CB Nanotool has received a large amount of attention internationally, it has also received a fair share of commentary and critique of its factors, parameters, and weightings. Therefore, it is important to address these inquiries for the reader's benefit.

Surface area

Professional consideration was given as to whether total surface area should be considered an exposure characteristic or a severity characteristic. Total surface area was not included as a severity characteristic because all the other severity characteristics pertained to properties inherent to a given NM or PM and did not consider dosage or exposure. However, as stated earlier, since particle size and particle shape are characteristics inherent to NM that would result in a greater total surface area at the same mass concentration, these were included as severity parameters. Surface area relating to exposure characteristics is captured in the dustiness/mistiness scoring factor and is accounted for in its greater weighting for probability of exposure. Elevated dustiness/mistiness levels for a given activity will have a higher concentration of airborne nanoparticulate and a much higher surface area concentration than lower dustiness/mistiness levels.

Dermal exposure

There were a few experts that questioned how dermal considerations were addressed in the design of the CB Nanotool. One issue was that the dustiness/mistiness input factor includes a design feature that defaults to "extremely unlikely" if there is no potential for airborne NM during a given process. It was mentioned during a third-party review of the CB Nanotool that this default appears to discount the potential for the dermal exposure route and, therefore, its relevancy (Ryman-Rasmussen et al., 2006). In actuality, the potential for dermal exposure and uptake through various external uptake routes (e.g., ocular, hair follicle) can be considered entirely influenced by highly dispersible nanoparticulate, affecting dermal exposure through both airborne routes as well as its deposition on working surfaces. If there is no airborne exposure, then dermal exposure is isolated to the source term, which can be controlled with personal protective equipment such as gloves and long sleeves, while handling the product. Another point of discussion was the weighting of the dermal toxicity parameters overall. As the research is indeterminate for the potential of dermal penetration of NMs through intact skin, the consideration of this route as an equivalent severity consideration was in question. The equal weight of NM dermal toxicity was given not only to address this one aspect but also in consideration of the other factors that encompass cutaneous toxicity in a manner, including potential for absorption as well as penetration.

Frequency and duration

Some analysis was given toward the inclusion and weighting of the duration and frequency of a given task in determining the potential for exposure. As a primary reference in support of this CB approach for NM, Maynard (2007) considered dustiness and amount as the only factors to be considered within the exposure index. The weight to these two factors is given in protecting the employee first, regardless of the frequency and duration of a given task. In the CB Nanotool, the greatest weighting in the probability scoring is given to the dynamics of the source term—dustiness and amount—since these are the focus of the controls that are derived from the toolkits' application. However, the consideration of frequency and duration, in addition to number of employees potentially exposed, gives a practicality counterweight to the probability of exposure. Consideration of these additional factors was not thought to conflict with the two primary factors but rather supplement them. That is, if a task takes a few minutes and is performed a couple of times a year, this must also be given consideration in affecting the overall potential for exposure.

OEL of PM

Giving only 10% of the severity weight to a well-researched, professionally derived, and science-based OEL for the PM was considered by some to be insufficient. In consideration of the relative value of the PM OEL, the authors of the CB Nanotool felt that its 10 points did

not stand in isolation. The toxicologic and epidemiologic aspects that drive a PM's OEL to lower and more conservative values are often the same as the identified critical effects (e.g., carcinogenicity, reproductive toxicity, mutagenicity, dermal, and asthmagen) which would each add an additional 5% to the severity weighting up to a theoretical maximum of 30%.

Number of employees

The 15% weight given to the number of employees as a factor of probability has received the attention of some experts. This particular weighting factor was decided upon by the expert working group for this category due, in part, to the large research population at the Lawrence Livermore National Laboratory (LLNL). There can be quite a number of researchers working on any given phase of an NM project, and they perform multiple tasks in this role. Therefore, even with engineering controls in place, both working habits and approaches to NM research provide an individual variability that exposure potential from this must be taken into account with an equivalent weighting as frequency and duration. It is worth noting here that no risk assessment approach, especially when qualitative in nature, should be adopted prima facie. Although national organizations have adopted the CB Nanotool directly as a best practice (IRSST, 2009), all weighting factors applicable to a given implementation should be evaluated in line with a given working facility.

Unknown uncertainty

Some national and local regulations do not consider any exposure to NMs acceptable, since there too much uncertainty associated with NMs. In balancing the vast potential for NM research to improve health, as an example, it is difficult to restrict any work from occurring simply due to a lack of information. The CB Nanotool does allow work to occur with a lower level of engineering control (e.g., RL1 and RL2), and the assignment of 75% of the rating score of high for "unknown" factors appears to have gained approval from a growing number of international experts. Here, erring on a safe side with a conservative approach for working with relatively unknown materials affords a path forward for research utilizing available information within a burgeoning science.

Validation

Appropriately, many experts have questioned the ability to develop the parameters to truly validate the CB Nanotool. The problem is that there is a lack of a gold standard to accomplish this for NMs. In practice, this question remains a major topic of discussion for chemical control CB strategies; however, publications have begun to fill this research need that is building confidence in the approach in the face of uncertainties (NIOSH, 2009; Zalk and Nelson, 2008; Marquart et al., 2008; Tielemans et al., 2008). This question is more appropriately compared with the scarcity of publications on validation for CB schemes utilized in the pharmacologic industries. CB has been an accepted practice for the risk assessment and control of new and more potent pharmaceutical components and has been successfully in place within the industry for over a decade, although very little validation data

has been presented in research publications (Farris et al., 2006; Naumann et al., 1996). Often in this industry, it is the recommended control that has been put in place that is monitored for its containment effectiveness using standardized, mock particulate (e.g., lactose) that have established analytical detection methods. In a similar manner, quantitative particle counters have been used in selected screening opportunities to compare rogue NM particle counts with background levels. During the implementation and evaluation of the pilot CB Nanotool, this approach was used to facilitate the assignment of the appropriate dustiness/mistiness level to specific operations. The scenarios presented as case studies in Zalk et al. (2009) focused on a sampling of representative and existing research and development (R&D) activities within the LLNL institutional safety document database. Prior to the existence of the CB Nanotool, expert IH advice was used to select the most appropriate controls for a given activity with NMs. The IH would also utilize best practices such as the National Institute for Occupational Safety and Health (NIOSH) publication *Approaches to Safe Nanotechnology*. Therefore, outcomes were directly compared with existing professional expertise, which is as close as we can come to a validating method without the existence of a gold standard. Specific validation examples can be found within the Paik et al. (2008) and Zalk et al. (2009) articles and good agreement was found at the time between the expert and the CB Nanotool.

Field testing

Despite the limitations presented, the CB Nanotool is a transparent and logical method. Although much research has been performed within the sciences relating to NMs, data on NM health effects is still limited, and it is expected that this stream of information will continue to expand rapidly (Yang et al., 2008; Warheit et al., 2008; Hallock et al., 2009). Therefore, as specific studies are published, severity parameter scores that where once "unknown" can now be more accurately portrayed, and users of the tool can adjust their input and affect the severity score. More importantly, as one cannot control the pace of science, users of the CB Nanotool can immediately seek to address some of the parameters relating to the probability of exposure to reduce the overall RL. For experts in IH, this is a common activity; however, for CB Nanotool users who may be new to the exposure sciences, this is an essential learning opportunity in a simple and practical format. A total of 32 risk assessments with the CB Nanotool were summarized in Zalk et al. (2009), and the CB Nanotool recommendation was equivalent to the existing controls for 20 of them, a higher level of control for 8 of them, and a lower level of control for 4 of them. These data suggest that the CB Nanotool produced control recommendations that were generally equal to or in some cases more conservative than the existing controls that were implemented by expert IHs. The CB Nanotool's qualitative risk assessment approach may tend to err toward the conservative at times; however, occupational hygiene experts also agree that it is better to err toward overcontrol rather than undercontrol (Zalk and Nelson, 2008). The results were consistent with what the authors hoped to achieve through the tool, which was to develop a consistent approach that would generally err on the safe side, in light of the uncertainty associated with NM health effects. An unexpected, but welcome, outcome of this qualitative risk assessment process has been a basis for risk

communication between occupational hygienists and workers. This has been an excellent educational opportunity for experts as well as users in considering methods and work practices that can create task-based adaptations that can reduce the overall RL (Zalk et al., 2009). This standardized language for the discussion of risk between experts and non-experts can open the door for a greater understanding of the potential hazards during this activity.

6.7 Quantitative Validation of the CB Nanotool

In an independent study published on September 28, 2010, the Lawrence Berkeley National Laboratory (LBNL), in conjunction with RJ Lee Group, Inc., conducted a quantitative validation of control bands initially assigned to various R&D scale activities (Casuccio et al., 2009, 2010). The Casuccio et al. (2010) study was Phase 3 of a four phase study that involved data collection (Phase 1), preliminary control band development (Phase 2), validation of preliminary control band assignments (Phase 3), and an environmental monitoring plan for unbound engineered nanoparticles (Phase 4). The Phase 3 study focused on the evaluation of worker exposures and emissions to the environment through the use of various quantitative methods, including direct-reading particle counters (TSI Condensation Particle Counter 3700, Grimm SubMicron Aerosol Spectrometer 1.108) and cassette filters (37-mm PVC filters for gravimetric and elemental analysis and 25-mm PC filters for electron microscopy analysis). The preliminary control bands were assigned using the 4×4 matrix used by the CB Nanotool, where control bands were determined from the severity and probability characteristics of the engineered nanoparticles. Although the determination of the severity and probability levels appeared to be a slight simplification of the CB Nanotool process, the approach was generally consistent with the CB Nanotool algorithm. It was also noted that some of the preliminary control band assignments were upgraded on the basis of specific requirements of the institution. A summary of the quantitative validation was presented in Table 9.1 of the report (Table 6.2 below) and reproduced below, with Roman numerals replaced by Arabic numerals for ease of viewing:

It was noted in the report that the Phase 3 evaluation was based on data from samples collected over a longer period (up to 70 min) and using higher flow rates (approximately 7 L/min) than is typical for those operations. This was done to increase the ability to detect and quantify low airborne levels of engineered nanoparticles. Hence, the estimates from the quantitative data were considered to be conservative. Specifically related to the control band validation, the report concluded the following:

1. The preliminary control bands for many of the processes were conservative.
2. Controls for all processes evaluated meet or exceed the controls suggested by the validated control band.

Further exploring the first conclusion above, the preliminary control band was the same as the quantitatively validated control band for 10 or the 12 activities and more conservative in

Table 6.2 Comparison of preliminary, actual, and validated control bands for evaluated processes

	Phase II		Phase III
Activity	Preliminary Control Band	Actual Control Level	Validated Control Band
John Kerr, Building 62, Lab 246			
Fumed silica used in fume hood	3	2	2
Carbon black and acetylene black used in fume hood	2	2	2
Fumed silica used in glovebox	2	3	2
Carbon black and acetylene black used in glovebox	2[a]	3	2
Thomas Richardson, Building 62, Lab 342			
Carbon black and acetylene black used in glovebox	2[a]	3	2
Vincent Battaglia, Building 70, Labs 295/297/299			
Carbon black and acetylene black used in fumehood	2[a]	2	2
Silicon used in fumehood	3	2	2
Carbon black and acetylene black used in glovebox	2[a]	3	2
Vincent Battaglia, Building 70, Lab 218			
Carbon black and acetylene black used in fumehood	2[a]	2	2
Robert Kostecki, Building 70, Lab 295/297/299/108			
Carbon black and acetylene black used in glove box	2[a]	3	2
Graphene used on countertop	1	1	1
Don Lucas, Building 70, Labs 291/293			
Toxic species detection using nanogold in fumehood	2	2	2

[a]Originally assigned to Control Band I; revised to Control Band II to reflect LBNL requirements.

2 of the 12 activities. Further exploring the second conclusion above, the actual control band used for activity was the same as the validated control band for 7 of the 12 activities and more conservative in 5 of the 12 activities. Although the sample size was relatively small in this study (12 activities were assessed) and the preliminary control bands were assigned on the basis of a simplified algorithm of the CB Nanotool and in accordance with institution-specific requirements, the report conclusions were largely consistent with the conclusions from the Paik et al. (2008) and Zalk et al. (2009) studies, which concluded that the CB Nanotool designations were typically equivalent to or more conservative than IH expert control recommendations (Casuccio et al., 2010).

6.8 Considerations for the Nanotechnology Industry

The CB Nanotool was designed for use at a U.S. research laboratory with a large working population focused on R&D but was never intended to be a static tool for a

given task or procedure. The inclusion of the CB Nanotool by the ISO (2014) as an example approach for proactive risk assessment is seen as a formalized understanding of the potential expansion of its utility as an initial step in the risk management process for NMs. This value has also been seen in research as both the valuation of "unknowns" for the risk factors as well as the relative valuation of each risk factor within the CB Nanotool, which affords a path forward in the face of the paucity of IH experts on the topic of NM in industry and decades-long issues of obtaining appropriate information on potential health effects relating to NMs. The CB Nanotool was designed in a way that also affords users an opportunity to revisit their evaluation once more knowledge is obtained on any or all of the risk factors deemed "unknown" in the initial qualitative evaluation. In the same manner, the tool itself can be updated in terms of any and all of its individual risk factors as more research on the adverse effects of NMs becomes more standardized in publications.

Consideration is now being given for a CB Nanotool approach for NMs within industry as opposed to R&D. First and foremost, the mass utilized will more likely be orders of magnitude greater than the mass typically used in R&D applications and may therefore be the primary factor affecting variations in the probability of exposure among the different activities. Perhaps here the weighting and scores for both mass and dustiness/mistiness can be increased by reducing, or perhaps eliminating, the number of employees factor. To aid in consistency for the scoring inputs of an industrial CB Nanotool strategy, there should be process specific information that is uniform to manufacturing. As proposed in research, there should be task-based "airborne" factors derived by industry for standardization (Schneider, 2008). The utility of "dustiness" within a set range is already a uniform application in many CB strategies and exposure models (Tielemans et al., 2008; Zalk and Nelson, 2008). In addition, quantitative evaluations of control effectiveness should be considered an essential part of the validation effort. However, perhaps in a manufacturing process, there should also be the expectation of SDSs for the product to be used and that the SDS would be designed to communicate both NM and PM parameters that could be directly transferred into an industrial CB Nanotool.

6.8.1 SDS Improvement

The majority of SDSs for NMs, if they are available, provide the majority of their environmental health and safety information based on the bulk PM. The opportunity for SDSs to become an integral part of NM risk assessment, exposure prevention, and risk management needs to be addressed. The majority of chemical control CB strategies utilize R-phrases as inputs to the toolkit in order to derive appropriate controls and reduction of work-related exposures (Zalk and Nelson, 2008). The majority of NM experts agree that research parameters affording comparisons and sharing of findings is a primary requirement

for controlling exposures (Warheit et al., 2008; Yang et al., 2008; Liao et al., 2009). In practice, the toxicologic information available on nanoparticles is minimal and will require deference toward "unknown" for an individual NM property until this standardization occurs. The real question is not when will this information be put forward but whether it will be put forth in a consistent manner that will be useful and interpretable for future users of the CB Nanotool. Currently, the research publications that are in circulation seem to be more appropriate for expert dissemination and not necessarily for health and safety professionals in general, let alone managers and technicians (Zalk and Heussen, 2011). The request for uniformity of NMs, captured in a database of set research parameters, should also be listed on SDSs, which would afford users of the CB Nanotool the latest and most accurate input factors for product appropriate hazard information that would lead to a process specific risk assessment.

6.8.2 CB Nanotool within Risk Management Programs

As part of the LLNL's comprehensive nanotechnology safety program, the CB Nanotool plays a central role in assessing risk and determining controls for all activities that involve unbound engineered nanoparticles. The CB Nanotool outcomes not only provide documented risk assessments for the activities, which are integrated into LLNL's institutional integrated safety management program but also form the basis for both engineering and administrative controls as part of a holistic risk management process. The engineering control requirements are based on the RL outcome, which determines the control band (e.g., containment, local exhaust ventilation, etc.). In terms of administrative controls, the CB Nanotool results are used, in addition to SDSs, to communicate hazards pertaining to the specific nanomaterials that are being handled or transported, onsite or offsite. The CB Nanotool outcomes also provide the basis for exposure assessment and medical surveillance requirements. Consistent with a risk-graded approach, air monitoring using real-time nanoparticle measurement devices and offline filter cassettes for morphologic analysis are required for RL 3 and RL 4 activities. Nanoparticle workers are also grouped into two medical surveillance programs based on whether they conduct RL 1/2 activities versus RL 3/4 activities. The higher risk medical surveillance program requires periodic evaluations (every 2 years) in addition to the baseline evaluation that is required for all nanoparticle workers. Specific medical tests may also be specified for the higher risk groups. Also included within this risk management program are requirements for labeling, signage, training, and environmental expectations for managing NMs within waste streams and response to spills.

6.9 Conclusion

The need for standardization of toxicologic parameters has been emphasized by researchers in nanotoxicology to afford better utility and consistency of research with NMs as their use and

exponential growth in application continue. A standardized database of toxicologic research findings harnessed and presented in a format, preferably captured in SDSs, and feeding directly into the CB Nanotool's severity and probability risk matrix would be an important step toward achieving this standardization. Making the latest research available for experts and practitioners alike in this manner would play an important role in the protection of workers in the nanotechnology industries. The CB Nanotool's structure, weighting of risks, utility for exposure mitigation, and improvements place the CB Nanotool in the middle of directing the research still to come, maximizing its effectiveness for all those involved in the nanotechnology industries. Perhaps it is the CB Nanotool's overall utility that has led to its recommendation for use at the international, national, and local levels and the consideration of its adoption by the ISO (2014) and directly into national regulations. At the scientific level, the CB Nanotool's approach has been found by numerous researchers to have the potential to offer the greatest utility to NM producers at both the micro- and macro-levels. However, it should be recognized that CB toolkits must always be used with some degree of caution. The different factors considered, weighted, and influencing the overall risk levels and control bands are determined as "educated guesses" as to factor importance and range delineation. Any qualitative risk assessment requires frequent use, validation, and evaluation of recommended control effectiveness. The authors, therefore, strongly encourage the further utilization of this or other similar tools for a wide range of applications because these efforts will undoubtedly improve and refine the tool.

CB strategies have been known over decades to offer a simplified control of worker exposures when there is an absence of firm toxicologic and exposure information and the nanotechnology industry fits this classification perfectly. The overwhelming uncertainties of work-related health risks posed by NMs have appropriately led many experts to suggest CB as a solution for these issues. The CB Nanotool was created to fulfill this request and its applications internationally continue to grow. As presented, the CB Nanotool has been developed, implemented, and been proven to afford a qualitative risk assessment toward the control of nanoparticle exposures. In addition, the international evaluation and use of the CB Nanotool reflects on its need, its possibilities, and its potential. Continuing expansion of its use, evaluation, and validation will assist in ensuring that risk assessments by NM users are accurate, accessible, and affordable, which would ultimately assist in protecting workers as the science of nanotechnology grows.

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CHAPTER 7

Controlling Nanoparticle Exposures

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Chapter Outline

7.1 Introduction

In many cases, assessing nanoparticle exposures establishes a need to control the exposures should they present unacceptable risks to human health. The Merriam-Webster Online Dictionary (2010) defines the verb form of "control" as "to reduce the incidence or severity of especially to innocuous levels." When exposures exceed innocuous levels (e.g., greater than occupational exposure limits), control measures must be instituted to reduce the concentrations. The success of these measures to control exposures must be

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determined by reassessing exposure concentrations. If concentrations still pose unacceptable risks, then additional control measures may be warranted.

This chapter focuses on control measures for airborne nanoparticles in work environments. First, the hierarchy of control measures is presented and ways to prioritize control options within that hierarchy are discussed. Then, the suitability of different types of control measures to reduce nanoparticle exposures is considered, with particular emphasis on the ability of filters to capture airborne nanoparticles.

In practice, airborne nanoparticles may occur individually or as aggregates—chains of multiple nanoparticles. Nanoparticle aggregates are large particles, for which many control options are available. In contrast, individual nanoparticles may be closer in size to gas or vapor molecules than they are to super-micrometer particles. Therefore, measures that are used to control exposures to gases and vapors may be appropriate for controlling exposures to individual nanoparticles. A recurring theme in this chapter is that many of the control measures that are presently used to control exposures to gaseous and particulate pollutants can be implemented successfully for nanoparticles. Novel control methods are generally not necessary to reduce exposures to below innocuous levels.

7.2 The Hierarchy of Control

Figure 7.1 illustrates the hierarchy of control. The hierarchy provides a preference ranking for broad categories of control measures in the absence of mitigating factors such as cost or availability. Elimination—the complete removal of a hazardous agent from the workplace—is on the top tier of the hierarchy because the exposure potential is eliminated completely. Prohibition of smoking in a restaurant or bar illustrates this concept in that

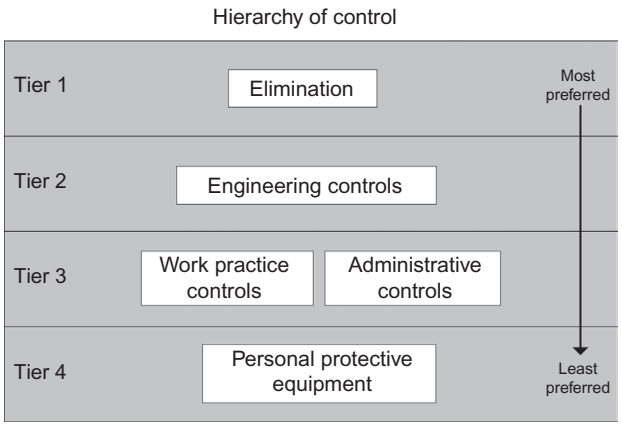

Figure 7.1
A conceptual diagram of the hierarchy of control.

workers have no opportunity for exposure to environmental tobacco smoke. Nanoparticles, however, are often produced or incorporated into a process or product because of their unique, beneficial properties imparted by their size. Therefore, elimination is often impractical for nanoparticles without decreasing the value or functionality of the process or product.

Engineering controls are physical, chemical, or biological changes made to a process or a product that reduce human exposure to a hazardous agent. These measures are second in the hierarchy because, although not eliminating the agent from the workplace, they offer reduced exposures particularly for those workers at risk without placing the responsibility of implementation on the exposed workers. Engineering controls include substitution of a less hazardous material or process step for one that is more hazardous, automation of a process, isolation of a hazardous process or product from workers or the workers from the process or product, and ventilation with or without the use of air pollution control equipment. Engineering controls are among the most frequent measures used to reduce exposures to airborne nanoparticles.

Work-practice controls are changes in how work is performed to reduce exposures. For example, a wet mop instead of a broom can be used to clean dusty floors, while dramatically reducing the resuspension of potentially hazardous powders. These kinds of measures are lower in the hierarchy than engineering controls because they rely on management to institute these changes and on workers to implement them. However, work-practice controls can be broadly effective when implemented properly.

Administrative controls are changes in when or by whom work tasks are performed. For example, a change to conduct tasks with high exposure potential from day to night may place substantially fewer workers at risk. Similarly, workers can rotate through tasks with varying exposures to distribute health risk among several workers so that no one worker will receive a dose of a potentially harmful agent that presents an unacceptable risk. Administrative controls are lower in the hierarchy than engineering controls because they do not reduce the dose each time a worker performs the tasks. These measures may spread the dose around among several workers, or they may reduce the number of workers nearby at the time the tasks are performed. One advantage of administrative controls is that the responsibility for change is not placed on each worker individually. However, the role of a supervisor is critical to ensure that changes are carried out according to plan.

Personal protective equipment (PPE) is a device or clothing worn by workers to reduce their exposure to potentially hazardous agents. This control measure is lowest on the hierarchy of control because PPE does nothing to eliminate the hazard from the workplace and places responsibility on the workers to don and use the PPE properly every time they wear it. Examples of PPE include respiratory protection, chemical protective clothing, gloves, and protective eyewear.

7.3 Criteria for Prioritizing Control Options

With all else being equal, control measures on higher tiers of the hierarchy are preferable to those on lower tiers. However, other factors—especially cost—may make options higher in the hierarchy unacceptable, and options lower on the hierarchy might need to be considered. Measures from multiple tiers may be instituted together to provide larger reductions in exposures than possible with individual measures. Even within each tier, selections among several control options may need to be made. Therefore, additional criteria for choosing from among control options may need to be considered.

The effectiveness of the control measure may be the most relevant factor to consider. A control measure that reduces nanoparticle exposures by 90% will be more effective than one that reduces concentrations by 50%. Effectiveness may be especially important if exposures must be reduced to reach an occupational exposure limit (OEL). Typical examples of engineering controls that have different effectiveness are local exhaust ventilation (LEV) systems that include full enclosures around a process versus LEV systems that include an exhaust opening adjacent to, but not surrounding, a nanoparticle generation source. A well-designed enclosure provides better capture of nanoparticles than an adjacent duct opening.

Cost is also one of the most important criteria when selecting among several control measures. Two primary components must be considered: (i) the capital costs required to install a measure and (ii) operating costs after the measure is implemented. Capital expenditures include capital costs and installation costs for pieces of equipment. Operating costs may include energy-related expenditures, parts, labor costs for maintenance, and labor costs for tasks that may take longer in PPE or if different work practices are used. Engineering control measures may be deemed unfeasible due to costs, or a low-cost LEV system with a duct opening adjacent to the nanoparticle generation source may be considered effective enough if it costs much less than an LEV system with a full enclosure around the source.

Several other factors should be considered when prioritizing control options. These factors include:

- *Reliability:* Is the potentially hazardous agent so toxic that you need a control measure that has little risk of failure? Should you implement redundant control measures in case one fails?
- *Exposed populations:* Do you need to consider protecting the public in addition to workers? Do some control measures protect a larger proportion of the workforce than others?
- *Exposure setting:* Are you concerned about exposures in just certain parts of the facility, such as the packaging area? Do you need to worry about exposures of your customers?

- *Frequency of exposure:* Are you producing product continuously or is the equipment adjusted between batches? Are you instituting control measures for tasks that are undertaken only a few times a year for which costly measures may not be feasible?
- *Acceptability of intervention:* Does an intervention make it difficult to control a process? Does a control measure make it difficult for a worker to perform certain tasks?

Integrating these factors together with the hierarchy of control and information on effectiveness and costs helps occupational health specialists select a control measure or a combination of several measures that best suits a particular situation.

7.4 Form of Nanomaterials

Airborne nanoparticle exposures can be reduced substantially if nanomaterials (NMs) are placed in a form that makes aerosolization difficult. For example, exposures can often be reduced by handling a liquid suspension of nanoparticles compared with a dry powder. Similarly, nanoparticles incorporated into a polymer matrix are difficult to remove from that matrix. Bello et al. (2009) investigated the cutting of composites of carbon and alumina fibers in an epoxy resin. Carbon nanotubes were included in some of the composites but not in others. Although particle number concentrations increased dramatically as cutting occurred, concentrations were similar or lower when the nanotubes were part of the composite than when they were excluded. There was no evidence that individual nanotubes were aerosolized when they were present.

7.5 Local Exhaust Ventilation

Local exhaust ventilation involves the capture of air contaminants at a source. A local exhaust ventilation system consists of a hood or enclosure to capture a contaminant, an air pollution control device to clean the air, and an air mover to provide air flow through the system. These systems range from small portable units, such as a high-efficiency particulate arrestance (HEPA)-vacuum system (Figure 7.2a), to extensive, permanent installations typical of large industrial facilities (Figure 7.2b).

As illustrated in Figure 7.3, two forms of capture are most relevant to the control of nanoparticles: exterior hoods and ventilated enclosures. Exterior hoods require exhaust sufficient to draw particles into the hood opening. In contrast, enclosures surround the source of airborne nanoparticles and typically require low air flow to prevent particles from escaping through the openings in the enclosure.

7.5.1 Exterior Hoods

Airborne nanoparticles tend to follow air streamlines in the absence of large temperature gradients, electrostatic fields, or magnetic fields. Consequently, nanoparticles are likely to

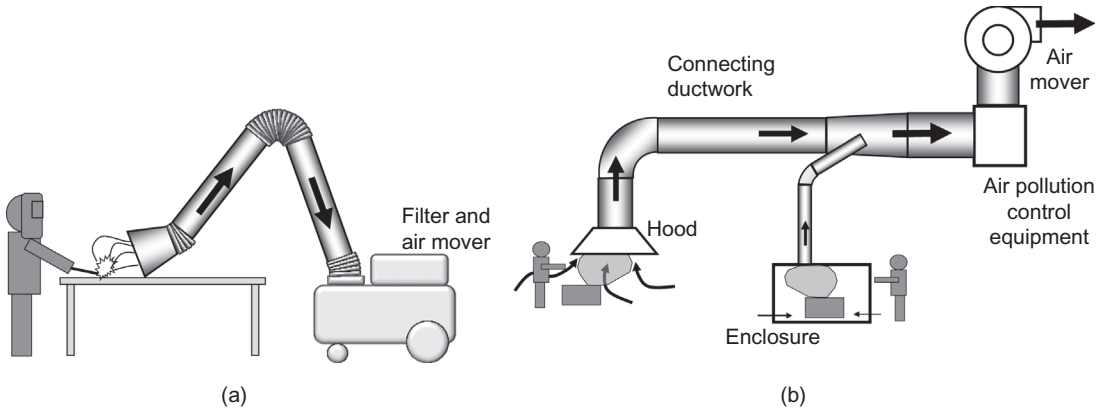

Figure 7.2
Local exhaust ventilation systems range in size from small, portable units such as those used for control of welding fume (a) to large, permanent installations (b).

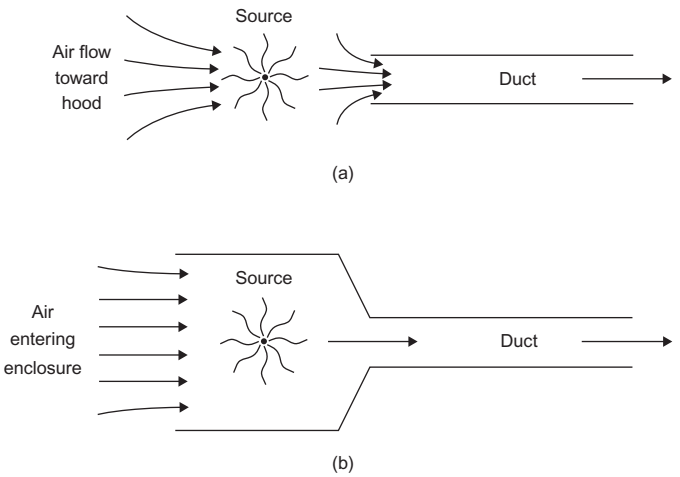

Figure 7.3
Conceptual diagrams of two types of local exhaust ventilation: (a) an exterior hood and (b) a ventilated enclosure.

be captured by an exterior hood to the extent that air is drawn into the hood (Schulte et al., 2008). Therefore, the goal of exterior hood design for effective nanoparticle capture is to draw in as much of the contaminated air as possible.

Design procedures for exterior hoods are largely empirical based on past experience in most cases, as described by the American Conference of Governmental Industrial Hygienists (ACGIH, 2013) and Burgess et al. (2004). Key factors that affect the design of an exterior hood are the size of the region across which nanoparticles are released into the air, the

distance from the hood opening to the release points, and the magnitude of air currents in the room that can interfere with the air flowing into the hood. The designer must first decide how large a "capture velocity" is required for the hood to overcome any air currents in the room and to ensure that the contaminated air is drawn into the hood. Then, the designer must determine the air flow that is necessary to achieve that capture velocity given the opening size of the hood.

Exterior hoods can be used effectively for the control of nanoparticle exposures. Old and Methner (2008) measured the airborne particle concentrations during cleanout of a reactor for producing metal catalytic NMs with and without an exterior hood. As shown in Figure 7.4, the exterior hood consisted of a portable fume extractor with a round, flanged opening positioned adjacent to the cleaning process. Airborne concentrations were reduced from 75% to 96% by mass and from 85% to 100% by number.

Several issues may compromise the effectiveness of an exterior hood. A selected capture velocity that is too low or one that requires the hood to be positioned closer to the source than is practical can lead to incomplete capture of nanoparticles. Frequently, nearby workers may disrupt air flow into an exterior hood. For example, real-time measurements were made of the ability of an exterior hood to capture engineered nanoparticles dried as a thin nanopowder on a support belt in a machine as the nanopowder separated from the belt and dropped into a hopper. During most periods, nanoparticle concentrations were indistinguishable from background particle concentrations. However, nanoparticle concentrations rose markedly each time the machine operator checked on the process, indicating that the operator drew contaminated air away with her as she left the machine.

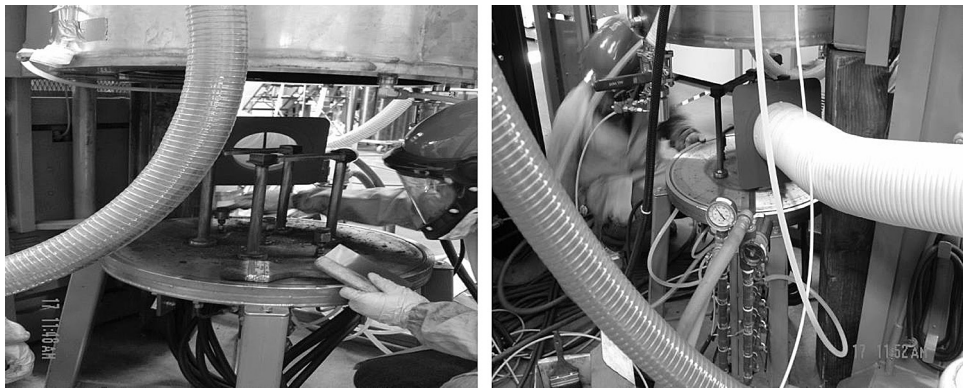

Figure 7.4
Photographs of an exterior hood from a portable fume extractor used to collect particles produced during the cleaning of a reactor that produced nanoscale metal catalytic materials. *From Old and Methner (2008).*

7.5.2 Ventilated Enclosures

Examples of ventilated enclosures include booths and tunnels in production processes and laboratory hoods in research facilities. Enclosures are superior to exterior hoods for two reasons. First, enclosures contain emitted particles at the point of their release rather than drawing them from within the workplace into the LEV system. Second, compared with exterior hoods, enclosures require substantially lower air flows because they must ensure only that particles do not escape from openings in the enclosure. Openings include those present at all times and additional ones that may be created as workers interact with the process, such as a door or access port. Examples of these interactions could include a researcher opening a sash on a laboratory hood or a production operator entering a panel to make an adjustment to a piece of equipment.

In most cases, enclosures are designed so that the velocity at the face of any openings is in the range of 0.5–1.0 m/s (100–200 ft/min) (Burgess et al., 2004). For laboratory hoods, face velocities of about 0.5 m/s (100 ft/min) are typical because higher velocities tend to create eddies in front of workers standing at the openings to hoods. These eddies can draw contaminated air out of the hood into the worker's breathing zone (Kim and Flynn, 1991). Other design considerations include making the enclosure as complete as possible and ensuring that airflow is distributed as evenly as possible across openings (Burgess et al., 2004).

Fume hoods are an essential engineering control to protect those working with NMs in laboratories (NIOSH, 2012). However, the hoods must be operated properly to ensure maximum protection of the workers. Tsai et al. (2009a) evaluated the ability of a conventional constant-flow laboratory hood with its sash set to different heights to contain airborne nanoalumina particles generated by a pouring operation. Nanoalumina particles escaped the hood when a low sash produced a high face velocity of 1.0 m/s (200 ft/min), but not at higher sash heights when face velocities were only 0.6 m/s (120 ft/min) and 0.4 m/s (80 ft/min). Thus, having too high a face velocity is disadvantageous for controlling nanoparticles generated in a hood.

Some types of laboratory hoods contain nanoparticles more effectively than others. In constant-velocity hoods, also called *variable air volume* hoods, fan speed is varied as sash height is changed to maintain constant velocity at the hood face. Tsai et al. (2009b) demonstrated that at least 99.4% of nanoscale particles generated by a reactor producing single-walled carbon nanotubes (SWCNTs) or multiwalled carbon nanotubes (MWCNTs) were contained by a constant velocity laboratory fume hood. In air-curtain hoods, a sheath of clean air flow is passed downward across the face of the hood to more effectively separate the worker from the contaminant in the hood. Tsai et al. (2010) observed effective containment of nanoparticles during transfer and pouring of nanoalumina using a constant-velocity hood operating with a face velocity of 0.5 m/s (100 fpm) and an air-curtain hood, but not with a

conventional constant-flow hood. When the sash of the constant-velocity hood was opened to its high level, the 0.5 m/s face velocity could not be maintained, allowing nanoalumina particles to escape when poured. Cena and Peters (2011) observed that a biosafety cabinet with an air curtain reduced respirable dust concentrations for workers sanding a nanocomposite containing MWCNTs much more effectively than a constant-flow, custom-built fume hood.

Schulte et al. (2008) discussed ventilation of nanoparticles according to different types of workplaces: research settings, development facilities, and production/manufacturing. Laboratory hoods are typically available and readily used in research settings, whereas full enclosures are often appropriate for production/manufacturing-scale operations. For development activities such as laboratory scale-up, process development, and product development, frequent modification to operations may preclude the use of full enclosures, and reliance on exterior hoods is more common. However, as stated earlier, the effectiveness of exterior hoods is dependent on proper placement in relationship to the nanoparticle generation source. Consequently, the effectiveness of exterior hoods should be assessed more frequently than other hood types.

7.6 Air Pollution Control Devices

A variety of control measures are available for removing particles from contaminated air streams. The most common technologies include gravitational settling, centrifugal collection, wet scrubbing, electrostatic precipitation, and filtration. Of these devices, electrostatic precipitation and filtration are typically used for nanoparticles and will be discussed further. Gravitational settling units and centrifugal collectors, such as cyclones, are only effective for removal of large particles (nominally >10 μm). Wet scrubbers are typically not selected for nanoparticles because they require treatment of water before discharge and are generally considered ineffective for particles smaller than 500 nm in diameter (ACGIH, 2013).

7.6.1 Electrostatic Precipitators

Electrostatic precipitators (ESPs) operate by charging incoming particles in high-voltage environments. As shown in Figure 7.5, two primary configurations are available in electrostatic precipitation: single-stage and two-stage collectors. In a typical single-stage collector, particle-laden air moves through a series of highly charged wires strung between grounded plates. The particles are charged by the electrical fields and the ions generated by the charged wires and then migrate toward and collect on the grounded plates. In a typical two-stage collector, particles are charged in a short, first-stage charging section with a geometry similar to the single-stage collector. Particles are then collected in a second stage that has alternating charged and grounded plates. The collection efficiency of two-stage ESPs is often higher than single-stage ESPs because the collection plates can be operated much closer together.

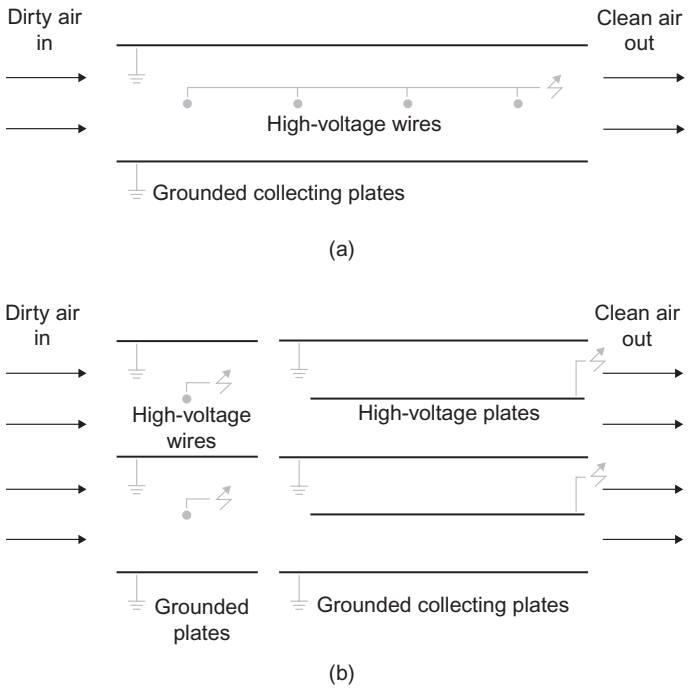

Figure 7.5
Conceptual drawings of (a) a single-stage electrostatic precipitator (ESP) and (b) a two-stage ESP.

In ESPs, field charging is the predominant mechanism for charging particles with diameters larger than 1 μm, whereas diffusion charging is predominant for particles smaller than 100 nm (Hinds, 1999). However, particles a few hundred nanometers in diameter are more difficult to collect by electrostatic precipitation because the combined mechanisms are not as effective as at larger or smaller sizes. In addition, applying charge to particles smaller than about 75 nm in diameter is challenging, leading to decreases in efficiency for the smallest nanoparticles when ESP voltages are not sufficiently high (Zhuang et al., 2000).

Huang and Chen (2002) studied the ability of both single-stage and two-stage ESPs to capture nanoparticles under a variety of operating conditions. As shown in Figure 7.6, they were able to collect nanoparticles with close to 0% penetration (100% collection efficiency) in both configurations at high voltages. These researchers concluded that a two-stage ESP was more economical to collect particles larger than 16 nm in diameter, whereas a single-stage ESP was more efficient for smaller particles.

Cost considerations generally limit single-stage systems to large applications such as power plants (Burgess et al., 2004). Two-stage precipitators can be found in heating, ventilating, and air conditioning (HVAC) systems, as stand-alone units designed to collect pollutants such as smoke or welding fumes, and as part of some LEV systems. However, they are less

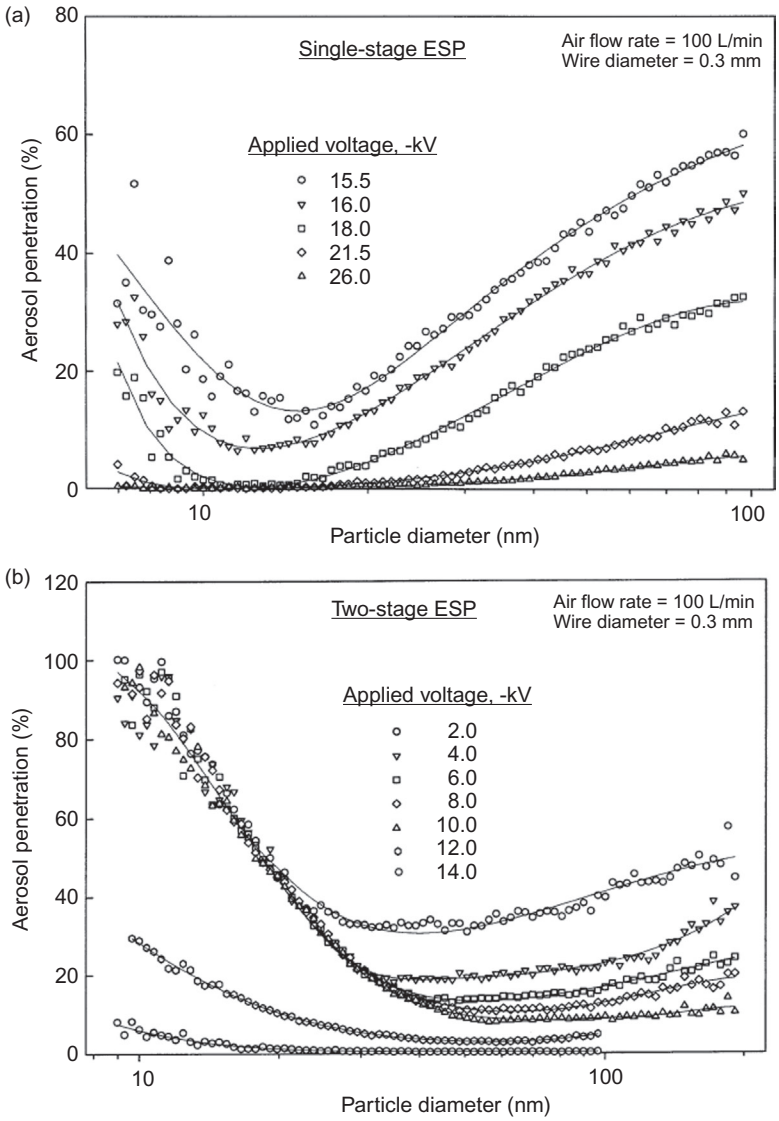

Figure 7.6
Particle penetration versus diameter for (a) single-stage and (b) two-stage electrostatic precipitators (ESPs) over a range of applied voltages. *From Huang and Chen (2002).*

prevalent than filtration systems for several reasons. First, relatively few manufacturers sell precipitators that are suitable for workplaces. Second, they are typically more expensive to purchase than equivalent filtration systems, although their operating costs are usually lower because of a lower resistance to air flow. Third, the collection plates must be cleaned regularly or the precipitator will lose efficiency. This may be a special difficulty with nanoparticles that

tend to stick well to surfaces. Systems are available for washing the plates, but then the wash water requires treatment before discharge.

7.6.2 Air Filters

Air filtration is relatively easy and flexible to implement, making it widely used throughout nanotechnology. Fabric and fibrous filters are used for airborne particle control. Fabric filters are composed of woven and felted fabrics that collect particles primarily on a dust cake that develops over time on their surface. They are frequently used in large industrial applications in the form of bags that are hung within a large housing. Fibrous filters, used more frequently in workplace applications, consist of a nonwoven mat of individual fibers oriented randomly and perpendicular to air flow. Particles are frequently collected throughout the depth of a fibrous filter rather than just on its surface. The range of fiber diameters for a given filter is usually broad, and these diameters can range from smaller than 1 μm to several hundred micrometers. Fibers are made from a variety of materials, including fiberglass and various polymers. Investigators have studied the mechanisms by which fibrous filters collect particles theoretically, experimentally, and using numerical modeling.

The most predominant mechanisms contributing to particle collection are interception, inertial impaction, and diffusion. Interception occurs when a particle moving with air flow around a fiber passes within one particle radius of the fiber. Larger particles are collected with higher efficiency by interception than smaller particles because of their larger radius. In inertial impaction, the inertia of a particle causes it to persist in moving toward and hitting a fiber rather than following the curved streamlines around the fiber. Collection efficiency by impaction increases with particle diameter squared. Collection of particles by diffusion is caused by Brownian motion, the irregular jittering of an airborne particle caused by constant bombardment by air molecules. This jittering sometimes causes a particle to hit a fiber as it moves with air flowing around the fiber. Because Brownian motion increases as particle diameter decreases, the capture of particles by diffusion increases as particle size decreases.

The net effect of these forces is presented in Figure 7.7, which shows a typical curve for collection efficiency as a function of particle size. Particle collection efficiency is high for large particles because of interception and inertial impaction and for small particles because of diffusion. However, these collection mechanisms are minimally effective together for particles around 200–300 nm in diameter, resulting in a minimum efficiency. The particle diameter at which the minimum efficiency occurs is termed the most penetrating particle size (MPPS).

In certain situations, electrostatic attraction and gravitational settling may also contribute to particle capture. Although gravitational setting is negligible for nanoparticles, electrostatic attraction can be important for particles of all sizes. Electrostatic attraction can be used to enhance collection efficiency of filters by attaching permanent electrostatic charges to

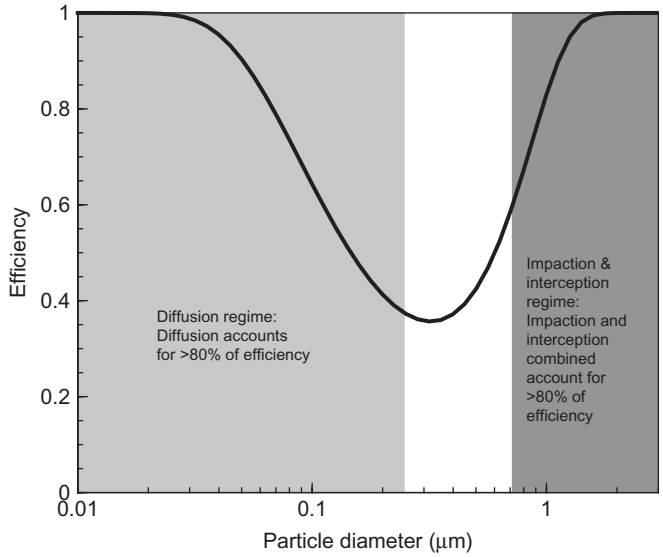

Figure 7.7
Filter efficiency as a function of particle diameter predicted from theory for a conventional fibrous filter having a uniform fiber diameter of 5 μm, a packing density of 0.05, a thickness of 2 mm, and operating at an air flow velocity of 10 cm/s. Particle density is 1 g/cm^3. The diffusion and impaction/interception filtration regimes are indicated on the figure.

synthetic polymer fibers. The charged fibers attract oppositely charged particles and induce a temporary dipole in similarly charged particles. Both phenomena move the particle closer to the fiber as the air passes through the filter, thereby increasing collection efficiency. Properly designed electrostatically enhanced filters have higher efficiency than conventional filters for the same resistance to air flow, or less resistance to air flow for the same efficiency. Capture by electrostatic attraction increases with particle diameter, leading to a smaller MPPS for filters made with charged fibers (typically 40–100 nm) compared with those made with noncharged fibers (Brown, 1993; Rengasamy et al., 2009).

Wang and Kasper (1991) suggested that nanoparticles smaller than 10 nm may be sufficiently small and have enough Brownian motion to act like air molecules rebounding from a fiber rather than sticking to it. Balazy et al. (2004) presented experimental results which suggested that rebound occurred for particles smaller than 20 nm in diameter. However, Heim et al. (2005) showed that the condensation particle counter used by Balazy et al. had low and potentially inconsistent counting efficiency for particles smaller than 12 nm in diameter. These authors used other instruments that indicated that the measured efficiency matched the theoretical efficiency and exhibited no sign of rebound for particles as small as 2.5 nm in diameter. Measurements by Kim et al. (2007) showed no rebound for particles larger than 2 nm in diameter. As shown in Figure 7.8, Kim et al. (2006) observed an increase in

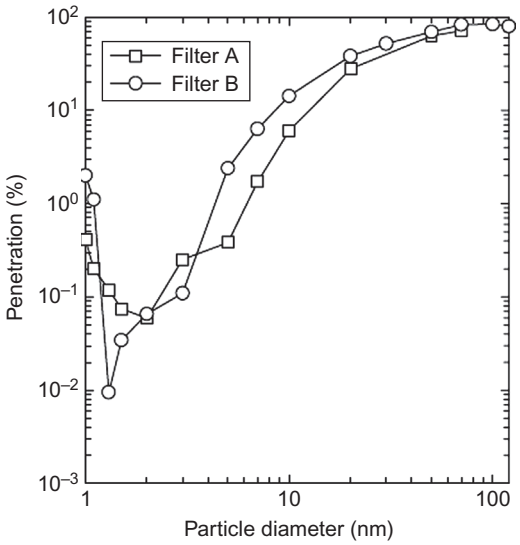

Figure 7.8
Filter penetration as a function of particle diameter for two test filters. *From Kim et al. (2006).*

penetration, which is a decrease in efficiency, for two filters, but only for particles smaller than 2 nm in diameter.

The evidence is clear that particle rebound occurs only for particles smaller than about 2 nm in diameter. In most real-world situations, particles with diameters 2 nm or smaller will not be present in an atmosphere for long because they tend to agglomerate quickly, effectively becoming larger particles that can be readily filtered. HEPA filters are available that have efficiency ≥99.97% even at the MPPS. For particles with diameters between 2 nm and the MPPS, HEPA filter users should be confident that the efficiency will be at least 99.97% when the filter is new and installed correctly.

Filtration measurements indicate that nonspherical nanoparticles are collected effectively by filters. Seto et al. (2010) found that MWCNTs with mobility diameters of 200–300 nm were collected with higher efficiency compared with spherical particles having the same mobility diameter. Similarly, Kim et al. (2009) observed that agglomerated particles having mobility diameters from 100–300 nm were collected at higher efficiency than nonagglomerated spherical particles with the same mobility diameter.

Most nanoparticles remain trapped on filter fibers when filters are changed. However, some may become airborne, especially for filters that are heavily loaded with particles, presenting an important exposure risk to maintenance personnel. The National Institute for Occupational Safety and Health (NIOSH, 2013) recommends removing air filters that have collected NMs directly into plastic bags to reduce exposures during filter change-outs. Some manufacturers

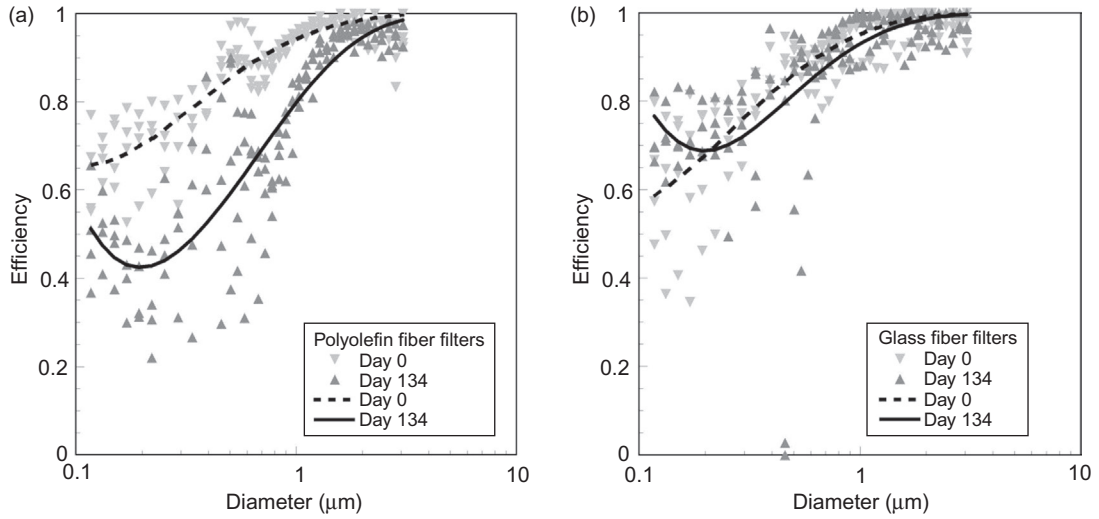

Figure 7.9
Filter efficiency as a function of particle diameter for filters made from (a) synthetic polymer fibers carrying electrostatic charge and (b) conventional glass fibers when the filters are new and clean (Day 0) and after 134 days of use. *From Raynor and Chae (2004).*

sell bag-in/bag-out housings to facilitate this procedure. Maintenance workers should wear appropriate PPE during this task.

7.6.3 Filter Performance Over Time

As filters collect particles, their performance has the potential to change. Raynor and Chae (2004) and Raynor et al. (2008) found that the efficiency for filters made from synthetic fibers that carried electrostatic charge declined dramatically for particles with diameters between 100 nm and 3 μm as the filters collected atmospheric particles. Fiberglass filters collecting the same atmospheric particles exhibited essentially no change in efficiency. The results from Raynor and Chae (2004) are presented in Figure 7.9. The likely explanation for the efficiency decrease for the synthetic filters is that the charges on the fibers were blocked and made ineffective by the collected particles.

Raynor and Chae (2003) showed that the efficiency decline for synthetic filters occurred as the filters collected atmospheric particles comprised primarily of nanoscale particles, but not when filters were loaded with particles primarily larger than 1 μm in diameter. This suggests that synthetic filters collecting nanoparticles in workplaces may experience efficiency reductions as they are used. Until measurements are performed to determine how important these efficiency reductions are for nanoparticles in workplace environments, a conservative approach should be taken by assuming that efficiency reduction will occur to some extent for

filters made from synthetic fibers carrying electrostatic charges. For the purposes of control, fiberglass filters are a safer approach for capturing nanoparticles with a consistent efficiency over time, even though they have greater resistance to air flow than electrostatically enhanced filters with the same initial efficiency.

For most workplace applications, filters are the best collection method for capturing nanoparticles from air streams. Theory and measurements both indicate that HEPA filters made from fibers that do not carry electrostatic charges will collect nanoparticles with high efficiency both when the filters are new and after they have been used for a long period. The lifetime of these filters is likely to be limited primarily by increases in pressure drop across the filters as particles continue to load onto them. As in other applications, filters must be seated properly in their housings to prevent leakage of contaminated air around the filters.

7.7 Work Practices

The way that nanopowders are handled can influence the generation of nanoparticles in dry operations. In general, more airborne particles are generated when greater energy is part of a powder handling process. The height from which a powder is dropped during handling is typically the most important factor dictating particle aerosolization during handling because it is strongly correlated to the energy imparted to the powder (Plinke et al., 1995). Tsai et al. (2009a, 2010) found that transferring nanoalumina powders with a spatula generated fewer airborne nanoparticles than pouring the same quantity of powder. Not surprisingly, these authors also observed that handling smaller quantities of powder reduced the concentrations of airborne nanoparticles. Process design is a critical determinant of exposure. At one site, Heitbrink et al. (2015) reported that worker exposures to airborne nanoparticles were virtually eliminated by simply waiting 30 min before harvesting nanographene product at the end of a batch process.

NIOSH (2009) offers an excellent summary of work practices to consider when cleaning areas where tasks with NMs have occurred. Work surfaces should be cleaned at least once per shift to prevent buildup of particles that could be transferred to the worker. Whenever possible, damp cleaning methods should be utilized to keep deposited nanoparticles from being resuspended. In particular, activities such as dry sweeping and using compressed air to blow off a surface should be avoided. A wet mop or sponge is better for cleaning floors and surfaces. If surfaces must be vacuumed, only vacuum cleaners with certified HEPA filtration should be used. In addition, the vacuuming should occur without vigorous rubbing of the surface being cleaned.

Suitable hygiene practices can also contribute to reduction in worker exposures to nanoparticles (NIOSH, 2009). Before eating, drinking, smoking, or leaving the workplace, workers should wash their hands thoroughly. Showering and changing clothes before leaving

work can prevent transfer of NMs from the workplace to the home environment. Food and drink should not be consumed or stored in locations where NMs are handled. Storage containers for NMs should be sealed tightly, whenever possible.

7.8 Personal Protective Equipment

NIOSH (2009) recommends the use of protective clothing and gloves to prevent dermal exposures to nanoparticles, especially to cover skin that is injured. Respiratory protection may be required if airborne nanoparticle concentrations are above exposure guidelines. Eye protection should generally be worn in laboratory and industrial settings; splash protection may be needed for the eyes if NMs are contained in liquid suspensions. Table 7.1 presents a list of the types of PPE that might be utilized to reduce worker exposure to nanoparticles along with a description of different options available and situations in which each might be used.

Table 7.1 Types of personal protective equipment (PPE) frequently used when working with nanoparticles

Category of PPE	Specific Types Available	Common Uses
Gloves	Work gloves	• Partial barrier to nanopowders • Limited protection against nanoparticle suspensions • Nanoparticles may penetrate or migrate through glove fabrics
	Thick, reusable, chemical-resistant gloves; many materials available	• Good protection against splash and immersion exposures to nanoparticle suspensions • Useful in production operations
	Thin, disposable nitrile or latex gloves	• High level of finger dexterity • Suitable for most laboratory work • Can be used under work gloves or thicker chemical-resistant gloves
Protective clothing	Laboratory coat	• Protects garments and skin from direct deposition of airborne nanoparticles or contact with nanopowders • Nanoparticles may penetrate or migrate through fabrics
	Liquid-resistant apron	• Protects clothing from splashes and sprays from nanoparticle suspensions • Coverage usually strongest for front of body and weaker for sides and back
	Disposable suits	• Protects skin and clothing from airborne nanoparticles and nanopowders • Provides protection against small amounts of splashing from nanoparticle suspensions • Can include integral hoods and foot coverings

(Continued)

Table 7.1 Types of personal protective equipment (PPE) frequently used when working with nanoparticles (Continued)

Category of PPE	Specific Types Available	Common Uses
Eye protection	Safety glasses	• Protects eyes against small direct splashes from nanoparticle suspensions • Unsuitable for protection against sprays or large splashes because glasses do not fit tightly to face • Provides impact protection
	Tight-fitting goggles	• Protects eyes against splashes and sprays from nanoparticle suspensions and against secondary exposures from liquids on face • Unvented goggles prevent any penetration of liquids into interior of goggles
	Face shields	• Provides protection to entire face against direct splashes from nanoparticle suspensions • Limited protection against sprays because shield does not fit tightly to face
Respiratory protection	Disposable filtering facepiece respirator	• Ideal for short duration tasks • N95 is the most common designation • Typically, the respiratory protection most readily accepted by wearers
	Half-mask or full facepiece elastomeric air-purifying respirators	• Fit of respirator to face can be checked easily each time the wearer puts the respirator on • Full facepiece respirators provide eye protection in addition to respiratory protection • Filter cartridges less susceptible to damage than filtering facepiece respirator
	Powered air-purifying respirator (PAPR)	• Provides high level of protection with a tight-fitting full facepiece • Loose fitting hoods, helmets, and facepieces can be used for workers with facial hair or scars • Filter cartridges less susceptible to damage than filtering facepiece respirator

7.8.1 Protective Clothing and Gloves

The ability of protective clothing materials to prevent penetration of nanoparticles is difficult to assess because no standard methods have been developed to test this property. Researchers have used filter test methods to evaluate particle penetration under the assumption that some air will flow through protective clothing as it flexes when the wearer moves. Golanski et al. (2009) measured particle penetration through three fabrics for particles ranging between 10 and 100 nm in diameter at a velocity of 0.6 cm/s through the fabrics. The results of their measurements are presented in Figure 7.10. Penetration across all fabrics and particle diameters ranged from 0.6% to 27%, indicating that a significant fraction of particles can penetrate a fabric with air flow. Penetration through a nonwoven high-density polyethylene

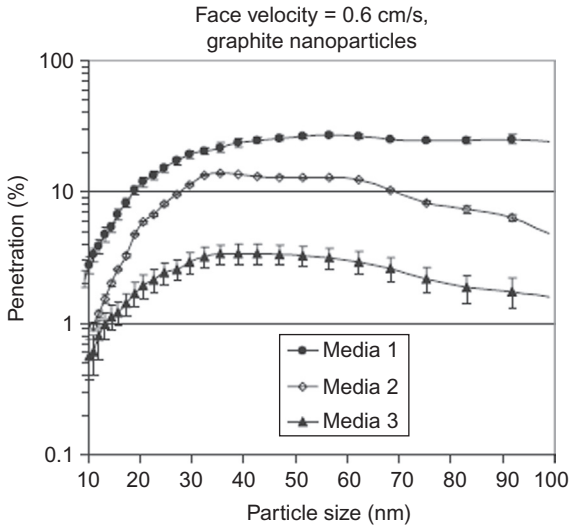

Figure 7.10
Penetration of woven cotton (Media 1), nonwoven polypropylene (Media 2), and nonwoven high-density polyethylene textile (Media 3) fabrics by graphite nanoparticles at a face velocity of 0.6 cm/s. *From Golanski et al. (2009).*

textile fabric was approximately an order of magnitude lower than penetration through a woven cotton fabric. Penetration through a nonwoven polypropylene fabric was in between.

Golanski et al. (2009) also measured the ability of various kinds and sizes of nanoparticles to pass through fabrics by diffusion in the absence of bulk air flow through the fabrics. These authors found that two distributions of graphite nanoparticles peaking at roughly 40- and 80-nm particles were able to penetrate through a woven cotton fabric at a rate 2500 times greater than through a nonwoven high-density polyethylene textile fabric. Similarly, penetration of 10 nm-diameter titanium dioxide (TiO_2) and platinum nanoparticles through a woven cotton fabric by diffusion alone was three orders of magnitude greater than penetration through a nonwoven high-density polyethylene textile fabric (Golanski et al., 2010).

Chemical-protective gloves should be worn when handling materials containing nanoparticles to protect the hands from exposure to dry particles or from splashing or immersion in suspensions containing nanoparticles. Golanski et al. (2010) measured the penetration of airborne TiO_2 and platinum nanoparticles 10 nm in diameter through 100-μm thick nitrile, 150-μm thick latex, and 700-μm thick neoprene gloves by diffusion. The researchers did not observe any particles penetrating the gloves. On the other hand, Vinches et al. (2013) found that nano-TiO_2 particles in a liquid suspension could pass through thin nitrile gloves after the gloves were repeatedly deformed to simulate use. Additional tests are needed to evaluate penetration of airborne particles and liquid particle suspensions through different types of gloves over long periods and with the gloves stretched to identify conditions for which gloves may not be sufficiently protective.

7.8.2 Respiratory Protection

If respiratory protection is required, the choice of respirator is made by comparing measured personal exposures to an occupational exposure limit. Until definitive and/or regulatory occupational exposure limits are widely available for airborne nanoparticles, ad hoc limits or benchmark exposure levels may be used for choosing a class of respirator. NIOSH has developed a "selection logic" to help users choose appropriate respiratory protection (Bollinger, 2004). The selection logic must be used in conjunction with the assigned protection factors in Table 7.2 to determine which levels of respiratory protection are acceptable for each nanoparticle application. Assigned protection factors (APFs) are specified in the United States by Occupational Safety and Health Administration rules to define the ability of a class of respirator to provide a particular level of protection taking into consideration both respirator fit to the wearer's face and penetration of particles through a filter or gases and vapors through a sorbent cartridge (OSHA, 2009). An APF is the factor by which a class of respirators can be expected to reduce exposure concentrations.

In most cases, the respirators used for personal protection against nanoparticles are air purifying respirators, respirators that pass air contaminated with nanoparticles through a filter material before it is breathed in by the wearer. Disposable filtering facepiece respirators use a filter material as the entire facepiece or as a primary part of the facepiece. Half-mask respirators have nondisposable elastomeric facepieces that cover the nose and mouth of the wearer and must be used with disposable filter cartridges that attach to the facepiece. Full-facepiece respirators cover the entire face, providing eye protection and better fit, while using the same kinds of filter cartridges as half-mask respirators. Powered air purifying respirators (PAPRs) use a battery-powered blower with intakes filtered by cartridges to provide a flow of air to a facepiece, which ensures outward flow around the facepiece should

Table 7.2 Assigned protection factors (APFs) for types of respiratory protection that are likely to be used to reduce exposures to airborne nanoparticles (OSHA, 2009)

Type of Respirator	APF
Disposable filtering facepiece respirator	10[a]
Half mask elastomeric air-purifying respirator	10[a]
Full facepiece elastomeric air-purifying respirator	50[a]
Half-mask powered air-purifying respirator (PAPR)	50[a]
Full facepiece PAPR	1000[a]
PAPR with helmet or hood	25/1000[b]
PAPR with loose-fitting facepiece	25

[a]Wearers must pass a fit test with this type of respirator to qualify for the APF.
[b]To qualify for an APF of 1000 for a specific model of PAPR with a helmet or hood, the employer must possess evidence provided by the manufacturer that testing of that model demonstrates that it can provide a level of protection of 1000 or greater.

it not fit tightly to the wearer's face. PAPRs can be used with tight-fitting or loose-fitting respirators, providing an option for those who cannot wear other air-purifying respirators because they cannot achieve a tight fit to the face due to facial hair.

In the United States, filters used in air-purifying respirators are designated by NIOSH using a letter and a number. The letter designations are as follows:

N = Not resistant to oil aerosols
R = Resistant to oil aerosols for 8 h
P = Oil-proof

The number designations are as follows:

95 = Achieves at least 95% filtration efficiency in NIOSH standard test
99 = Achieves at least 99% filtration efficiency in NIOSH standard test
100 = Achieves at least 99.97% filtration efficiency in NIOSH standard test

Respirator and filter combinations must be certified by NIOSH before they can be sold and utilized legally as respiratory protection. The designations of filters used most commonly are N95 and P100. The European Union has a similar series of designations in its regulations for respirators.

Respirators can only be used in the United States as part of a written respiratory protection program as indicated in 29 CFR 1910.134. The written program must be specific to the work site and have a named individual identified as its administrator. Important elements of a respiratory protection program include provisions for respirator selection and issuance, medical evaluations for wearers, initial and annual fit testing for wearers, proper respirator use, and inspection, cleaning, maintenance, and storage of respirators. Training must be provided to wearers on the hazard for which the respirator is being used and on the proper utilization of the respirator.

Most respirator filters utilize the three primary mechanical filtration mechanisms discussed earlier—impaction, interception, and diffusion—in addition to permanent electrostatic charges to provide capture of incoming particles at a relatively low resistance to air flow that makes breathing easier. Rengasamy et al. (2009) measured the penetration of eight models of filtering facepiece respirators, four sold in the United States and four sold in Europe, as a function of particle diameter. As shown in Figure 7.11, these authors found that the MPPS for these filters ranged from 30 to 60 nm. All filters performed to their rated designations. When the same filter models were exposed to isopropanol to dissipate the electrostatic charges, the MPPS shifted to the 200–300 nm range and particle penetration far exceeded the ratings for the filters.

The findings of Rengasamy et al. (2009) suggest that any process that could block or render ineffective the electrostatic charges on the filters could lead to unacceptable penetration of

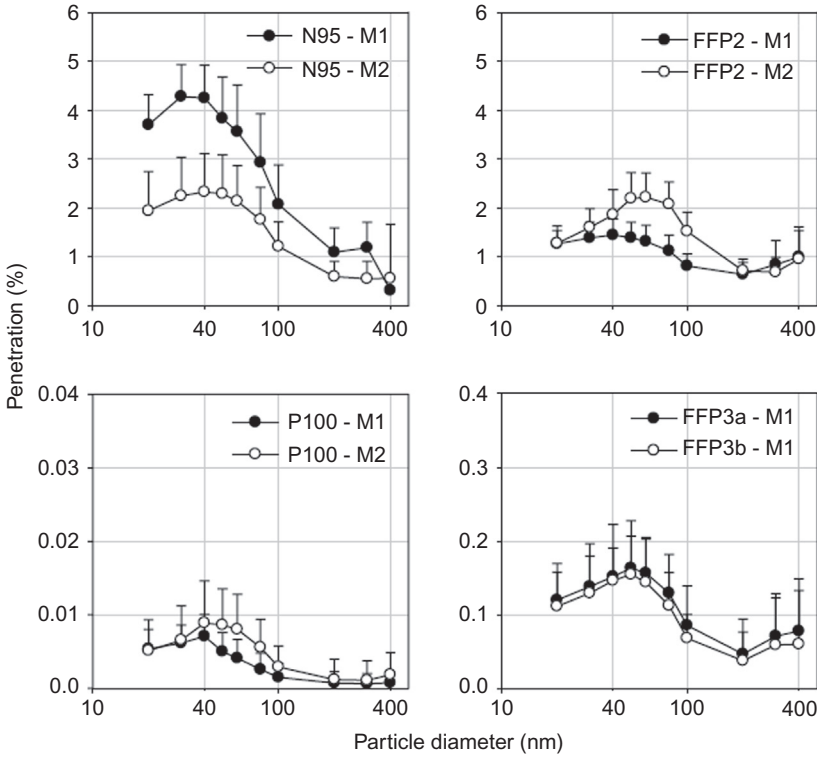

Figure 7.11
Penetration as a function of particle diameter for eight different models of filtering facepiece respirators. *From Rengasamy et al. (2009).*

particles through the respirator filter media. As shown previously, the deposition of significant levels of atmospheric particles can cause substantial increases in particle penetration for synthetic filters that rely on electrostatic charge (Raynor and Chae, 2004; Raynor et al., 2008). Moyer and Bergman (2000) conducted tests on filtering facepiece respirators that showed similar results for intermittent loadings with sodium chloride aerosol particles. Clearly, the potential exists for some level of deposition of nanoparticles on respirator media that carry electrostatic charges to cause a similar large increase in penetration. The duration of use that would cause a significant degradation of performance is expected to be many days, but this is uncertain. Therefore, a conservative recommendation for workers wearing air purifying respirators for protection against nanoparticle exposures is to replace filtering facepieces or filter cartridges at least daily if the filters are regularly collecting airborne nanoparticles. If the respirators are being worn primarily as a precaution in the event of an unanticipated release, the change period could be longer.

As with all situations in which air purifying respirators are used, the most important factor for matching the expected performance of the respirator is to ensure that the fit of the device to

the wearer's face is adequate. A good fit can be achieved by suitable fit testing on an annual basis and by fit checks each time workers don their respirators.

7.9 Summary and Recommendations

Options highest on the hierarchy of controls (e.g., elimination and substitution) should be considered first in the control of nanoparticles, although they are often impractical. Local exhaust ventilation, in contrast, is widely applied to effectively control worker exposures to airborne nanoparticles. Ventilated enclosures that surround nanoparticle sources are better at controlling exposures than exterior hoods that must draw the nanoparticles in after they are released. Laboratory hoods in research facilities are capable of containing nanoparticles, but some designs such as air-curtain hoods work better than others such as constant-flow hoods. Any laboratory hood can be defeated if the user is careless in hood settings and in their own work practices. LEV used in product development operations may perform less than optimally because development work typically involves frequently altered batch operations that are not amenable to enclosure and that are larger than laboratory hoods can contain. These operations require careful consideration in exposure control.

Filters are the most widely used and effective air pollution control devices to capture nanoparticles from moving air streams. Several reputable studies show that high-efficiency filters can effectively capture almost all airborne nanoparticles larger than about 2 nm in diameter. For filters made from synthetic fibers that rely on electrostatic forces to capture particles, the loading of the filters with nanoparticles over time may lead to substantial decreases in collection efficiency. Using filters made from glass fibers is the safest approach for providing consistent filtration performance, with a penalty of higher energy costs due to greater resistance to air flow. Electrostatic precipitators can be designed with high efficiency for nanoparticles. However, fewer options are available than for filtration systems, capital costs are high, and high voltages are required for high capture efficiency.

Work practices can minimize worker exposures to nanoparticles. Energy input should be minimized when transferring NMs. In particular, the height that nanopowders are dropped should be minimized, wherever feasible. The cleaning of areas in which deposited nanoparticles could be present should be accomplished primarily through wet cleaning rather than by vacuuming, sweeping, or wiping with dry cloths. Workers should wash hands before eating, drinking, smoking, or leaving the workplace.

Although the effectiveness of clothing and gloves at preventing dermal exposure to NMs is still uncertain, published research to date suggests that protection can be adequate. Thin, disposable latex and nitrile gloves appear to have little potential for being penetrated by dry nanoparticles. In addition, nonwoven high-density polyethylene textile fabrics (e.g., Tyvek) appear to have low penetration for NMs.

Filtering facepiece respirators and filter cartridges used in other air-purifying respirators can capture nanoparticles with high efficiency. A P100 filter designation will provide the highest level of protection for workers wearing these kinds of respiratory protection. With use, the performance of respirator filters may degrade if the filters rely on electrostatic charging to capture particles. Therefore, changing filtering facepieces and filter cartridges on a daily basis is a sensible approach for workers potentially exposed to nanoparticles. Maintaining a good fit of the facepiece to the wearer's skin is essential for effective respirator performance.

As stated at the beginning of the chapter, many of the control measures that are presently used to control exposures to gaseous and particulate pollutants can be implemented successfully for nanoparticles. However, the occupational health and safety specialist must keep in mind the special properties of nanoparticles to ensure that these "tried and true" control measures work as well for nanoparticles as they do for other workplace pollutants.

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CHAPTER 8

Addressing the Risks of Nanomaterials under United States and European Union Regulatory Frameworks for Chemicals*,†

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Chapter Outline

* This chapter builds on and updates chapter four of Securing the Promise of Nanotechnologies: Towards Transatlantic Regulatory Cooperation by Linda Breggin, Robert Falkner, Nico Jaspers, John Pendergrass and Read Porter (Chatham House, 2009).

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8.1 Introduction

The "nanotechnology revolution"[1] can be traced to a 1959 lecture by Richard Feynman titled "There's Plenty of Room at the Bottom,"[2] which called for research into the manipulation of substances at the molecular scale. Largely unnoticed at the time, Feynman's lecture has since proved prophetic: in the subsequent decades, nanotechnology research has grown exponentially, leading to a wide range of applications, especially in the areas of improved production processes, data processing and new materials. Future applications are expected in areas of medical treatment and health care; air, water and soil quality advancement; and clean energy production, storage and transportation—to name just a few.

This chapter focuses on nanomaterials[3] currently in production. Some existing nanomaterials have unique properties related to their stiffness, conductivity, color, or magnetism, and a number of other physicochemical properties, when compared with bulk materials. Carbon in the form of nanotubes, for example, is one of the strongest and stiffest of all currently existing materials. Some of the unique properties of nanomaterials, however, may be harmful

to human health and the environment in unconventional and unexpected ways. The effects of inhaling some forms of carbon nanotubes, for instance, may cause harm in ways reminiscent of asbestos fibers; releasing silver nanomaterials with antibacterial properties into waste water may have negative environmental effects; and the ability of certain nanomaterials to penetrate cells in living organisms may cause human health concerns.[4] To be sure, nanomaterials are not inherently harmful, and in many cases, their risk profiles may be similar to that of the same material in bulk form, but scientific uncertainty surrounding the known and unknown effects of nanomaterials poses a challenge for regulators.

It is for this reason that policy makers, civil society, industry representatives and scientists have called for a careful review of whether current regulatory frameworks are equipped to deal adequately with the potential risks related to some nanomaterials. This chapter outlines the U.S. and European Union (EU) regulatory frameworks for chemicals and provides a comparative analysis of the regimes. The chapter explores and compares the way in which the same hypothetical nanoscale substance would be treated under the U.S. and EU frameworks. It is important to note that chemicals regulations are not the only vehicles for addressing the environmental, health, and safety risks posed by nanomaterials. For example, food and cosmetics regulations as well as media-specific environmental laws may also apply to nanomaterials.[5]

8.1.1 Terminology: Nanosciences, Nanotechnologies, and Nanomaterials

Nanosciences and nanotechnologies have been described as ill-defined fields. They "encompass a broad and varied range of materials, tools, and approaches. Apart from a characteristic size scale, it is difficult to find commonalities among them, complicating clear definitions of relevant terms."[6] In the past decade, substantial efforts have been directed at development of agreed definitions through international standard-setting organizations, governments, and the private sector.[7] Despite substantial effort to develop consensus on definitions through the International Organization for Standardization's (ISO) nanotechnology technical committee (TC 229),[8] among other venues, reviews in both the EU and United States note that agreement remains elusive, particularly for broader terms, including *nanotechnologies* and *nanosciences*.[9]

Different definitions have been offered to describe and regulate the development and use of nanosciences and nanotechnologies. For example, the Royal Society and the Royal Academy of Engineering produced the following definition:

> Nanoscience is the study of phenomena and manipulation of materials at atomic, molecular and macromolecular scales, where properties differ significantly from those at a larger scale.
>
> Nanotechnologies are the design, characterisation, production and application of structures, devices and systems by controlling shape and size at the nanometre scale.[6]

The National Nanotechnology Initiative (NNI) in the United States adopted a single definition that encompasses both science and technology: "Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications."[10,11] ISO definitions contain similar provisions, defining nanomaterials to be those materials with dimensions in the nanoscale of 1 to 100 nanometers, and nanotechnology as the manipulation and control of nanoscale materials to take advantage of properties and phenomena that exist at that scale.[12,13]

Nanotechnology (in the singular) can thus be taken to refer to a wide range of different technologies. In this chapter, we refer to "nanotechnologies" and "nanotechnology" throughout, with the latter signifying the wider field of science and technology that encompasses the full range of nanotechnologies and applications. We refer to "nanomaterials" as a generic term for the structures, devices and systems created through nanoscale engineering.

8.1.2 Different Generations of Nanotechnologies

It is common to differentiate between four different conceptual categories, or "generations," of nanotechnologies.[14] As outlined in the 2007 Nanotechnology White Paper,[15] issued by the U.S. Environment Protection Agency (EPA), the first generation of nanotechnologies focuses on manufacturing coatings, polymers, and more reactive catalysts, among others. A second generation includes nanoparticles for targeted drug delivery systems, adaptive structures, and actuators, for example. Both first- and second-generation nanotechnologies are currently in the research, development and/or commercialization stage. Third-generation nanotechnologies, which may not be ready for commercial use for another decade, include novel robotic devices, three-dimensional networks, and guided assemblies. Even further into the future are fourth-generation nanotechnologies, which may result in molecule-by-molecule design and self-assembly capabilities. Although first-generation nanotechnologies have mostly led to the so-called passive nanostructures, second-, third-, and fourth-generation nanotechnologies will lead to nanostructures that may perform an "active" function.[16] Although commentators have noted a shift in research toward active nanostructures and nanosystems,[17] this chapter focuses on first-generation nanomaterials.

8.1.3 Commercial and Economic Dimensions

Nanosciences and nanotechnologies have wide-ranging and ever-expanding commercial applications. Existing products deriving added value from nanotechnologies include cars, clothing, airplanes, computers, consumer electronics devices, pharmaceuticals, processed food, plastic containers, appliances, and other products.[18] This diversity of commercialization has led some to consider nanotechnology a "general purpose" or "platform" technology like biotechnology and the Internet.[19] Nanosciences and nanotechnologies will thus drive the

development of a broad array of products and industries in various industry sectors ranging from manufacturing and materials, to electronics and information technology, health care, and life sciences.

The diversity of potential commercial pathways and the complexity of the nanotechnology value chain make it difficult to predict precisely how nanotechnology will develop. However, the commercial promise of nanotechnology is beyond doubt: increasing economic value of nanotechnologies in different market sectors, proliferation of innovations, as reflected in patent filings, and continuing investment in research and development by both private companies and national governments all suggest that nanotechnology is to assume an ever expanding role in industrial society.[20]

The growth of commercial products incorporating nanotechnology is difficult to measure but clearly increasing rapidly. Previous projections for the value of commercial applications of nanotechnology by 2015 ranged from $1 trillion to $3.1 trillion.[21] Revenue from nano-enabled products exceeded the lower of these estimates in 2013, and a more recent estimate predicts a $4.4 trillion world market for products containing nanomaterials by 2018.[22] Because nanotechnologies are enabling technologies, such estimates do not always distinguish clearly enough between the more limited value-added of nanotechnologies and the larger face value of products that "contain" nanotechnology product.[23] However, there is a clear upward trend in commercial value of the nanotechnology economy, both as a whole and within specific economic sectors.[24]

Another way to gauge commercial development is to consider the number and type of nano-enabled products on the market. An inventory of consumer products containing nanomaterials, maintained by the Project on Emerging Nanotechnologies (PEN) at the Woodrow Wilson International Center of Scholars, lists over 1800 nano-enabled products that are currently on the market in 30 countries—a substantial increase on the approximately 1000 products listed on the inventory in 2010.[25] The vast majority of these products is in the cosmetics, clothing, personal care, sporting goods, sunscreens and filtration sectors and are available on markets primarily in the United States, East Asia, and Europe. Nanoscale silver, carbon, titanium, silicon, zinc, and gold are the materials most frequently contained in products. Although the PEN inventory relies on crowdsourced products and may thus overstate and/or understate the true degree of commercialization of "nanoproducts," it is indicative of the wide range of commercial applications of nanotechnologies in consumer products.

The growing commercial importance of nanotechnologies is expressed through the proliferation of patent filings for discoveries at the nanoscale. Between 1985 and 2005, the U.S. Patent and Trademark Office (USPTO) issued a total of 4995 nanotechnology patents and maintained a backlog of 2714 published applications.[26] In contrast, in 2013 alone, the USPTO issued more than 6000 nanotechnology patents, a 17% annual increase

from 2012. According to research supported by the U.S. National Science Foundation, in 2006, the USPTO published 1156 nanotechnology patents, and the European Patent Office (EPO) published 679 patents.[27] And in 2013, the USPTO alone issued more than 6000 nanotechnology patents.

8.1.4 Environment, Health, and Safety Risks: Scientific Knowledge and Uncertainty

With the commercialization of first-generation products of nanotechnologies proceeding at an ever-increasing pace, a gap has emerged between the development of nanotechnologies and our understanding of how nanomaterials interact with the environment and human health. Research into the environment, health, and safety (EHS) risks of nanomaterials and the possibility of safer materials has been stepped up in recent years. For example, in the United States, the U.S. Governmental Accountability Office (US GAO) reported in 2012 that funding for EHS research more than doubled from 2006 to 2010, from $38 to $90 million.[28] These investments reflect a growing recognition that, as Klein notes, "our understanding of the interaction of nanoscale objects with living matter, even at the level of single cells, has not kept pace with the explosive development of nanoscience in the past decades."[29]

A central problem in establishing whether nanomaterials pose a risk is that they may react differently to the equivalent material in bulk form.[30] A workshop on predicting nano-biointeractions organized by the International Council on Nanotechnology (ICON), for instance, found that "because nanoparticles change as they interact with living systems, it is unlikely that their physicochemical properties at any one stage in the life cycle alone will predict biological behaviour."[31] Moreover, "when a nanoparticle is put into a biological fluid or the environment, it becomes coated with bio-molecules in a complex and dynamic matter that is not well understood."[31] Traditional approaches to researching EHS risks for bulk materials may thus not be sufficiently robust for establishing the safety of nanomaterials.

The potential risks associated with certain nanomaterials may depend on their chemical composition, their state of aggregation and agglomeration, the number of particles per unit mass, their physical form, the median size and size distribution, their surface area and surface charge, their solubility or miscibility, their state of dissolution, and their partition coefficient.[31] All these qualities are to be taken into account when categorizing and evaluating nanomaterials for potential (eco)toxicity. In practice, risks are also affected by exposure during manufacturing, use, or disposal of nanomaterials—a particular concern for nanomaterials used in consumer and commercial applications.[32]

Early results of research into EHS risks suggests that the safety of all nanomaterials cannot be taken for granted. Following studies indicating health risks associated with exposure to some forms of multiwalled carbon nanotubes (MWCNTs),[33] the U.S. National Institute

of Occupational Safety and Health (NIOSH) has released recommended exposure limits for individuals working with carbon nanotubes.[34] Further life-cycle analysis is needed to establish likely exposure levels—for factory workers, consumers, and the environment.[35]

In light of initial findings of such EHS risks, scientists have called for the development of better and more adequate testing methods.[36] Conventional toxicologic methods are seen by some as too slow, too expensive, and not able to accurately capture all risks presented by new nanomaterial properties.[30] Developing alternative research and testing methods for EHS risks of nanomaterials is complicated by the multitude of nanotechnology applications, properties expressed, routes of exposure, and means of disposal. Case-by-case risk assessment of specific materials and their use patterns is needed. As Maynard notes, "nanotechnology more closely represents a way of thinking or doing things […] than a discrete technology," which "makes it particularly difficult to discuss potential risks in general terms."[37]

In addition, the ongoing expansion of nanoscience and nanotechnologies is likely to produce novel nanostructures that may cause currently unknown forms of hazard. This is likely to further complicate the search for adequate risk regulation approaches, as the EPA has noted:

> The convergence of nanotechnology with biotechnology and with information and cognitive technologies may provide such dramatically different technology products that the manufacture, use and recycling/disposal of these novel products, as well as the development of policies and regulations to protect human health and the environment, may prove to be a daunting task.[38]

Thus, regulators face a number of challenges in dealing with the potential risks of nanomaterials. These challenges include uncertainties with regard to the development and commercial application of nanomaterials, hazards and exposure pathways, and the direction and speed of technologic change. It is in the context of these uncertainties that regulators must determine the suitability and effectiveness of existing regulatory frameworks. Reacting effectively and proportionally is a key imperative for regulators and policy makers as much as for industry and civil society—and yet these myriad uncertainties make the task of regulating appropriately extremely challenging. This chapter examines the tools that are at the forefront of addressing the risks posed by nanomaterials—the laws and regulations in the United States and EU that are used to regulate chemicals. The chapter first examines the use of U.S. chemicals laws to regulate nanomaterials and then turns to the EU's chemical regulations. It ends by comparing the U.S. and EU approaches.

8.2 U.S. Chemicals Regulation

Two principal laws govern chemicals regulation in the United States: the Toxic Substances Control Act (TSCA) and the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). The former provides certain authorities to the EPA to regulate most industrial chemicals, and the

latter addresses chemicals used as pesticides in particular.[39] In theory, the EPA also can regulate nanomaterials released into the environment under media-specific laws such as the Clean Air Act; the Clean Water Act; the Comprehensive Environmental Response, Compensation and Liability Act; and the Resource Conservation and Recovery Act,[40,41,42] but to date, the EPA has relied on the TSCA and the FIFRA as the primary vehicles for regulating nanomaterials.[43]

8.2.1 The Toxic Substances Control Act

The TSCA was enacted in 1976 with three principal policy objectives. First, "adequate data should be developed" on the effects of chemicals on health and the environment, and the development of data "should be the responsibility" of chemical manufacturers. Second, the law states that "adequate authority should exist to regulate" chemicals. Third, this regulatory authority over chemicals "should be exercised in such a manner as not to impede unduly or create unnecessary economic barriers to technological innovation while fulfilling the primary purpose … to assure that such innovation and commerce … do not present an unreasonable risk of injury to health or the environment."[44]

The TSCA aptly has been characterized as a statute with "dramatic strengths and weaknesses."[45] The statute covers a broad range of chemicals and provides far-reaching regulatory tools for the EPA to address unreasonable risks posed by chemicals, yet it also imposes numerous substantive and procedural hurdles that have limited the extent to which these authorities are used.

As a result, a multitude of TSCA critiques exist, characterizing the statute, for example, as being a "serious underperformer among U.S. environmental laws,"[46] as having "significant shortcomings"[47] and as providing "limited assurance that health and environmental risks are identified."[48,49] Nevertheless, the TSCA also has had its supporters. For many years, the EPA generally maintained that the TSCA provided the statutory tools necessary to protect public health and the environment, particularly when coupled with the agency's voluntary reporting initiatives.[50]

However, under the Obama Administration, the EPA shifted course and, in 2009, called for TSCA reform, issuing a set of legislative principles and starting several administrative initiatives intended to improve under its existing authorities the implementation of the TSCA.[51,52] The EPA now asserts that it "will not be able to successfully meet the goal of ensuring chemical safety now and into the future" without statutory amendments, including those that enhance its ability to require information from chemical companies.[53]

Leading environmental advocates and several states also have issued reform principles.[54,55] In addition, the principal trade association for the chemical industry, the American Chemistry Council, which traditionally praised the TSCA as a "strong, robust regulatory framework" that "protects health and the environment, promotes innovation, and addresses new questions about

hazards, exposures and potential risks,"[56] acknowledges the need for "modernization" of the statute.[57] Nevertheless, despite sporadic indications that momentum was building for reform in the 111th, 112th, and 113th Congresses, legislation was not enacted. Reform efforts appear stalled after the November 2014 elections and could remain so indefinitely in the new Congress.

We now look in detail at the specific regulatory authorities under the TSCA and how they have been used to address potential risks posed by nanoscale materials.

New chemicals and significant new uses of chemicals

General regulatory authorities

Section 5 of the TSCA requires that manufacturers, importers, producers, and processors (hereinafter collectively referred to in this Section as "manufacturers") of chemical substances notify the EPA at least 90 days prior to manufacturing or introducing a new chemical by filing a premanufacture notice (PMN). In addition, the statute requires that notice be provided prior to manufacturing or introducing a "significant new use" of a chemical.[58]

For "significant new uses" of chemicals, however, the EPA must first issue a rule (Significant New Use Rule (SNUR)) before the requirements apply. Such rules must be based on the application of certain statutory criteria that determine whether a "significant new use" exists.[59] In order to conclude that a use is "new," the use may not be "ongoing."[60] SNURs are subject to public comment; although the procedures may vary, depending on whether the SNUR covers a new or an existing chemical.[61]

A SNUR does not impose "regulatory" restrictions on the PMN chemical. Rather, a SNUR imposes manufacturing, processing, or use limitations on the PMN submitter, restrictions that are similarly imposed upon subsequent producers of the same chemical. If an entity wishes to deviate from the terms of the SNUR, it must submit a Significant New Use Notice (SNUN) to EPA, which is essentially the same as a PMN.[62]

Both PMNs and SNUNs must include "reasonably ascertainable" information, including, but not limited to, the known environmental or health effects of the chemical, the proposed categories of use, reasonable estimates of the total amount to be manufactured or processed, and reasonable estimates of the number of individuals who will be exposed to the substance in their places of employment.[63] Premanufacture testing, however, is not a required component of premanufacture or SNUN requirements.[64] The EPA estimates that "most premanufacture notices do not include test data of any type and only about 15% include health or safety test data."[65]

In lieu of reliance on chemical-specific data, the EPA typically predicts potential exposure and levels of toxicity of new chemicals by using models and comparing new chemicals to chemicals with similar molecular structures for which toxicity data are developed.[66] The EPA also can require the submission of test data under certain circumstances.

In addition, the statute and the EPA's implementing regulations provide exemptions to these premanufacture notice reporting requirements that could apply to certain nanomaterials. These include, but are not limited to, exemptions for low volume;[67,68] low release and low exposure;[67] polymers;[67] and research and development.[69] Of the estimated 1500 new chemical notices the EPA receives annually, approximately half are exemption requests.[70]

In most cases, the exemptions have associated record-keeping requirements.[71] Some of the exemptions such as the polymer and research and development exemptions are "self-executing" and do not require regulatory approval. The EPA's regulations provide, however, that certain exemptions, such as the low-volume exemption and the low-release, low-exposure exemption, "may" be granted by the EPA "if it determines that the chemical will not present an unreasonable risk of injury to health or the environment."[67]

Upon review of a premanufacture notice, if the agency finds a "reasonable basis" to conclude the chemical presents an "unreasonable risk," it may prohibit or limit the amount of the chemical that may be manufactured, processed, or distributed in commerce.[72] The TSCA provides the agency with several regulatory options, including, for example, requiring any substance containing the chemical to be labelled or accompanied by warnings and instructions; regulating the manner or method of commercial use; and directing manufacturers or processors to give notice of unreasonable risk of injury to distributors.[73] This authority is rarely used, however, in response to a new chemical notice.

The statute also allows the EPA to regulate a new chemical when it determines that there is insufficient information to evaluate health and environmental effects and the chemical "may present an unreasonable risk of injury to health or the environment" or will be produced in "substantial quantities" that could result in significant human and environmental exposure.[74] In such cases, the EPA may issue an order, typically in the form of a consent order,[75] which may prohibit or limit the manufacture, processing and distribution in commerce, use or disposal of a chemical, but only pending development of information.[76] The EPA explains: "When information available … is not adequate to make predictions of toxicity, data will be required as part of PMN." EPA further explains that based on experience it groups "PMN chemicals with shared chemical and toxicological properties into categories, enabling both PMN submitters and EPA reviewers to benefit from the accumulated data and past decisional precedents allowing reviews to be facilitated." The EPA states that this approach "has streamlined the process for Agency review of new chemical substances."[77]

Leading TSCA practitioners at the law firm of Latham & Watkins LLP explain:

> The Agency will typically communicate its concerns to the PMN submitter and request that the PMN submitter voluntarily suspend the review period . . . . [T]he PMN submitter must decide whether to await the issuance of a proposed unilateral order and then file objections and oppose an injunction action in district court, withdraw the PMN . . . or attempt to negotiate a consent order with the Agency. Under these circumstances, submitters have generally elected either to withdraw the PMNs or negotiate consent orders.

The practitioners conclude that the approach is an "effective and efficient mechanism for addressing risk and testing issues for new chemicals," although they recognize the controversy over whether certain testing should be required for all chemicals.[41]

Nevertheless, the EPA reviews approximately 1500 premanufactured and significant new-use notices annually,[78] and a 2010 EPA Inspector General study found that, on average, only 8% of these chemicals are regulated, 5% are withdrawn, and the rest—(87%) are not regulated.[79,80] Similarly, the EPA reported in 2005 that of the 40,000 chemicals it had reviewed under the TSCA, it had restricted 1600, almost all under its authority to regulate on a temporary basis pending development of information. A similar number were withdrawn voluntarily by industry, "often in the face of EPA action."[78]

Regulatory actions specific to nanomaterials

A key issue in the regulation of nanomaterials under the TSCA is whether a particular nanomaterial is considered a *new* chemical. This determination is significant from a regulatory perspective because *existing* chemicals are not subject to premanufacture notice requirements and the corresponding process that provides the EPA with the opportunity to perform an assessment and identify and address potential risks prior to manufacture and distribution. If a chemical is determined to be on the Inventory, the chemical may be manufactured without review in most cases.

In its "TSCA Inventory Status of Nanoscale Substances – General Approach," published in early 2008, the EPA described the manner in which it determines whether a nanoscale substance is a new or existing chemical substance. According to the document, if a nanoscale material has the same "molecular identity," which the EPA defines as the same structural and compositional features as opposed to physical and chemicals properties, as a chemical substance listed on the TSCA Inventory, it is considered an "existing" chemical substance.[81] More specifically, the agency recognized that although "a *nanoscale* substance that has the same molecular identity as a non-nanoscale substance listed on the Inventory differs in particle size and may differ in certain physical and/or chemical properties resulting from the difference in particle size, EPA considers the two forms to be the same chemical substance."[82,83] The debate preceding and following the issuance of the EPA's statement was divisive, with industry generally supporting its position and NGOs opposed to it.[84]

Later in 2008, the EPA published a Federal Register notice in which it clarified that carbon nanotubes "are not necessarily identical to graphite or other allotropes of carbon" and if "a particular CNT [carbon nanotube] is not on the TSCA Inventory, anyone who intends to manufacture or import that CNT is required to submit a PMN (or applicable exemption) under TSCA Section 5 at least 90 days before commencing manufacture."[83] In 2014, the EPA explained, for example: "Each [carbon nanotube] is considered a distinct chemical substance," and "key parameters" include "[number] … of walls, inner diameter, outer diameter and length, functionalization, capped or open ended, straight … and branched, or tree structure."[85,86,87]

In December 2011, the EPA Office of Inspector General reported that since 2005, the EPA had received 120 new chemical notices for nanoscale materials, including carbon nanotubes, fullerenes, and nonmetal oxides.[88] The EPA states that that it has "taken a number of actions to control and limit exposures" to nanoscale materials submitted for a TSCA new chemical review. These include limiting the uses of the nanoscale materials; requiring the use of personal protective equipment such as impervious gloves and NIOSH approved respirators, and limiting environmental releases. The EPA also states that it has "required testing to generate health and environmental effects data."[89] Specifically, the EPA has permitted limited manufacture of new chemical nanoscale materials by using administrative orders under Section 5(e) of the TSCA and/or Significant New Use Rules under Section 5(a) (2) of TSCA.[89] An EPA official recently explained that "100%" of potential nanomaterials receive further review and "usually" are regulated." The review and regulation process can take between 6 and 24 months for each substance.[90]

In 2010, the EPA issued its first SNURs for certain carbon nanotubes,[91] and since that time, it has issued numerous more chemical-specific SNURs for nanomaterials. For example, in 2013, the EPA issued 17 final SNURs for carbon nanotubes and fullerenes; and in 2014, it issued 19 final SNURs for carbon nanotubes.[92]

Details about the EPA's regulatory actions in some cases are unavailable to the public because of confidential business information (CBI) claims that prevent public disclosure of information submitted by companies to the EPA.[93] According to a 2005 Government Accountability Office report, approximately 95% of all premanufacture notices contained some CBI assertion.[94] CBI is discussed in more detail below, including a description of the EPA's recent reforms to CBI procedures.

With respect to the number of nanomaterial exemptions from premanufacture notice requirements, the EPA has not provided data to the public since 2008, but that year the EPA allowed fewer than 10 new nanoscale materials to be manufactured under the terms of regulatory exemptions and "only in circumstances where exposures were tightly controlled to protect against unreasonable risks (using, for example, specific protective equipment and stringent environmental release limitations)."[95,96] Some stakeholders, however, have noted that it may not be reasonable to assume that traditional approaches to controlling exposure to chemicals will work in the context of nanomaterials.[97]

It is difficult to estimate the extent to which the research and development exemption has been relied upon with respect to nanomaterials because it is self-executing and does not require prior regulatory approval. However, 60 of the approximately 100 nanoscale materials for which information has been reported under the EPA's Nanoscale Materials Stewardship Program (NMSP) are used exclusively for research and development, which suggests at least the potential for substantial reliance on the exemption.[98]

Finally, with respect to testing nanomaterials, since 2007, the EPA has been developing the Toxicity Forecaster (ToxCast), which uses automated chemical screening technologies called *high-throughput screening assays* to examine the potential toxic effects of chemicals. In the second phase of ToxCast, the EPA screened 1800 chemicals, including nanomaterials. According to the EPA Inspector General, the ToxCast approach shows promise because "[g]iven EPA's resource limitations, potential budget cuts, and the findings in our prior TSCA evaluation, the costs associated with current methods to develop toxicological data may not be suited for nanomaterial data generation."[99]

Regulation of existing chemicals

General regulatory authorities

TSCA Section 6 grants the EPA certain authorities to regulate existing chemicals or those already listed on the TSCA Chemical Substance Inventory (commonly referred to as the "TSCA Inventory").[100] If the agency determines that there is "a reasonable basis to conclude that the manufacture, processing, distribution in commerce, use, or disposal of a chemical … presents or will present an unreasonable risk of injury to health or the environment," it may impose a range of requirements or restrictions "to protect adequately against such risk," provided it uses the "least burdensome requirements" possible.[101,102]

In ordering such restrictions, the TSCA requires the EPA to publish a statement that addresses the human health and environmental effects and magnitude of exposure to the chemical.[103] Significantly, the agency also must address the benefits of the chemical for various uses and the availability of substitutes, in addition to the "reasonably ascertainable economic consequences of the rule, after consideration of the effect on the national economy, small business, technological innovation, the environment, and public health."[104] Since the TSCA was enacted in 1976, the EPA has issued rules under this authority for only five chemicals: polychlorinated biphenyls (PCBs), fully halogenated chlorofluoroalkanes, dioxin and asbestos and hexavalent chromium. In most cases, the EPA restricted specific uses or sources of the chemical but did not ban the chemical.[105]

The burden on the EPA for regulating the existing chemicals under the TSCA is compounded by the standard for judicial review of challenges to rules it issues under the statute. Specifically, an EPA rule is "unlawful" if a court finds that it is not supported by "substantial evidence" in the rulemaking record.[106] This is a more stringent standard than the "arbitrary and capricious" standard of judicial review that governs the review of most federal environmental rules.[107] It is not surprising that the EPA told the GAO in 2013 that it considers using Section 6 authority "only after exhausting all other available options."[108]

In recent years, however, the EPA has utilized other approaches, including increased use of SNURs under Section 5, to address the use of certain chemicals. For example, the GAO found

that EPA had quadrupled the number of SNURs in recent years, issuing 540 rules between 2009 and 2012 that affected 25% of the 2180 chemicals subject to SNURs since 1976. It concluded, however, that "it is too early to tell" whether SNURs and other actions "will reduce chemical risks."[109]

Finally, in certain limited circumstances, the EPA has the authority under TSCA Section 7 to seize an "imminently hazardous" chemical substance or mixture.[110] Such chemicals are defined to include those that present an "imminent and unreasonable risk of serious or widespread injury to heath or the environment" that is likely to result before a final rule can be issued under TSCA Section 6, discussed above, to protect against the risk.[111] This authority is rarely used, however, and to do so EPA must commence a civil action in district court.[110]

Regulatory actions specific to nanomaterials

In fall 2009, the EPA announced that it would develop a significant new use rule to regulate nanoscale chemicals already listed on the TSCA inventory in their conventional form.[112] In November 2010, the EPA sent the draft proposed rule to the Office of Management Budget (OMB) as required under Executive Order 12866, which requires review of all proposed "significant regulatory actions."[113] The rule would have designated any use of nanoscale materials as a "significant new use" and required that manufacturers notify the EPA at least 90 days before manufacturing started. According to the EPA, the objective was to allow it to evaluate the use of the nanoscale materials and take steps if needed to protect against unreasonable risks to human health or the environment.[114]

The OMB failed to act on the proposed rule for almost 4 years, and the EPA ultimately withdrew the rule in October 2014. At least one critic attributed the OMB's actions to resistance within the Obama Administration based on the concern that regulation could impede promotion of nanotech by stigmatizing nanomaterials.[115]

In addition, as discussed below, in October 2014, the EPA requested the OMB to review a proposed reporting and recordkeeping rule for nanomaterials in commerce that would require reporting of available use, production volume, exposure, and toxicity data.[116,117]

Testing

General regulatory authorities

The TSCA provides the EPA with the authority to issue rules that require manufacturers, importers, and processors to undertake testing to "develop data with respect to the health and environmental effects" of certain chemicals, provided the agency first makes certain findings.[118] First, it must find that either (i) the chemical may present an "unreasonable risk of injury to health or the environment" or (ii) the chemical "will be produced in substantial

quantities" and "may reasonably be anticipated to enter the environment in substantial quantities" or result in "substantial human exposure."[119] Second, it must determine that current data are "insufficient" to determine or predict the health and environmental effects of the chemical.[120] Third, it must find that testing is "necessary to develop such data."[121] After making these findings, it must then issue a proposed test rule for public notice and comment prior to issuing a final rule. The process can take up to 10 years.[122]

In 2013, GAO reported that the EPA had promulgated test rules for only 197 chemicals since the TSCA was enacted in 1974 but that since 2009 the EPA had stepped up the pace. From 2009 to 2013, the EPA required testing of 34 chemicals. In addition, the EPA planned to require testing for 23 more chemicals.[123]

Partly because of the burdensome test rule process, the EPA historically has used voluntary approaches to gather data. For example, as an alternative to the rule-making process, it can negotiate agreements with companies to conduct testing. As of 2013, the EPA had required testing for 68 chemicals in enforceable consent agreements.[123] In addition, the agency has relied on voluntary reporting programs such as the High Production Volume (HPV) Challenge Program.[124]

Regulatory actions specific to nanomaterials

Consistent with its prior use of voluntary reporting programs to collect environmental, health, and safety data, the NMSP was the EPA's first and most high-profile nanotechnology governance initiative.[125] Under this voluntary program, the agency requested data to inform appropriate risk assessment and risk management practices for nanoscale chemical substances.[125] The NMSP consisted of two parts. The Basic Program requested that manufacturers and importers provide information on their current use of engineered nanoscale materials. The In-Depth Program asked participants to partner with the EPA to identify data gaps, engage in testing, and develop new data.

In its 2009 Interim Report on the program, the EPA stated that as of December 8, 2008, 29 companies and trade associations had submitted information covering 123 nanoscale materials based on 58 different chemicals, and another seven companies had committed to submit information. Four companies agreed to participate in the in-depth program.[126]

The EPA concluded:

> Most submissions included information on physical and chemical properties, commercial use (realized or projected), basic manufacturing and processes as well as risk management practices. However, very few submissions provided either toxicity or fate studies. Because many submitters claimed some information as confidential business information, the Agency is limited in the details of what it can report for any particular submission.[127]

It further concluded that "nearly two-thirds of the chemical substances from which commercially available nanoscale materials are based" and "approximately 90% of the different nanoscale materials that are likely to be commercially available" were not reported under the Basic Program. Furthermore, a number of the submissions did not contain exposure or hazard-related data, but "exposure and hazard data are two of the major categories of information EPA identified in its concept paper for the NMSP that are needed to inform risk assessment and risk management of nanoscale materials." Finally, it notes that the low rate of engagement in the In-Depth Program "suggests that most companies are not inclined to voluntarily test their nanoscale materials."[128]

The EPA states in the report that owing to "the limited participation in the In-Depth Program," of the NMSP, it will "consider how best to apply rulemaking under TSCA Section 4 to develop needed environmental, health, and safety data."[128] The report led to renewed calls for mandatory reporting and testing of nanomaterials,[129] and in 2010, after its release, the EPA stated in its Unified Regulatory Agenda in spring of 2009 that a Section 4 test rule "may be needed" for multiwall carbon nanotubes.[130] Since that time, the EPA has indicated its intent to issue a proposed test rule for "certain nanomaterials"[131] but has not moved forward and appears unlikely to do so.[132]

Record-keeping and reporting requirements

General regulatory authorities

The TSCA imposes certain record-keeping and reporting requirements on manufacturers, distributors and processors of chemicals. For example, they are required to maintain records of "adverse reactions to health or the environment" caused by a chemical and must submit copies of records if requested by the EPA.[133] In addition, manufacturers must immediately notify the EPA if they obtain information that a chemical "presents a substantial risk of injury to health or the environment."[134] In 2010, the EPA announced a "new general practice" for CBI claims in connection with Section 8(e) submissions. If the health and safety study involves a chemical identity that is already listed on the public portion of the TSCA Chemical Substances Inventory, the EPA "expects to find" that the "chemical identity clearly is not entitled to confidential treatment." The EPA explained that it "believes this new general practice will make more health and safety information available to the public."[135]

Under Section 8(a) of TSCA, the EPA also has authority to require manufacturers and processors, *other than small manufacturers and processors*,[136] to maintain and submit records with respect to a wide range of information about a chemical "insofar as known to the person making the report or insofar as reasonably ascertainable." For example, it may require submission of information about a chemical's molecular structure, the total amount manufactured or processed, all existing data concerning the environmental and health effects, the number of individuals exposed, and reasonable estimates of the number of workers who will be exposed in their places of employment and the duration of such exposure.[137]

Pursuant to its authority under Section 8(a), in 2011, the EPA issued its Chemical Data Reporting (CDR) rule which amended its Inventory Update Rule (IUR).[138] The CDR requires companies to submit information on the manufacturing, processing, and use of chemicals, including information on production volumes and manufacturing sites. The new reporting requirements increase the data reported to the EPA by lowering the reporting threshold in certain cases and increasing reporting frequency.[139] CDR data can be designated as CBI by the manufacturer, which means the agency protects the information from disclosure when it aggregates the data for public use. The CDR, however, imposes limits on the information that can be treated as confidential and requires upfront substantiation of processing and use data.[140]

The EPA is also authorized to issue rules that require chemical companies to submit lists or copies of existing health and safety studies. By 2007, it had used this authority approximately 50 times for 1000 chemicals.[141]

Finally, the TSCA provides the agency with subpoena authority, although it rarely is used. It can require witness testimony and the production of reports, papers, documents, answers to questions, and other information.[142]

Another possible approach to obtaining data has not been fully utilized by the EPA, according to the GAO, which maintains that the EPA should be more assertive in seeking toxicity and exposure data submitted to the European Chemicals Agency (ECHA) under Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH). For example, the EPA has not pursued a formal agreement with the ECHA, but instead, it has an informal agreement or Statement of Intent for sharing of information.[143] The EPA also has not used its authority under Section 8 to require such information from manufacturers, nor has it used it potential subpoena authority, discussed earlier, to obtain the data. This situation led the GAO to recommend in 2013 that the EPA pursue a formal agreement and also "consider promulgating a rule under TSCA Section 8, or take action under another Section, as appropriate, to require chemical companies to report chemical toxicity and exposure-related data they have submitted to the European Chemicals Agency."[123]

Regulatory actions specific to nanomaterials

In assessing the results of its voluntary program, the EPA stated that it had received reports related to nanomaterials under Section 8(e), which as discussed above, requires manufacturers to report to it substantial risk of injury to health or the environment. Many of the details have been unavailable to the public, however, because the information is protected as confidential business information.[144,145] It also said it would "consider how to best apply regulatory approaches under TSCA Section 8(a) to address the data gaps on existing chemical nanoscale material production, uses, and exposures."[146]

In 2010, the EPA submitted to the OMB for review a draft proposed record keeping and reporting rule. The draft proposed test rule, along with the draft proposed SNUR rule discussed above, was held at the OMB for almost 4 years.[147] The EPA withdrew the proposed

rule from the OMB in October 2014 and resubmitted it the same month.[148] The rule would require covered chemical manufacturers of nanomaterials to report certain information to the EPA, such as production volume, available health and safety data, and exposure and release information.[149] The EPA has indicated it plans to propose the new rule in early 2015.

Nevertheless, in 2011, the EPA Inspector General issued a report entitled "EPA Needs to Manage Nanomaterial Risks More Effectively," in which it noted that "even if mandatory reporting rules are approved, the effectiveness of EPA's management of nanomaterials remains in question for a number of reasons. …" These include that the EPA's plan to regulate nanomaterials as chemicals is constrained by the "existing limitations" of the governing statutes and that "the EPA's management of nanomaterials is limited by lack of risk information and reliance on industry-submitted data."[150]

Confidential business information

Information that firms are required to submit to the EPA under the TSCA may contain commercially sensitive information such as information about new products, new technologies, and manufacturing schedules. The TSCA seeks to protect this information by prohibiting the EPA from disclosing CBI except in very limited circumstances.[151] These exceptions include disclosure when necessary to protect health or the environment against an unreasonable risk of injury.[152] The statute does not contain an exception for disclosure to foreign (or state, local, or tribal) governments; however, CBI may be shared with other countries' governments in certain notices of regulatory action taken against chemicals exported to other countries.[153]

The statute also specifically states that it "does not prohibit" the disclosure of health and safety studies submitted for chemicals that are (i) offered for commercial distribution or (ii) that are subject to testing under Section 4 or the PMN process. The statute tempers this provision by stating that it does not authorize the release of any data that disclose processes used in the manufacturing or processing or disclose the portion of a chemical mixture that comprises any specific chemical in the mixture.[152]

In practice, companies claim as CBI substantial amounts of information that they submit under the TSCA and, therefore, the information is not available to the public. As noted earlier, historically no less than 95% of all premanufacture notices contained some CBI assertion.[154] In 2005, the GAO explained that "chemical companies claim much of the data submitted as confidential … [a]lthough EPA has the authority to evaluate the appropriateness of these confidentiality claims, EPA states that it does not have the resources to challenge large numbers of claims."[155]

As a result, the CBI provisions in the statute and the manner in which they have been implemented have both been subject to substantial criticism. In 2007, the GAO recommended that Congress consider amending the TSCA to:

- clarify that health and safety data cannot be claimed as confidential business information;
- require substantiation of confidentiality claims at the time that the claims are submitted to the EPA;

- limit the length of time for which information may be claimed as confidential without reaffirming the need for confidentiality;
- establish penalties for the false filing of confidentiality claims; and:
- authorize states and foreign governments to have access to confidential business information when they can demonstrate to the EPA that they have a legitimate need for the information and can adequately protect it against unauthorized disclosure.[156]

These concerns are echoed by nongovernmental organizations. As explained by Environmental Defense Fund:

> Although health and safety studies and associated data are not eligible for CBI protection, chemical identity can be eligible. This allowance can lead to perverse outcomes, such as that a chemical's adverse effects on mammalian reproduction must be disclosed but identification of which chemical causes the effect may be kept a secret.[157]

The chemical industry emphasizes the critical importance of protecting CBI because of the rapidly developing and highly competitive nature of the industry.[158] In recent Congressional testimony, the President of the American Chemistry Council testified, however, that "EPA should have the authority to share appropriate confidential business information with state, local and select foreign governments when it is relevant to a decision on chemical safety and when there are appropriate safeguards against inappropriate disclosure."[159]

In 2010, the EPA launched an effort to "increase transparency and provide more valuable information to the public by identifying programs where non-CBI may have been claimed and treated as CBI in the past."[160] These efforts include modifications to the former IUR rule, referenced above, which set out new requirements such as upfront substantiation in writing for CBI claims for processing and use data.[161] In addition, as noted above, the EPA announced a "new general practice" that limits CBI chemical identity claims for Section 8(e) submissions regarding information about substantial risks of injury to health or the environment.[162]

In 2013, the GAO found that the EPA had made progress in reviewing confidentiality claims, making public over 600 chemical identities that were formerly confidential and over 780 health and safety filings.[163]

8.2.2 The Federal Insecticide, Fungicide, and Rodenticide Act

Chemicals that are pesticides are regulated separately under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Pesticides are defined under the statute as substances or mixtures of substances intended for preventing, destroying, repelling or mitigating pests. Pesticides include not only insecticides but also herbicides, fungicides, and other pest control substances.[164] The EPA has stated that pesticide products that use nanomaterials will be subject to FIFRA review and registration requirements.[165]

Pesticide registration

The FIFRA requires that new pesticides, with limited exceptions, be registered with the EPA before they can be distributed or sold.[166] To register a pesticide, an applicant is required to submit certain information, including the pesticide label and directions for use, the formula, and a description of the test data upon which the claims are based, citations to data in the public literature, or data previously submitted to the EPA.

Regulations issued under the statute detail the required contents of applications, which specify data required by the agency to determine that using the pesticide according to label directions will not cause unreasonable adverse effects on the environment. In addition, the regulations require applicants to provide "any factual information" regarding adverse effects of the pesticide on the environment that the statute requires registrants to report after a pesticide has been registered.[167] The EPA recognizes that the FIFRA application process "often requires the submission of extensive environmental, health, and safety data."[168]

The EPA also recognizes that "because nanoscale materials may have special properties, EPA's data requirements may need to be tailored to the specific characteristics of the product under consideration."[169] According to the agency, the "special properties that make nanoscale materials of potentially great benefit also can present new challenges for risk assessment and decision-making." As a result, it is "currently examining potential hazard, exposure, policy, regulatory, and international issues that may be associated with pesticides that are a product of nanotechnology or that contain nanoscale materials."[169]

In its analysis of the application of the FIFRA to nanomaterials, the American Bar Association's Section on Environment, Energy and Resources observes that the EPA's authority to regulate "existing" chemicals under the FIFRA is "more comprehensive" than its authorities to regulate "new" chemicals under the TSCA. This is, in part, because the FIFRA expressly provides the EPA with the authority to require the generation of data necessary for risk assessment.[170] The EPA may register a pesticide either unconditionally or with conditions. The EPA must grant an unconditional registration if it makes certain determinations based on the application materials submitted. These determinations include, but are not limited to, the following: (i) The pesticide "will perform its intended function without unreasonable adverse effects on the environment"; and (ii) "when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment."[171,172]

The statute defines "unreasonable adverse effects on the environment" to include (i) any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide, or (ii) a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard under (Section 408 of the Federal Food, Drug, and Cosmetic Act).[173]

The agency specifies the approved uses and conditions of use that must be set out on the product label, including safe methods of pesticide storage and disposal. Furthermore, it may classify and register a pesticide product for general or restricted use. It may restrict the use of a pesticide because it determines that it is necessary to protect the pesticide applicator or the environment. Restricted-use pesticides can be applied only by or under the direct supervision of people who have been trained and certified.[174] Furthermore, as part of the registration process, if a pesticide is proposed for use on a food crop, the EPA must determine a safe level of pesticide residue, or a "tolerance."[175]

In some cases, the agency may issue conditional registrations for new pesticides while the data needed for a full analysis of the pesticide are being developed. Conditional registrations are authorized in several types of cases, including for pesticides containing an active ingredient that is not contained in any currently registered pesticide. The registration only may be issued, however, for a period reasonably sufficient for the generation and submission of required data. Such registrations are conditioned upon the EPA receiving the required data and the data not meeting or exceeding regulatory risk criteria. In addition, a conditional registration of this type only may be granted if the EPA determines that use of the pesticide during the designated period will not cause "any unreasonable adverse effect on the environment and that use of the pesticide is in the public interest."[176] In *Woodstream Corporation v. Jackson*,[177] the Federal District Court for the District of Columbia upheld the EPA's interpretation of the statute that it may impose conditions unrelated to data requirements when it conditionally registers a pesticide under Section 3(c)(7) of the FIFRA.

In March 2008, the Agency's Region 9 office issued a $208,000 fine against the computer company IOGEAR for violations of the FIFRA that involved a nanobased pesticide. According to the EPA, the company had failed to register as pesticides nano-silver products designed to repel germs prior to distribution and had made unsubstantiated claims about their effectiveness.[178] Although the enforcement action involved a pesticide that contained nanomaterials, the presence of nanomaterials was not the basis of the action. Rather, the action was brought for failure to register a pesticide and for unproven claims about its effectiveness. Specifically, the EPA clarified that "not all products containing silver, whether nanoscale or not, are pesticides … [but any] product containing silver—in any form—that makes claims to control pests must first be evaluated and registered by the EPA to ensure it meets the FIFRA human health and environmental safety standards before it can be distributed or sold."[169] In August 2014, similar enforcement action was taken against WalkFit, a manufacturer of orthotic shoe inserts that were claimed to have antibacterial, antifungal, and germ-killing properties due to being treated with nano-silver.[179] The EPA ordered the company to pay $210,316 in civil penalties for making unsubstantiated claims, and the company has since stopped making the those claims.

In May 2008, the International Center for Technology Assessment (ICTA) and a coalition of consumer and environmental groups filed a petition with the EPA, asking it to review approximately 260 nano-silver products under the FIFRA.[180] The petition included the request that the EPA classify nano-silver as a pesticide, issue "stop sale, use, or removal orders" for unapproved nano-silver products, and develop labelling and registration requirements specific to nano-silver products.[181] On November 19, 2008, the EPA made the petition available for public review and comment.[182] In December 2014, the ICTA and the Center for Food Safety (CFS) filed suit in the U.S. District Court for the District of Columbia against the EPA over its failure to regulate novel nanomaterial pesticides. The CFS stated in its press release that "nearly six years later the agency has still failed to respond to Plaintiffs' 2008 Petition, a failure that violates the mandates of the Administrative Procedure Act (APA)."[183] The CFS asserts that since the 2008 petition was filed, "hundreds of new pesticidal nano-silver products have reached the market without any pesticide oversight from the EPA." The CFS asked the court to order the EPA to respond to its petition "without further unlawful delay."[184]

Although the EPA has not taken formal action on the petition, it has made steps toward regulating nanoscale substances in pesticides. In November 2009, the EPA convened a meeting of the FIFRA Scientific Advisory Panel (SAP) to address a number of questions associated with exposure to nano-silver and other nanoscale metal-based pesticides. The SAP advised that the toxicity of nano-silver could be higher than other forms of silver and also noted that the coating and inert ingredients of nano-silver pesticides could change its environmental effects.[185]

In part due to the advice from the SAP, the EPA proceeded to increase the regulation of nano-silver in pesticides. On July 6, 2012, the EPA announced the establishment of a registration review docket for nano-silver. According to the EPA, the registration review is a "periodic review of pesticide registrations to ensure that each pesticide continues to satisfy the statutory standard for registration, that is, the pesticide can perform its intended function without unreasonable adverse effects on human health or the environment."[186] The EPA was inclined to establish the review docket after it was made aware that some silver-based pesticide products were registered without disclosing to the EPA the presence or characteristics of the nano-silver in the products. The EPA also issued for public comment a draft document entitled "Nanomaterial Case Study: Nanoscale Silver in Disinfectant Spray." The EPA explained that the draft "aims to identify what is known and unknown about nanoscale silver to support future assessment efforts."[187] In 2013, the EPA issued a final Pesticide Registration Notice, announcing the formation of the Silver Task Force of North America to jointly develop data to support registration review of pesticide products containing silver or silver compounds as active ingredients under Section 3(g) of the FIFRA.[188] Also in 2013, the EPA proposed to register Nanosilva, a nano-silver product "used as a non-food-contact preservative to protect plastics and textiles (e.g., in household items, electronics, sports gear, hospital equipment, bathroom fixtures and accessories) from odor and stain causing bacteria, fungi, mold and mildew."[189]

In addition, in December 2010, the EPA announced that the presence of nanomaterials in a pesticide must be reported to EPA under FIFRA Section 6(a)(2). The EPA also confirmed that an active or inert ingredient is "new" if it is a nanoscale substance—even when the conventional form of the substance already is a registered product.[190] The EPA also has indicated it is considering nano labeling requirements and information collection through "data call-ins." [191]

In December 2011, the EPA decided to conditionally register a pesticide containing nano-silver as a new active ingredient.[192] The Natural Resources Defense Council challenged this conditional registration in the U.S. Court of Appeals for the Ninth Circuit. The court largely affirmed the EPA's decision, but vacated the EPA's calculated margin of exposure of risk to toddlers who touch or ingest nano-silver.[193]

Post-registration reporting requirements, cancellation, and suspension

The statute contains a host of provisions that allow the EPA to address EHS concerns that may arise after a pesticide is registered. It requires registrants of pesticides to submit adverse effects information about their products to the agency, which has issued regulations and guidance documents that outline for registrants details on "what, when and how" to report this information.[194] Some observers have noted: "Given the inherent uncertainties currently associated with the toxicological and environmental properties of nanoscale materials, there would appear to be a need for additional EPA guidance" with respect to the application of the adverse effects reporting requirement for nanoscale materials.[195]

The EPA may take steps to cancel or change a pesticide's registration if it "appears" that a pesticide or its labelling does not comply with statutory requirements or "when used in accordance with widespread and commonly recognized practice, generally causes unreasonable adverse effects on the environment." The EPA is required, however, to provide notice to the public and the registrant. It also must consider certain factors in making a determination to issue a cancellation notice, including the impact on "production and prices of agricultural commodities, retail food prices, and otherwise on the agricultural economy." In addition, the agency must notify the Secretary of Agriculture and give her an opportunity to provide comments.[196]

The statute also provides the EPA with the authority to issue an immediate ban on the production or distribution of a pesticide; it may order the immediate suspension or an emergency suspension of a pesticide if it determines the action is necessary to prevent "an imminent hazard," during the time required for cancellation or a change in classification of a pesticide registration. The EPA must first provide notice that includes its findings and then must provide an opportunity for an expedited hearing on the question of whether an imminent hazard exists. If it determines that an emergency exists that does not permit it to hold a hearing before suspending a registration, it may issue an emergency order.[197]

Pre-registration experimental use permits and exemptions

The EPA may issue a pre-registration experimental use permit (EUP) if it finds that the applicant needs the permit in order to accumulate information necessary to register a pesticide under the statute. If the use of a pesticide may reasonably be expected to result in any residue on or in food or feed, the EPA may establish a temporary tolerance level for the residue of the pesticide before issuing the EUP. The EPA may subject the experimental use to conditions and time limits. If the EUP is issued for a pesticide containing any chemical or combination of chemicals that are not included in a previously registered pesticide, the EPA may require studies to be conducted "to detect whether the use of the pesticide under the permit may cause unreasonable adverse effects on the environment." The results of the studies must be reported to the EPA before the pesticide can be registered.[198]

Pesticide imports and exports

Imported pesticides are subject to the same requirements of testing and registration as domestic products. The Secretary of the Treasury is required to notify the EPA and to provide samples upon request of pesticides that arrive in the United States. The statute provides authority to bar the pesticide from admission into the United States if the pesticide is in violation of statutory standards.[199]

Exports of pesticides, however, are not regulated in the same way under the FIFRA. Producers of exported pesticides are subject to recordkeeping requirements, certain procedural, and labeling and data requirements related to the safe storage, disposal, handling, and transportation of the pesticides, but producers are not subject to the registration requirements. In 2013, the EPA amended its pesticide export regulations to clarify the labeling requirements for unregistered pesticides intended for export.[200] In addition, if a pesticide is not registered in the United States, the exporter must obtain a statement from the foreign purchaser that acknowledges the pesticide is unregistered.[201]

Confidential business information

The FIFRA provides for the protection of CBI by allowing applicants to mark and separately file data they believe to be "trade secrets or commercial or financial information."[202] The statute and regulations set out procedures that the EPA must follow if it seeks to disclose CBI under any of the exceptions set out in the statute.[203] The statute requires that most EHS data must be available to the public.[204] It specifies, however, that the EPA may not disclose certain information related to manufacturing or quality control processes, methods for testing, detecting or measuring the quantity of deliberately added inert ingredients, and the identity or percentage quantity of such ingredients—*unless* it determines that "disclosure is necessary to protect against an unreasonable risk of injury to health or the environment."[205] In addition, CBI information concerning production, distribution, sale, or inventories of a pesticide may be disclosed in connection with a public proceeding to determine whether a pesticide "causes

unreasonable adverse effects on health or the environment, if the Administrator determines that such disclosure is necessary in the public interest."[206]

The FIFRA does not specifically address sharing of information with foreign governments for purposes of regulatory coordination.[207] The regulations do, however, encourage submitters to include a statement that allows the EPA to share information with state and foreign governments and provides that it will inform the state or foreign government of any of the confidentiality claims associated with the information.[208]

8.3 European Union Chemicals Regulation

8.3.1 Registration, Evaluation, Authorization, and Restriction of Chemicals

Background

European chemicals regulation has been consolidated and integrated with the creation of a single new EU Regulation on the REACH.[209] Having entered into force in June 2007, REACH is gradually replacing the patchwork of over 40 separate pieces of regulation that have hitherto covered different aspects of chemicals oversight in Europe. It has been described as the biggest piece of legislation the EU has ever undertaken,[210] and its full impact will only be felt once all of its elements have been implemented in the coming years.

In addition, certain provisions relating to the classification and labeling of substances were previously covered by REACH but are now dealt with in a separate Regulation on Classification, Labelling, and Packaging (CLP)[211] of substances. The CLP Regulation, which came into force in January 2009, replaces the previous rules on classification, labeling, and packaging of substances (Directive 67/548/EEC) and mixtures (Directive 1999/45/EC) after a transitional period lasting until June 2015. It aligns European regulation with the UN Globally Harmonized System (GHS) and provides the general framework for the classification and labeling of substances, including nanomaterials, independently of their quantity of production.[212] REACH and CLP are expected to play a critical role in addressing the EHS risks of nanomaterials, not least because many such substances enter the market as chemical substances for use in a variety of industrial processes and products.[213] Because of this, the application of REACH and CLP to nanomaterials will have an important impact on the EU's broader approach to nanotechnologies.

The overarching aim of REACH is to "ensure a high level of protection of human health and the environment including the promotion of alternative methods for assessment of hazards of substances, as well as the free circulation of substances on the internal market while enhancing competitiveness and innovation."[214] REACH explicitly states that it is based on the precautionary principle.[215]

REACH has introduced several significant changes to previous regulations. These include the scope of substances covered by the regulation has been expanded to include a wide range of substances that are manufactured, imported, used as intermediates or placed on the market, either on their own, in preparations or in articles;[216] the responsibility for developing and assessing data and information on chemicals and specifying conditions needed for their safe use rests with industry—manufacturers, importers, and downstream users[217] of chemicals—rather than regulatory authorities; and the provision of regulatory authorities with a graduated approach to regulating chemicals, from the comprehensive classification and labelling system for hazardous substances to the staggered registration system of quantities of one ton or more up to the more selective and interventionist authorization and restriction requirements for substances of very high concern. The notification of product- and process-oriented research and development (PPORD) to the ECHA complements this system with basic information on substances in research and development.

In addition, certain implementation aspects of REACH have been centralized at the European level in an effort to promote greater consistency among member states. The ECHA, which is located in Helsinki, Finland, was created in June 2007 to manage the registration and notification database and carry out technical scientific and administrative roles in support of REACH. The agency's main role is not only to evaluate industry's data and testing submissions and to check compliance with registration requirements but also to investigate, in coordination with national authorities, any chemicals with perceived risks. Furthermore, the ECHA is responsible for the dissemination and public access to information provided for in REACH and CLP, in addition to the protection of confidential business information.

The contrast between REACH and preceding EU Regulations and Directives is particularly evident with regard to the treatment of chemicals already on the market versus newly introduced substances. The previous system distinguished between "existing" (on the market between January 1, 1971, and September 18, 1981)[218] and "new" chemicals (on the market after September 18, 1981)[219] and required toxicologic and ecotoxicologic tests only for the latter.[220] This meant that only limited hazard information existed for the large majority of chemicals in use, and the introduction of new, and potentially less dangerous, chemicals was often hampered by comparatively more burdensome regulatory requirements.[221] As of February 1, 2015, the ECHA had granted 40791 new registrations covering 8162 unique substances (the majority of which are phase-ins) compared with 9963 registrations covering 5292 unique substances granted based on having been notified under the pre-REACH system.[222,223] REACH seeks to address this imbalance by subjecting all chemicals to the same regulatory requirements, thereby attempting to create a more level playing field between existing and new products and to encourage greater technological innovation in chemicals.

Full implementation of REACH will take years to complete. Given the large volume of chemicals that need to be registered, REACH phases in the registration requirement over an

11-year period, focusing initially on substances that are manufactured or imported in large quantities and those with potentially high toxicity. Substances in quantities over 1000 tons per year, substances that cause cancer, or mutation or interference with the body's reproductive function (CMRs), and substances in quantities over 100 tons per year that are "very toxic" to aquatic organisms had to be registered by December 1, 2010; all other relevant substances in quantities over 100 tons per year by June 1, 2013; and chemicals in quantities over one ton per year by June 1, 2018. Since the start of REACH, 9084 registrations were received for the 2013 deadline, with a total of 6598 chemicals having been registered successfully.[224]

To facilitate implementation of REACH and CLP, the EC is conducting REACH Implementation Projects (RIPs) in order to develop guidance documents and other materials. In October 2009, it started a process of publishing a series of three RIP for nanomaterials (RIP-oN), which addressed definition and identification, information requirements, and chemical safety assessment for nanomaterials.[225]

Registration

REACH applies a "no data, no market" principle to the commercialization of chemicals that reflects its stated aim that manufacturers, importers, and downstream users "should ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment."[226] In the past, public authorities had held the primary responsibility for carrying out comprehensive risk assessment; however, industry now must provide data and, in many cases, assessments of chemical safety in order to register its chemical substances.[227]

Under REACH, in order to reduce the cost to industry and to reduce animal testing, data obtained by vertebrate animal testing must be shared among potential registrants of a substance, in exchange for payment. Other information must be shared upon request of a potential registrant. REACH establishes Substance Information Exchange Forums (SIEFs) to bring registrants together to share existing test data and information and agree on the generation of new test data.[228]

The specific information requirements are set out in Annexes to REACH and vary according to the tonnage at which a substance is manufactured and its potential toxicity. The quantitative bands are set at 1 ton, 10 tons, 100 tons, and 1000 tons. The higher the band, or the more hazardous the substance, the more information is required. Information can be gathered through a variety of means, depending on factors detailed in REACH. These include use of existing data, modeling, and testing. In order to reduce industry costs and avoid unnecessary animal testing, REACH only requires new tests when it is not possible to provide the information using a permissible alternative.[229]

In addition, manufacturers and importers that place a hazardous substance on the market, either on its own or contained in a hazardous mixture, or that place on the market a substance

that is subject to registration under REACH are generally required to notify the ECHA of the identity, classification, and labeling of the substance. The information provided must include the forms or physical states in which the substance will be placed on the market.[230]

REACH also applies to substances in *articles*[231] that are produced or imported in an amount over one ton per producer or importer per year, and if those substances are intended to be released from the article during "normal and reasonably foreseeable conditions of use."[232] In addition, substances of very high concern that are present in articles above a concentration limit of 0.1% weight by weight and present above one ton per year are covered by REACH, and safe use[233] instructions are required, unless exposure to humans and environment can be excluded during normal conditions of use including disposal.[234] The ECHA may require, however, the registration of a substance in an article at any time when it considers its release to pose a "risk to human health or the environment."[235]

Manufacturers or importers of chemical substances are required to produce a *technical dossier* that contains information on the properties, uses and classifications of substances, in addition to guidance on safe use. With respect to determining the properties of a substance, REACH sets out in line with the Regulation on Test Methods (440/2008/EC) specific information requirements in its Annexes that vary, in part, according to the tonnage in which the substance is manufactured or imported.[236]

Manufacturers or importers of substances in quantities over 10 tons also are required to provide a *chemical safety report* together with the technical dossier.[237] This must include a chemical safety assessment that considers not only the use of the substance on its own and also its use in a *preparation*, in an *article*, and at all stages of the life cycle of the substance.[238] REACH states that "risk management measures should be applied to ensure … that exposure to these substances … throughout the whole life-cycle is below the threshold level beyond which adverse effects may occur."[239] Moreover, the chemical safety assessment should include (i) a human health hazard assessment; (ii) a human health hazard assessment of physicochemical properties; (iii) an environmental hazard assessment; and (iv) a PBT (persistent bioaccumulative and toxic) and a vPvB (very persistent bioaccumulative and toxic) assessment.[240] However, the chemical safety report need not include consideration of human health risks from end uses of a chemical substance in food contact materials or cosmetic products, which are both covered by other regulations and directives.[241]

Information on hazardous properties and on substance classifications in the technical dossier must be submitted to the ECHA jointly by the lead registrant on behalf of other manufacturers and importers when a substance is first registered.[242] Chemical safety reports may be, but are not required to be, submitted jointly. If the ECHA or a member state seeks to obtain information in addition to that submitted in a registration, it must follow a specific process for requesting such information, as discussed below in the section on confidential business information.

Although REACH continues to be the overarching policy that guides nanotechnology development in Europe, the Council of Europe (CoE) Parliamentary Assembly has recently taken the initiative in focusing more specifically on nanotechnology as a separate issue. The CoE has shown particular interest in renewing commitment to the precautionary principle. In November 2012, at the meeting of the CoE Committee on Social Affairs, Health, and Sustainable Development, the CoE commissioned an expert report titled "Nanotechnology: balancing benefits and risks to public health and the environment."[243] The report was publicly debated before the entire Parliamentary Assembly of the Council of Europe (PACE) in Strasbourg on April 26, 2013.

As a result, the PACE created a list of guidelines for monitoring the benefits and risks of nanotechnology for public health and the environment. According to the eight suggested guidelines, nanotechnology development should (i) "respect the precautionary principle while taking into account freedom of research and encouraging innovation"; (ii) "allow for consistent application to all nanomaterials under regulations across borders and regardless of their origins (synthetic, natural, accidental, manufactured, engineered), functional uses or biological fate"; (iii) "seek to harmonise regulatory frameworks, including the areas of risk assessment and risk management methods, protection of researchers and workers in the nanotech industry, consumer and patent protection and education (including labelling requirements taking into account informed consent imperatives), as well as reporting and registration requirements, in order to lay down a common standard"; (iv) "are negotiated in an open and transparent process," including multiple governmental and non-governmental stakeholders; (v) "can be used as a model for regulatory standards worldwide"; (vi) "first take the form of a Committee of Ministers recommendation, but could also be transferred into a binding of the legal instrument if the majority of member States so wish"; (vii) "allow for the creation of an international, interdisciplinary centre to be the world's knowledge base in the field of nanosafety in the near future" that can provide financial support for ongoing projects aimed at determining potential risks of nanomaterials; and (viii) "promote the development of an assessment system of ethical rules… regarding research projects and consumer products."[244] Despite the PACE's strong endorsement of stricter rules for regulating nanotechnology, it appears that no binding policies have directly resulted.

In 2014, the European Commission also wrapped up a 3-month public consultation period on transparency measures for nanomaterials in the market. The consultation period is part of a broader impact assessment intended to "identify and develop the most adequate means to increase transparency and ensure regulatory oversight on nanomaterials."[245] In its current form, the impact assessment offers policy objectives, descriptions of preliminary policy options under consideration, and a timetable for Impact Assessment Steering Group meetings through the end of 2014. Currently, there are a number of policy options under consideration. The first option involves a baseline scenario, in which no new regulatory policies are added. The second option involves the adoption of a "best practice model" for nanomaterial

regulation by EU member states looking to establish a national system; this approach is viewed as the soft law option. A third option is to create a "Nanomaterial Observatory" for the collection of information on nanomaterials throughout the EU. The final options include stronger regulatory actions such as creating an EU nanomaterial registry with one annual registration per substance for each nanomaterial manufacturer, importer, or distributor.

Confidential business information

If manufacturers or importers of chemical substances declare some of the information they submit in their registrations to be confidential business information, they must include a justification explaining why the publication of this information might be harmful to their commercial interest.[246] Article 118 of REACH specifically identifies the types of information the disclosure of which would normally be considered to undermine the protection of commercial interests, such as the full composition of a preparation and the precise tonnage of a substance or preparation manufactured or placed on the market.[247] Article 118 also provides, however, that where "urgent action is essential to protect human health, safety or the environment" the ECHA may disclose such information. REACH also sets out the types of information that must be made publicly available unless the party that submitted the information submits a justification that is accepted by the ECHA as to why publication would be potentially harmful to commercial interests.[248]

REACH also delineates a category of information that will be made available to the public free of charge over the Internet, which does not qualify for confidentiality protection. This includes information about classification and labeling, physicochemical data, results of toxicologic and ecotoxicologic studies, and guidance on safe use.[249]

Article 120 of REACH makes clear that confidential information received by the ECHA may be disclosed to another government or international organization pursuant to an agreement. The agreement must provide for any appropriate protection of the information and state that the purpose of the agreement is cooperation on the implementation or management of legislation concerning chemicals covered by REACH.[250]

Evaluation

REACH provides for two types of regulatory evaluations. The ECHA will perform *dossier evaluations* or completeness checks on registration materials that are submitted. It intends to conduct dossier evaluations for at least 5% of the dossiers submitted in each tonnage band. In an effort to avoid unnecessary animal testing, it will also evaluate testing proposals from registrants.[251]

REACH also provides for *substance evaluation*. In coordination with competent authorities in member states, the ECHA may conduct substance evaluations to clarify "suspicions of risks to human health or the environment."[252] To help implement these provisions, it

is developing risk-based prioritization criteria for substance evaluation and uses them to select substances for the Community Rolling Action Plan (CoRAP). The ECHA adopted the first CoRAP in 2012 for the 2012–2014 period and submits an annual CoRAP update to the Member States.[253] Member states may choose substances from the list to evaluate, but REACH does not specify the number or rate of evaluations that must be performed. Member state evaluations must be completed within 12 months. If a Member State does not prepare a draft decision that requests a registrant or downstream user to provide additional information during the 12-month period, the evaluation is deemed closed.

Any draft decision prepared by a Competent Authority of a member state requesting further information on a substance must either be accepted by all other member states' Competent Authorities, in which case the Agency takes the decision, or if an agreement cannot be reached, the Commission makes the decision.[252] The result of substance evaluations may be no action, a request to industry for further information on a substance and its safety or, as discussed further below, imposition of authorization or restriction procedures.

REACH also provides that manufacturers and importers may appeal dossier and substance evaluation decisions to the ECHA's Board of Appeals. REACH does not set a standard of review but states that the Board shall "examine whether the appeal is admissible." In addition, any decision by the agency's Board of Appeals or by the Commission can be appealed to the European Court of Justice.[254,255]

Authorization and restriction

Substances of "very high concern" (SVHC), such as CMRs, PBTs, or vPvBs, and substances posing potentially equivalent concern, may be subject to the additional process of *authorization.* Substances that are subject to authorization are listed in Annex XIV of REACH and producers or importers of such substances must apply for the authorization for "each use of the substance."[256,257]

The "comitology" procedure[258] is used to determine which substances are listed and subject to authorization. The process begins with the preparation of dossiers by member state Competent Authorities or the agency (on behalf of the European Commission); these are subject to public comment. The identified substances are considered candidates for prioritization. From the candidate list, the agency then recommends to the Commission the substances to be listed in Annex XIV.[259]

Authorization applications must include an analysis of whether suitable alternatives to the substance exist and, if so, a substitution plan also must be provided. A substance still may be authorized if the applicant can demonstrate that risks can be adequately controlled, provided it is a substance for which a safe level can be defined. If adequate control measures are not available, or the substance is an SVHC for which no safe threshold can be assumed to exist, such substances still can be authorized if the applicant can show that the "socio-economic

benefits of their use outweigh the risks and there are no suitable alternative substances or processes."[260] Authorization decisions will be reviewed within a specified time period that will be set on a case-by-case basis. Furthermore, because substances of very high concern will be "fed into the authorization system as resources allow," in some cases, substances may be placed on the market until an authorization decision is made.[261,262]

The second regulatory intervention that REACH provides is *restriction* of chemical substances, which means that the use of the substance is either subject to conditions or prohibited. In contrast to the authorization process, the burden rests with the regulators to establish that the restrictions are needed. The ECHA or the competent authorities in member states can propose restrictions by creating a dossier that demonstrates a risk to human health or the environment that must be addressed on a community-wide basis. This dossier must be reviewed by the ECHA's Committee on Risk Assessment and its Committee on Socio-economic Analyses. If neither objects to a restriction, the Commission can, in coordination with member states through the comitology procedure, restrict the manufacture, use and marketing of a chemical substance.[263]

As noted, to facilitate implementation, the EU established numerous REACH implementation projects, each of which includes the development of guidance documents[264] and other materials. Its project on "Guidance Documents for Industry" includes Guidance Documents on when and how to conduct a socioeconomic analysis under REACH[265] and on the process to be followed when applying for an authorization for manufacture and use of an SVHC.[266,267] Similarly, as part of its implementation project on "Guidance Documents for Authorities," the Commission developed a Guidance Document for the preparation of dossiers for proposed restrictions and plans to develop a Guidance Document on the criteria for prioritization of substances for its evaluation process.[268]

8.3.2 Pesticides

Pesticides used to be covered by the Plant Protection Products (PPP) Directive (91/414/EEC) and by the Biocidal Product Directive (BPD) (98/8/EC).

Regulation (EC) No 1107/2009 on the marketing of plant protection products now replaces Council Directive 91/414/EEC,[269] and the EU introduced further regulations in 2013 that deal with data requirements for plant protection products and active substances.[270]

The EU's rules establish a "dual" system, with the Commission approving the active substances contained in plant protection products and Member States authorizing these products on their territory and ensuring compliance with EU rules. The EU maintains a "positive" list of active substances that have been approved for use in plant protection products. Inclusion in this list is based on company submissions of dossiers on both the active substance and at least one formulated plant protection product containing that substance. The dossier is to provide information on the identity of the active substance, its physical

and chemical properties, effects on target pests and toxicologic and ecotoxicologic risks. The applying company first submits a dossier to a member state, which, in turn, evaluates the application and produces a report for further consideration by the European Food Safety Authority. Based on this, the Commission then produces a proposal for inclusion or noninclusion, which is subject to a vote by all Member States in the Standing Committee on the Food Chain and Animal Health. Regulations (EU) 283/2013 and 284/2013 provide comprehensive lists of the tests and studies required to support an active substance or plant production product for inclusion in the positive list.

The BPD (98/8/EC) was replaced in 2013 by the EU Biocidal Product Regulation (528/2012), which covers a wide range of biocidal product types, ranging from disinfectants to preservatives to pest controls. It requires a dedicated risk assessment for the nanomaterial form of a substance and excludes biocidal products with nanomaterials from the simplified version of the authorization procedure.[271] Both the active substances and the biocidal products that contain active substances require prior authorization before they can be placed on the market. Certain exceptions and provisional authorizations exist for substances and products currently under review. As in the previous regulatory system, active substances are approved at the EU level, while Member States are responsible for the subsequent authorization of the biocidal products, which can be extended to other Member States by mutual recognition. Unlike the previous system, the new Regulation also enables applicants to seek a new type of authorization at EU level. The Register for Biocidal Products will be used for the submission of applications, and for data and information exchange between applicants, the ECHA, Member States, and the European Commission.

8.3.3 REACH and Nanoscale Substances

Although REACH does not explicitly address nanoscale substances, it is clear from the above discussion that the new European chemicals regulation will play an important role in addressing nanotechnology-related EHS risks. What is less clear, however, is how specific REACH provisions will address existing and emerging nanoscale substances. Given the existing scientific knowledge gaps and the fast-changing nature of nanotechnology research and commercialization, this will depend not least on how the EU's new chemicals regime will be implemented in the coming years. The development of guidance documentation for REACH implementation will therefore be an important factor,[272] as will the future review of the regulation to close potential gaps in the regulatory oversight for nanoscale substances.

The importance of REACH's role in regulating nanomaterials was initially highlighted in the Second Implementation Report on the Nanoscience and Nanotechnologies: An Action Plan for Europe 2005–2009 (Action Plan 2007–2009), in which the Commission states that REACH will "provide knowledge about the safety of nanomaterials, their uses and volumes." It also explains that information from the implementation of REACH is "the foundation for a number of other legislative areas."[273]

As part of the updating of the EU's Action Plan, the Commission sponsored an online public consultation from December 2009 to February 2010 which attracted over 700 responses and comments from almost all European countries. One of the main conclusions of the report on the public consultation was that "major concerns regarding policy centre on the safety of nanomaterials and their regulation." References to REACH are found throughout the comments.[274]

A 2013 report commissioned by the EC, "Nanosafety in Europe 2015–2025: Towards Sage and Sustainable Nanomaterials and Nanotechnology Innovations," points to future steps in nanomaterial regulation. The report notes that throughout the next decade, the EC will focus on implementing and upholding the regulations laid out in the Strategic Nanotechnology Action Plan (SNAP) 2010–2015. Otherwise, the report states that "little progress has taken place" in creating further nanomaterial regulations.[275] A new definition of nanomaterials, developed by the European Commission in 2011, will be utilized in the Cosmetics Legislation, which will require labeling the presence of nanomaterials in cosmetics products produced after July 1, 2013. The report also notes slow progress in incorporating the new definition into EU legislation and into legislation from the governments of Austria, Belgium, Czech Republic, Denmark, France, Italy, Luxembourg, Spain, Sweden, Croatia, and The Netherlands.

As discussed in more detail below, one of the problems in discussing how REACH applies to different nanomaterials[276]—and especially how this compares with the situation in the United States—is the fact that REACH has been in force less than a decade. It introduces new and innovative regulatory principles that differ in important ways from earlier regulations and from corresponding regulations in other countries, but there is only limited experience with its implementation and how its principles apply particularly to nanomaterials. The European Commission has published a number of documents to address some of these uncertainties, but existing ambiguities inevitably leave scope for interpretation and debate among experts and stakeholders.[277]

As a result in part of these ambiguities, the European Parliament in April 2009 specifically called on the Commission to evaluate the need to review REACH concerning:

- simplified registration for nanomaterials manufactured or imported below one ton;
- consideration of all nanomaterials as new substances;
- a chemical safety report with exposure assessment for all registered nanomaterials; and
- notification requirements for all nanomaterials placed on the market on their own, in preparations or in articles.[278]

The Parliament's call for a review of REACH was part of a broader resolution on nanomaterials that deplored "the absence of a proper evaluation of the *de facto* application of the general provisions of Community law in the light of the actual nature of nanomaterials."

The resolution states that it does "not agree, before an appropriate evaluation of current Community legislation, and in the absence of any nano-specific provisions therein, with the Commission's conclusions that (a) current legislation covers in principle the relevant risks relating to nanomaterials, and (b) that the protection of health, safety and the environment needs mostly be enhanced by improving implementation of current legislation, when due to the lack of appropriate data and methods to assess the risks relating to nanomaterials it is effectively unable to address their risks."[279]

The resolution calls on the Commission to review legislation within 2 years "to ensure safety for all applications of nanomaterials in products with potential health, environmental or safety impacts over their life cycle, and to ensure that legislative provisions and instruments of implementation reflect the particular features of nanomaterials to which workers, consumers and/or the environment may be exposed." It also calls for a "comprehensive science-based definition of nanomaterials in Community legislation." In addition, it notes that is "particularly important to address nanomaterials explicitly within the scope" of certain legislation, including REACH.[279]

Following the resolution, it carried out a second regulatory review and published its findings in the form of a Communication, COM(2012) 572 final, in October 2012.[280] The document notes data limitations on manufactured nanoparticles in the workplace and the environment as well as technical challenges regarding the detection and monitoring of nanomaterials, referring to recent reports by scientific committees and agencies, but concludes that it is "possible to perform risk assessments of nanomaterials today." It points to the general registration requirement for all substances, whether in bulk or nano-form, under REACH, and notes that an upcoming review of REACH will assess regulatory options for clarifying how nanomaterials are addressed and their safety is demonstrated in REACH registrations. With reference to small volume nanomaterials, the Commission rejects the need to change existing rules for when a chemicals safety assessment is required. It also considers existing transparency and notification requirements for nanomaterials adequate. Overall, the Communication finds that "REACH sets the best possible framework for the risk management of nanomaterials when they occur as substances or mixtures" but notes that "more specific requirements for nanomaterials within the framework have proven necessary."[281]

The issues raised in the Parliament's resolution reflect a more general discussion during the last few years among stakeholder groups about how REACH applies to nanomaterials. To date, this discussion has generally focused on two questions: (i) whether it *covers* nanomaterials from a legal point of view (i.e., whether any gaps exist); and (ii) whether and how it can be successfully *implemented* with regard to potential EHS risks associated with nanomaterials. These two questions can be separated for analytical purposes but are, of course, closely related. For in practice the question of regulatory coverage and gaps depends

crucially on how existing legal provisions are being implemented, particularly in context of a rapidly evolving scientific field and uncertainties with regard to the identification of nanoscale substances and associated risks.

8.3.4 Nanomaterials as "Substances" Under REACH

With regard to the first question, the European Commission, in its 2008 regulatory review, states unambiguously that "nanomaterials are covered by the 'substance' definition in REACH" and are thus subject to the same regulations as other chemical substances.[282] This statement is supported by the broad definition of a substance, which is taken to mean "a chemical element and its compounds in the natural state or obtained by any manufacturing process."[283] In reaction to the Parliament's resolution, however, officials of the ECHA announced in mid-2009 a reconsideration of how nanomaterials are regulated. In particular, ECHA Executive Director Geert Dancet announced that a review of REACH's coverage of nanomaterials will be conducted during the more general legislative review that the Parliament demanded and that this will lead to "nanomaterials [being] covered in a more systematic way" after 2012.[284]

In 2011, the European Commission produced a definition of the term "nanomaterial" in Commission Recommendation 2011/696/EU, which is intended to be used by Member States, EU agencies and companies. A nanomaterial is defined as:

> … a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm–100 nm. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50% may be replaced by a threshold between 1% and 50%.[285]

As stated in the Second Regulatory Review on Nanomaterials, the Commission is aware of the need to review this definition and promote a more consistent approach in defining nanomaterials across different legislations and regulations.[286] For this reason, the Commission's Joint Research Centre (JRC) conducted a series of consultations with scientists, regulators, NGOs and industry regarding the implementation of the new definition. Having published two reports, JRC is currently preparing a third report, which will contain recommendations on how to revise the definition to improve its clarity and effectiveness.

The Commission has explained that REACH holds registrants responsible for updating the registration dossier whenever the composition, use, knowledge of risks, or classification and labeling of a substance changes (Article 22). This, according to the European Commission, means that "when an existing chemical substance, already placed on the market as a bulk substance, is introduced on the market in a nanomaterial form (nanoform), the registration dossier will have to be updated to include specific properties of the nanoform of that substance." The Commission further notes that "the risk management measures and

operational conditions will have to be communicated to the supply chain."[282] Similarly, CLP (Article 15) typically requires a new evaluation of the classification of a substance when a manufacturer, importer or downstream user becomes aware of new scientific or technical information or makes a change in the composition of a hazardous mixture.

8.3.5 Quantitative Thresholds

A further question that has arisen as REACH is being implemented is the quantitative threshold that serves as a trigger for the Regulation's registration requirement. This requirement applies to a chemical substance produced by a company only if the total production or import quantity is above one ton per year. While relatively unproblematic for conventional chemicals, this quantitative threshold raises the possibility that producers of newly introduced nanoscale substances are not required to register the chemical in nanoform and provide information that would be relevant to risk assessment. Because REACH's data requirements increase with growing production or import quantity, there is concern that the minimal requirements for low-quantity chemicals may not be sufficient to provide sufficient information to adequately evaluate a nanomaterial's risks.

These concerns were raised, for example, in the CARACAL subgroup on nanomaterials within the European Commission (CASG (Nano)) by stakeholders who questioned whether the current one-ton threshold for registration, which was designed primarily for "traditional" chemical substances, allows authorities to gather data adequately on certain nanomaterials. More recently, the one-ton threshold issue was highlighted in the Parliament's resolution, as well as a report for the Commission issued in 2010.[287]

In determining the quantity of a nanomaterial, however, the total quantity of the substance manufactured—in both bulk and nanoscale forms—is counted for the purposes of calculating whether the quantitative threshold is triggered.[288] Industry representatives have pointed out that most nanomaterials currently on the market are also on the market in bulk form in quantities above critical thresholds and would thus be covered by statutory requirements in REACH. Nevertheless, the European Commission previously acknowledged that it will need carefully to monitor the implementation of REACH and that current provisions such as quantitative triggers "may have to be modified" in the light of experience with evolving implementation.[289] So far, the Commission has not concluded that such modifications are needed.[290]

The threshold question under REACH is of particular importance because it may affect the generation of relevant data that are to be used in other regulatory contexts, including cosmetics, environmental protection, and worker safety. Because REACH will be an important first-step method of gathering relevant data that inform the risk assessment process throughout the life cycle of nanomaterials, any gaps in its coverage of nanomaterials are likely to be important issues in any regulatory review.

8.3.6 Inventories and Reporting Requirements

The importance of closing knowledge gaps about the development and commercial use of nanomaterials also is a key concern that has received considerable attention. The Parliament's resolution calls on the Commission "to compile before June 2011 an inventory of the different types and uses of nanomaterials on the European market, while respecting justified commercial secrets such as recipes, and to make this inventory publicly available [and] furthermore calls on the Commission to report on the safety of these nanomaterials at the same time."[278]

Following the resolution, a 2010 report for the Commission argued that current legislative frameworks in chemicals regulation are "unlikely to provide the complete range of information needed by regulators [to] assess the potential risks to public health and the environment from nanomaterials. An additional EU-level reporting system for nanomaterials on the market appears necessary."[291,292] Similarly, the public consultation on the new nanotechnology Action Plan for 2010–2015 revealed an "overwhelming demand" for an inventory of the types and uses of nanomaterials.[293] In addition, a study for the German Environment Ministry found that a product register is feasible from a legal perspective but recommends that such a register be organized at the European level.[294] Meanwhile, the Belgian EU Presidency in late 2010 proposed that such a register be established as part of the REACH regulation.[295] In response to these calls for a nanomaterials register, the Commission carried out several research projects for an impact assessment of transparency measures for nanomaterials. In 2014, the Commission also conducted a public consultation exercise in which it sought stakeholder views on currently available information on nanomaterials and the potential impacts of the introduction of additional transparency policy measures in the EU.[296] Although the European Commission has, so far, abstained from taking concrete measures to establish a mandatory nanomaterials register, individual Member States have introduced national measures to improve transparency in the market. The French government, in June 2010, adopted its "Grenelle II Act,", which includes a mandatory reporting requirement for "nanoparticulate substances."[297] In the United Kingdom, the Department for Environment, Food and Rural Affairs (DEFRA) introduced the Voluntary Reporting Scheme (VRS) for Engineered Nanoscale Materials[298] in 2006, Europe's first such scheme. Since the end of the scheme's 2-year pilot phase in September 2008, the DEFRA has been considering how to develop a future reporting scheme, not least since the voluntary project received only 12 submissions, representing about a third of the companies currently manufacturing nanomaterials in the United Kingdom.[299] Besides France, Denmark has initiated its own register, and Belgium has announced it will officially introduce one in 2016.[300] The European Commission, meanwhile, is in process of establishing a web platform with references to relevant information sources relating to nanomaterials, as stated in the Second Regulatory Review of 2012.[301]

8.3.7 Timing of REACH Implementation

Apart from the comprehensiveness of reporting requirements, the question of delays in producing relevant data has also raised concerns of some stakeholders about the appropriateness of REACH provisions for the purposes of nanotechnology oversight. For at least some stakeholders, the question of *when* and in what *form* certain data will be available is a critical issue as well as *whether* it will be available. As mentioned above, REACH operates a graduated system of deadlines by which different types of chemical substances need to be registered. Substances that have been manufactured in large quantities and those with potentially high toxicity are given highest priority for registration by December 1, 2010, with chemicals in quantities over 100 tons requiring registration by June 1, 2013, and chemicals in quantities over one ton needing to be "phased in" by June 1, 2018.

The question of when nanoscale substances are due to be registered depends, in part, on whether there is an equivalent bulk substance and, if so, how it is categorized under REACH (i.e., as phase-in or non-phase-in substance).[302] As described earlier, REACH requires data-sharing and preparation of a joint registration which is submitted to the ECHA by the lead registrant the first time a chemical is registered. Thus, when a nanoscale substance has a bulk counterpart that is produced in high quantities or is potentially of high toxicity, the registration materials that address the bulk and nanoscale versions of the substance were due as early as December 2010.

8.3.8 Bulk versus Nano-Forms of Substances

With regard to reporting timelines as well as data requirements, an important question is, therefore, whether nanomaterials and their counterparts in bulk form should be considered one and the same substance. In terms of coverage under REACH, substances are defined according to their chemical structure, purity, name (International Union of Pure and Applied Chemistry (IUPAC)) and Chemical Abstracts Service (CAS), and supporting spectral and analytical data. The European Commission, however, points out that "the fact that a substance has different properties can in itself not be used to decide if it is a new substance,"[302] and leaves open the possibility of extending the identification of a substance to include parameters such as particle size or geometry.[302] The introduction of particle size as a criterion may lead to a clearer distinction between nanoscale substances and bulk substances in some cases. However, further criteria may be needed if more complex nanomaterials are to be differentiated from chemically similar—but functionally different—bulk substances.

The Commission in its December 2008 report, CASG (Nano), reiterates a statement by the Commission Services and Member States Competent authorities that "[n]anomaterials having specific properties may require a different classification and labelling compared to the bulk material, also when the nanoform is derived from a bulk substance."[302] Moreover,

"the question needs to be clarified in which cases a nanomaterial is to be considered as a separate substance and in which cases it should be considered as a particular form of a bulk substance."[302]

The question of substance identification is of course of great practical relevance. For instance, the Commission had to amend Annex IV of REACH (substances for which sufficient information is known to be considered to cause minimum risk) through Regulation EC 987/2008 to remove carbon and graphite from the list of substances that are exempted from registration "due to the fact that the concerned EINECS (European Inventory of Existing Commercial Chemical Substances) and/or CAS numbers in Annex IV are used to identify forms of carbon or graphite at the nano-scale, which do not meet the criteria for inclusion in this Annex VI."[303] This decision was taken against the background of rising concerns on the hazards associated with certain forms of carbon nanomaterials and underlines the importance of distinguishing between chemical substances in nanoform and bulk form, with regard to potential hazards to human health and the environment.

8.3.9 Testing Methods

A further, and widely discussed, concern that regulators face in the implementation of REACH and CLP is the need to adjust current testing methods or develop new ones in some cases to detect specific hazards associated with certain nanomaterials. The European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) has raised this concern in a number of opinions published since 2005.[304] In its opinion of January 2009, the SCENIHR concludes that "[o]ne of the main limitations in the risk assessment of nanomaterials is the general lack of high quality exposure data both for humans and the environment … [and that] knowledge on the methodology for both exposure estimations and hazard identification needs to be further developed, validated and standardised."[305] This, of course, is a more generic problem in nanotechnology risk assessment, which concerns regulators worldwide. The SCENIHR did recognize, however, that "based on discussions in OECD and ISO working groups, a consensus is now emerging on the physical-chemical properties of nanoparticles that need to be addressed in the risk assessment process of nanomaterials."[306]

The CASG (Nano) recognized that the principles and approaches to risk assessment discussed in the REACH guidance on information requirements and chemicals safety assessment, although "considered to be applicable," do not yet address specific properties of substances at nanoscale and "will need further adjustments to be able to fully assess the information related to substances at the nanoscale/nanoform, to assess their behaviour and effects on humans and the environment, and to develop relevant exposure scenarios and risk management measures." It further recognized that to determine "specific hazards associated with substances at the nanoscale, current test guidelines may need to be modified"[307] and that "current risk assessment procedures may require modification for nanomaterials both regarding test

methods for hazardous identification and exposure assessment."[307] Thus, until revised and specific test guidelines for substances at the nanoscale exist, registrants will need to carry out toxicity testing, "according to already existing guidelines unless they have been shown to be inadequate and/or by corresponding test methods complying with the conditions laid down in … REACH."[307,308]

8.4 Comparative Analysis

This chapter builds on and updates Chapter 4 of *Securing the Promise of Nanotechnologies: Towards Transatlantic Regulatory Cooperation*, by Breggin et al. (Chatham House, 2009). The Section begins by highlighting key factors that should be considered in comparing the two approaches. The comparative analysis is not comprehensive but focuses on several important aspects of the regulatory programs: registration/notification requirements, information and data collection, and regulatory controls.

To compare how the regulatory systems would work in practice, a simple hypothetical scenario is added to highlight the potential differences in regulatory approaches. Use of a hypothetical case is particularly useful because REACH is in the early stages of implementation. The hypothetical case presented focuses on the laws and regulations that govern a range of industrial chemicals, as opposed to those specifically for pesticides, because the TSCA and REACH are likely to apply to a broad group of nanoscale materials.

8.4.1 Key Factors

Clear differences exist between the REACH and TSCA regulatory schemes. These disparities are well recognized.[309] Before examining these differences, it is important to view the comparative analysis of the two systems in a broad context.

First, REACH is less than a decade old. Implementation of its policies and regulatory tools is still being phased in. Accordingly, any comparison between the two regulatory systems must recognize that there is a long track record of TSCA implementation that allows for a more thorough assessment of how that system works in practice, while such an evaluation is not yet possible with respect to REACH.[310] At this stage, we rely primarily on legal authorities and stated policy objectives in analyzing REACH. As with any new program, many implementation challenges lie ahead, some of which could bear on the regulation of nanoscale materials. The Commission has begun to consider some of those challenges, including application of tonnage thresholds to nanoscale materials. Other implementation issues affect all chemicals regulated under REACH and will therefore also influence the regulation of nanoscale materials. These issues, as discussed above, include how to conduct a socioeconomic analysis in the context of reviewing SVHCs, prioritize substances for evaluation by the EC, and prepare dossiers for proposed restrictions.[311]

Second, although a track record exists under the TSCA for regulating chemicals generally, it is far more limited for nanomaterials. Until recently, there was only minimal information available to the public about EPA regulatory action regarding specific nanomaterials, and that information is still limited because of claims of confidential business information. Furthermore, the EPA's implementation approach is evolving and could change in significant ways in coming years as regulators gain more experience in addressing nanoscale materials. For example, as detailed above, in October 2014, the EPA sent for OMB review a proposed reporting and recordkeeping rule for nanomaterials in commerce that would require reporting of available use, production volume, exposure, and toxicity data.[312] In addition, in December 2010, the EPA announced that the presence of nanomaterials in a pesticide must be reported to the EPA under FIFRA Section 6(a)(2). The EPA also confirmed that an active or inert ingredient is "new" if it is a nanoscale substance—even when the conventional form of the substance already is a registered product.

Third, it is possible that the TSCA will be amended. As discussed, despite sporadic indications that momentum was building for reform in the 111th, 112th, and 113th Congresses, legislation was not enacted. Reform efforts appear stalled after the November 2014 elections and could remain so indefinitely in the new Congress. Nevertheless, the GAO has identified the chemicals program as a high risk area in need of reform,[313] Congressional hearings have been held in key committees[314] and legislation is likely to be introduced again in the new Congress.[315] Furthermore, the EPA Administrator has identified as a key theme "Taking Action on Toxics and Chemical Safety," including "providing technical assistance in support of bipartisan efforts to modernize the law,"[316] and prominent nongovernmental organizations continue their calls for legislative action and, in some cases, support bi-partisan approaches.[317] In addition, the principal trade association for the chemical industry recognizes the need to modernize the statute.[59]

The confluence of these factors, as well as the implementation of REACH, coupled with the data gap challenges presented by nanoscale materials, may eventually produce the political momentum needed to achieve legislative reform.[318] Some of these reforms could result in a statute that is more consistent with REACH, although the likelihood and substance of such reform are difficult to predict at this juncture.

Fourth, neither system is insular or completely independent. For example, multinational companies that operate in both the EU and the United States are subject to both regulatory systems and may choose to take similar approaches to the manufacture, use, and distribution of their chemicals that contain nanomaterials.[319] Furthermore, because EU importers are subject to REACH requirements, in some cases, they may rely on their suppliers, including U.S. exporters, to provide hazard data and safe use information required for registration.[320,321]

In addition to data generated through the projects of the Organization for Economic Cooperation and Development (OECD), data generated by companies under either system or by other entities such as university laboratories may ultimately be factored into regulatory

requirements and decisions under both systems. For example, as discussed above, companies are required to report any "reasonably ascertainable" information, including known EHS studies, as part of the TSCA premanufacture notice process, which should include any publicly disclosed studies that are submitted pursuant to the REACH registration process.[65] Dossiers prepared by industry for REACH registration similarly are required to incorporate "available information from assessments carried out under other international and national programmes,"[322] which presumably includes any information publicly disclosed through the TSCA PMN process. In addition, data obtained through one regulatory system could influence reporting under another. For example, data submitted through the REACH registration process could inform a company's obligation under the TSCA to notify the EPA when it obtains information that a chemical may present a substantial risk of injury to health or the environment. Similarly, data generated under REACH could be used by U.S. regulators to support actions to require testing of chemicals, obtain information or subpoena documents from regulated entities, or impose other restrictions.[323]

In addition, formal and informal consultations among regulators in the United States and the EU will continue to inform regulatory decisions under both systems. As discussed, although the EPA has not pursued a formal agreement with the ECHA it has instead entered into an informal agreement or Statement of Intent for sharing of information.[324]

The more informal and formal coordination and sharing of information on the regulation of nanomaterials, the more likely it is that the two approaches will result in similar regulatory decisions, despite differences in regulatory policies and authorities.

8.4.2 Comparative Analysis

REACH and the TSCA typically are viewed as very different regulatory regimes. REACH has been described as a response to the failings of the TSCA.[325] Perhaps the most frequently cited difference between the two regimes is the degree of precaution reflected in the regulatory approaches. REACH explicitly states in its first article that "[i]ts provisions are underpinned by the precautionary principle."[326] In contrast, the TSCA generally is viewed as less precautionary in approach. However, these differences may be less pronounced when it comes to actual regulatory decisions in the EU and the United States.

Despite the differences in the stated priority placed on precaution, both laws seek a balance between protection of health, environmental, and economic concerns. The TSCA states:

> Authority over chemical substances and mixtures should be exercised in such a manner as not to impede unduly or create unnecessary economic barriers to technological innovation while fulfilling the primary purpose of the Act to assure that such innovation and commerce in such chemical substances and mixtures do not present an unreasonable risk of injury to health or the environment.[327]

REACH seeks a similar balance: "This Regulation should ensure a high level of protection of human health and the environment as well as the free movement of substances, on their own, in preparations and in articles, while enhancing competitiveness and innovation."[328]

REACH and the TSCA differ, however, with respect to the burden placed on industry to develop data, to apply control measures to manage risks, and, in some cases, to ensure that the benefits of a particular chemical outweigh the costs. Because REACH places much of the burden on industry and for other reasons, many stakeholders perceive it as more precautionary in approach.[329]

Existing analyses provide useful comparisons of specific authorities and regulatory tools established under REACH and the TSCA.[330] This comparative analysis focuses on several important junctures in the regulatory process that are of particular importance to the oversight of nanoscale materials: registration and notification requirements, information and data collection, and regulatory controls. Accompanying the comparative overview of each regulatory component, we examine how the two regimes may apply in practice to a hypothetical nanoscale substance.

For our hypothetical case, we assume the following: a large private firm has developed and plans to manufacture a nanoscale substance that is derived from and has the same molecular identity as a chemical that the company manufactures in conventional form. It is the only company that manufactures the chemical in either form. The new nanoscale substance—which is manufactured as nanometer-scale particles—offers a number of functional advantages over the non-nanoscale form of the material: the smallness of the nanoparticles enables them to be incorporated into products with greater ease; the size of the particles allows functional products to be manufactured using significantly lower quantities of the substance; and changes in the reactivity of the substance when manufactured at the nanoscale allow the development of new uses.

This analysis is not intended to be a roadmap for how a particular nanoscale material will be regulated but is intended to demonstrate the differing approaches and types of questions raised at a few pivotal stages in the regulatory process. Accordingly, this analysis should not be used to inform any real-world decisions about the treatment or regulation of any actual nanoscale substance under either regulatory scheme, since that would require a more detailed analysis.

8.4.3 Premanufacture Review and Registration Requirements

The TSCA and REACH are fundamentally similar in that, for the most part, they both seek to prevent harm from chemicals before it occurs.[331] As a result, both require a company to determine prior to manufacturing a chemical whether it is subject to regulation. However, the factors that determine whether a particular chemical is subject to regulation differ considerably under the TSCA and REACH.

Both EU and U.S. regulators consider their regulatory authorities under REACH and the TSCA to cover nanoscale materials, although both regulatory schemes contain exemptions that could apply to particular nanoscale materials, as outlined above. A principal difference, however, is that REACH eliminates the distinction between new and existing chemicals, in an effort to subject all chemicals to the same regulatory oversight. Although it does not distinguish between new and existing chemicals in terms of regulatory requirements, it does delineate between non-phase-in (new) and phase-in chemicals (existing)[332] for purposes of registration time frames and, in some cases, data requirements imposed on manufacturers and importers (collectively referred to in this section as "manufacturers").[333] Furthermore, chemicals can be manufactured shortly after the registration is filed, regardless of whether the registration has been evaluated, unless the chemical is subject to authorization or restriction.

In contrast, the TSCA distinguishes between new and existing chemicals for purposes of the premanufacture obligations imposed on manufacturers and the regulatory tools available to the EPA. The most important difference is that only "new" chemicals are automatically subject to premanufacture notification and review, which allows the agency to determine whether restrictions should be imposed prior to allowing the chemical to be manufactured. A company may begin the manufacture of a chemical after 90 days in most cases, however, if the EPA does not take regulatory action. In addition, the agency can review a significant new use of an existing chemical, provided it has issued a SNUR that applies to the chemical. Otherwise, if a chemical is an "existing" chemical, a company may manufacture it without any prior regulatory review.

Hypothetical case: premanufacture review and registration requirements under the TSCA and REACH

TSCA

To determine whether it has any premanufacture regulatory obligations under the TSCA, the manufacturer would need to determine whether the nanoscale substance is a chemical substance that already is on the TSCA Inventory and thus is an "existing" chemical for purposes of regulation. Under the EPA's 2008 policy,[334,335] the key question is whether the hypothetical nanoscale substance and conventional substance have the same molecular identity, which the EPA defined as the same chemical or compositional features, as opposed to the same physical attributes such as size. Thus, it is likely that the EPA would consider our nanoscale substance an existing chemical under the policy.

If the chemical is an existing one, no further action is required prior to manufacture, unless the EPA had previously taken a regulatory action that now applies to the nanoscale substance. For example, if the EPA had issued a significant new use rule that applied to this particular nanoscale substance,[336] the manufacturer would be required to file an SNUN that includes reasonably ascertainable information, such as any known EHS studies. But the EPA has not issued a SNUR that specifically applies to the hypothetical nanoscale substance[337] or a SNUR

that covers a broad range of existing nanoscale substances.[338] Accordingly, it is likely that as an existing chemical, the nanoscale substance would not be subject to PMN reporting, and because it is not regulated by a SNUR, it would not be subject to SNUN reporting requirements.

Note: If the nanoscale substance was considered a "new" chemical, the manufacturer would need to file a PMN, unless the substance qualified for an exemption under the TSCA. It could fall under one of several exemptions. Because it would not be manufactured in small quantities for purposes of scientific experimentation or analysis, but rather for commercial purposes, it would not qualify for the research and development exemption, which is self-executing and does not require application to the EPA for approval. Other exemptions that would require EPA approval include, but are not limited to, the low- volume exemption and the low-release/low-exposure exemption. Requests for these exemptions must be made in writing to the EPA. The agency has reported on its approval of low-release/low-exposure exemptions for nanomaterials in limited cases. It has not reported publicly that it has approved any low-volume exemptions for nanoscale materials. If none of the exemptions applies to the hypothetical nanoscale substance, the manufacturer is required to file a PMN that includes any known EHS studies, which would provide the EPA with the opportunity for premanufacture regulatory review.

REACH

To determine whether the nanoscale substance is subject to REACH, the manufacturer would first decide whether any exemptions could apply to its nanoscale substance. For example, it could be exempt from REACH if it is adequately covered under other regulations (such as medicines), is a polymer, is listed in Annex V or is listed in Annex IV because sufficient information exists for it to be considered to cause minimum risk owing to its intrinsic properties.[339] In addition, if the nanoscale substance was to be manufactured for the purposes of PPORD, the manufacturer could qualify for a 5-year exemption (with additional extensions possible in some cases), provided it notified the ECHA of the exemption.[340]

If no exemptions apply, the manufacturer must determine whether the nanoscale substance will be manufactured in a quantity of one ton or more. The total quantity of the bulk chemical and the nanoscale counterpart are counted for the purposes of calculating whether the quantitative threshold is triggered.[288] Thus, the manufacturer must determine whether its nanoscale substance is the same as the bulk conventional substance it already manufactures (as is likely to be the case), by considering factors similar to those under the TSCA.[341]

If the one-ton threshold is met, the manufacturer may produce the nanoscale substance in quantities of one ton or more after it has submitted the registration information required, regardless of whether the ECHA has reviewed the technical dossier, chemical safety report, or any other information submitted as part of the registration process. Furthermore, the timing for submission of the registration materials could range from 2010 to 2018. For example, if

the nanoscale substance is a phase-in chemical (which would be likely if the conventional form has already been manufactured) and is produced in a quantity of one ton per year, the manufacturer may not be required to submit its full registration materials until June 1, 2018, but in the meantime could manufacture the nanoscale substance. However, if the nanoscale substance is a CMR, or is manufactured in quantities greater than or equal to one ton per year, or is classified as "very toxic to aquatic organisms" and produced in a quantity greater than 10 tons per year, it would need to be registered much earlier—by 2010. If the nanoscale material is not produced in sufficient quantities to trigger REACH jurisdiction when considered alone or with its conventional counterpart, it still could be regulated under REACH if it is listed as an SVHC subject to authorization or restrictions, as substances can be regulated under the authorization and restriction processes, discussed above, regardless of quantity.[342]

In summary, if the nanoscale substance is manufactured in quantities of less than one ton (when counted with its conventional counterpart) and is not an SVHC, it would not be subject to the REACH registration requirements. The manufacturer would not be required to submit registration materials and could manufacture it in amounts below the threshold, unless regulatory action was taken under the restriction or authorization process. If the nanoscale substance is covered by REACH registration requirements, following submission of the registration materials and a brief waiting period, the company could manufacture the substance.

8.4.4 Information and Data-Collection Requirements

The approaches and authorities granted to regulators to require manufacturers to produce information, including EHS data, differ significantly under the two systems. Nevertheless, in theory, both are science-based approaches that seek to assess the risk of chemicals based on data of some type.[343] As a result, although the two systems employ very different data standards and requirements, U.S. and EU regulators face fundamentally similar challenges in regulating nanomaterials. Specifically, both U.S. and EU regulators are faced with limited knowledge of the human health and ecotoxicologic effects of nanoscale substances throughout their entire life cycle. Furthermore, both need, in some cases, to adjust existing test methods or develop new ones to assess and evaluate these effects for regulatory purposes.

The key difference is that manufacturers and others subject to REACH are required to provide certain information—without action by a regulator—regardless of whether the information is already available or instead has to be generated. The scope of the information and data required and the time frame for submission vary considerably, however, depending on the quantity manufactured and potential toxicity of the chemical. Under the TSCA, manufacturers only are required to provide information automatically—without action by a regulator—if a chemical is "new" and, therefore, subject to premanufacture review. In addition, a manufacturer must provide information about "significant new uses" of existing

chemicals, but only if the EPA has issued a SNUR that applies to the chemical. Furthermore, the information that must be submitted in both cases is generally information that already exists and is reasonably ascertainable, as opposed to new information generated for the purposes of regulatory review.

Both the TSCA and REACH provide additional information-gathering authorities. For example, in order "to clarify a suspicion of risk," the ECHA may seek additional information beyond the minimum data set that is required to be submitted as part of the registration process. This process must follow an established procedure that involves notice and comment, as discussed above. Several factors will influence how this new process will work in practice, such as the resources available to the ECHA and member states to conduct dossier and substance evaluation; the extent of the need for additional information about nanoscale substances; and the efficiency of procedures required to ensure coordination among regulatory entities.

Similarly, the EPA has information-gathering authorities in addition to those associated with the premanufacture review process, but these tools must be used on a case-by-case basis, often imposing a considerable burden on the agency, and in some cases, the scope of information that can be obtained is limited. For example, the U.S. GAO has characterized the EPA's authority to require additional testing of chemicals under TSCA Section 4 as "costly and time-consuming" and notes that the EPA does not opt to "routinely test existing chemicals."[344] The EPA does use consent orders, which are less burdensome, to obtain data about chemicals. Although the agency is required to take affirmative action, it reports that it has streamlined its approach, in part, by developing chemical categories for chemicals with similar chemical and toxicologic properties. According to the EPA, this approach enables it to benefit from data accumulated over the years, as discussed above. Furthermore, the EPA often relies on structure activity relationships when it does evaluate chemicals and also seeks considerable amounts of data through a range of voluntary reporting programs.

REACH and TSCA also differ in terms of the obligations imposed on manufacturers to provide updated information to regulators. The EPA's 2011 CDR rule[345] requires reporting of information on the manufacturing, processing, and use of chemicals every 4 years. For the 2016 reporting year, the rule will apply to chemicals manufactured at a site in production volumes of 25,000 pounds or greater, with a lower threshold applied for certain chemicals.[139,140] In contrast, REACH does not require regular reporting (except as chemicals move to the next highest production quantity tier), but it does require that manufacturers notify regulatory authorities about changes in use, production quantity, and new information on risks to human health and environment and to update their registrations as appropriate. Both systems impose certain requirements with respect to reporting information about health and safety risks as it is learned.

Confidential business information is protected under both REACH and the TSCA, and both allow for its disclosure when necessary to protect human health or the environment. The systems vary considerably, however, in their treatment of CBI. As discussed above, the EPA has instituted some reforms to its CBI policies under the TSCA,[160,162] but as a general matter, manufacturers claim substantial amounts of the information they submit as CBI and are not always required to provide upfront justification for their claims. Furthermore, the EPA reviews CBI claims on a case-by-case basis and, partly because of resource constraints, has not historically reviewed or challenged large numbers of such claims, although it has stepped up its review efforts.[346]

REACH takes a different approach by delineating among types of information that (i) normally is considered CBI, (ii) must be made publicly available unless an acceptable justification is provided, and (iii) will be made available to the public free of charge. Finally, another notable difference is that REACH allows for the disclosure of CBI to foreign governments pursuant to agreements that provide for appropriate protection of the information. The TSCA does not contain an exception for CBI to be disclosed to foreign governments, except in the context of notices of regulatory actions taken against exported chemicals.

In addition to the differing regulatory authorities and tools, numerous factors will influence the breadth and depth of information that manufacturers are required to provide on nanoscale materials under each system. These factors include, for example, the extent to which the EPA uses its SNUR, test-rule, and information-gathering authorities to compel disclosure of information; how many nanoscale materials constitute new as opposed to existing chemicals under the TSCA; the number of nanoscale materials covered by REACH (e.g., that meet the quantitative threshold); how often chemical safety reports, in addition to technical dossiers, are required for nanoscale substances; and the extent to which the ECHA uses its authority to seek data on such substances, in addition to information that is required as part of the registration process.

Nevertheless, information collection is a key area in which the TSCA and REACH differ. As the U.S. GAO has concluded, REACH "generally places the burden on companies to provide data on the chemicals they produce." In contrast, "EPA's assessments of industrial chemicals under TSCA provide limited information on health and environmental risks."[347]

Hypothetical case: information and data-collection requirements under the TSCA and REACH

TSCA

Under the TSCA, the hypothetical manufacturer would not be required to provide any information to the EPA prior to manufacturing the nanoscale substance if the substance is considered an existing chemical and the EPA has not issued a SNUR that applies to the

nanoscale substance. If a SNUR applied to the nanoscale substance or it was considered a "new" chemical, the manufacturer typically would be required to file a "premanufacture" or "significant new use" notice that included any known EHS studies. In addition, the manufacturer would be required to comply with reporting requirements that govern existing chemicals under the TSCA, such as submitting upon request records of "adverse reactions to health or the environment" caused by the hypothetical nanoscale substance[133] and notifying the EPA if it obtained any information that the nanoscale substance "presents a substantial risk of injury to health or the environment."[348] If it manufactured the nanoscale substance in large enough quantities, it also could be required to comply with the CDR rule and provide certain information to the EPA every 4 years.[345] Finally, unless it is exempt as a small manufacturer, it would be required to provide information about the nanoscale substance that is requested by the EPA under Section 8(a) but only "insofar as known" or "reasonably ascertainable."[349]

The manufacturer would not be required to submit any additional information or data about the nanoscale substance unless the EPA took regulatory action under its test-rule, information-gathering, SNUR, or subpoena authorities.[350] As discussed above, the use and scope of some of these regulatory tools may be limited. For example, the scope of information that the EPA could compel the manufacturer to produce under several information-gathering authorities would be limited, for the most part, to information that is known or reasonably ascertainable, as opposed to new information generated by the manufacturer.

REACH

Under REACH, the manufacturer would automatically be required to submit certain information as part of the registration process. Because the nanoscale substance would be manufactured in conventional form by the manufacturer, the two would be considered together for the purposes of determining the information requirements for registration. The extent of information required could vary considerably depending on the quantity manufactured and potential toxicity. To take just two of the many possible scenarios, if the nanoscale is a phase-in substance that with its conventional counterpart will be manufactured in quantities of one ton or more per year, physicochemical property data would be required. Additional data would be required if the substance is an SVHC or is potentially dangerous to health or the environment and used in a dispersive manner.[351] If it is manufactured in quantities over 10 tons, the manufacturer would also be required to provide a chemical safety report that includes a wider range of toxicologic and ecotoxicologic information. Regardless of the scope of the information required, the manufacturer would need to include information specific to the properties of the nanoform if they differ from the conventional form, including, for example, any different classification and labeling, safety assessment, identified uses and exposure scenarios.[352]

Until specific test guidelines for nanoscale substances are developed, the manufacturer would need to carry out toxicity testing, according to existing guidelines, unless they are shown to

be inadequate, and/or by corresponding test methods that comply with the conditions set out in REACH.[353] Furthermore, it could rely on ECHA guidance on information requirements and chemicals safety assessment; however, it is recognized that the guidance will need to be adjusted to enable assessment of the behaviour of nanoscale substances and their effects on humans and the environment and to develop relevant exposure scenarios and risk management measures.[354]

Although the manufacturer would have an affirmative obligation to provide information, it may not need to file a full registration that addresses the nanoscale substance until the conventional substance is required to be fully registered, which could be as late as 2018. It is possible, however, that the production of the nanoscale substance could, in some manner, change the registration requirements and time frame that apply to the conventional substance by, for example, increasing the tonnage manufactured.[355]

The manufacturer would have no other reporting obligations unless there were significant changes in use or production quantity, or unless the ECHA, in coordination with the Competent Authorities of Member States, requested additional information in order to "clarify suspicions of risks to human health or the environment." As discussed, such requests must be made pursuant to an involved process and it is unknown how frequently this process will be used.[356]

Finally, the manufacturer could submit data on the nanoscale substance even if it is not required by regulation. The Commission encourages companies to consider voluntary options such as registering substances before the applicable relevant deadline, registering substances even if they are manufactured below the one-ton threshold, and generating further information beyond what is required to demonstrate that the risks of a nanoscale substance are controlled.[357]

8.4.5 Regulatory controls

The TSCA and REACH take differing approaches to regulating the manufacture, use, and distribution of chemicals. One of the most notable differences is the REACH authorization process, which provides for regulators to develop a list of SVHCs that are then subject to a prioritization process to determine which chemicals will be subject to authorization. Once a substance is subject to authorization, manufacturers must apply for authorization for each use and bear the burden of demonstrating that the risks associated with the use of the substance are adequately controlled or that the socioeconomic benefits outweigh the risks.[358] Manufacturers must also analyze whether a safer alternative exists and, if so, must prepare a substitution plan.[359]

The TSCA does not prioritize chemicals in this manner and does not require manufacturers to perform substitution analyses. Although the REACH approach is markedly different from the approach taken under the TSCA, several factors will influence how the prioritization process

works in practice. These include the efficiency and effectiveness of the process for identifying SVHCs and subjecting them to authorization; the extent to which SVHCs ultimately will be allowed on the market owing to the required consideration, in some cases, of adequate control measures and socioeconomic factors; and whether industry-performed substitution analyses result in a substantial number of replacements. Nevertheless, the authorization process represents a significant departure from the approach taken under the TSCA to prioritizing chemicals and addressing their risks.

Another key method under REACH for regulating chemicals is the restriction process, which bears some similarity to the TSCA chemical review and regulatory process. Both require regulators to examine chemicals on a case-by-case basis and determine whether controls are needed. As discussed, the substantive and procedural burdens placed on the EPA before it can impose restrictions vary, depending on whether the substance is considered a new or an existing chemical. There is a long history of efforts to restrict chemicals under the TSCA, and many argue this suggests the need for reform, particularly with respect to existing chemicals.[314] Under REACH, regulators also may seek to impose similar restrictions on chemicals, but the standards and process for doing so differ.

Under REACH, the same standard applies to all chemicals. Restrictions may be imposed when a Member State or the ECHA demonstrates an "unacceptable risk to health or the environment" that must be addressed on an EU-wide basis. It is difficult to determine at present how burdensome the review process will be to determine whether restrictions are needed and if so to make that showing and, therefore, how it will compare to the TSCA standards for imposing restrictions on new and existing chemicals. It also is unknown whether the involved procedures for imposing such restrictions under REACH will work effectively and efficiently, as restrictions can only be imposed if proposed in a dossier that is reviewed by the ECHA's Committee for Risk Assessment and Committee for Socio-Economic Analysis. The committees, in turn, must prepare and submit opinions on the proposed restrictions to the Commission, after obtaining public comment. It is only then that the latter can compose a draft amendment to REACH and decide on the restriction.[360] Furthermore, as many proposed restrictions will be based on dossier and substance evaluation, the use of the restriction process will depend, in part, on the resources available to regulators. Despite these considerations, however, in seeking to impose restrictions EU regulators will have substantial information and data available to them as a result of the registration process.

Finally, in addition to the authorization and restriction process, REACH requires through the registration process that manufacturers apply "appropriate measures to control risks" that they identify in their chemical safety assessments. It is difficult to determine the practical effects of this requirement, in addition to public disclosure of at least some of the required information, on the identification and implementation of control measures. For example, it is unclear how far resource constraints will influence regulators' ability to evaluate the appropriateness of the

control measures identified and whether they have been applied. Nevertheless, it is notable that REACH imposes on manufacturers an affirmative duty to assess risks, identify control measures and implement them. The TSCA does not have a corresponding requirement. Control measures may be imposed by regulators under Sections 5 and 6 of the statute under certain circumstances, discussed above. In addition, manufacturers may apply such measures voluntarily and report them as part of the PMN or SNUN process in order to inform the EPA's review, but the TSCA does not impose an affirmative duty on manufacturers with respect to such measures.

Hypothetical case: regulatory controls under REACH and TSCA

TSCA

If the nanoscale substance is considered an existing chemical on the TSCA Inventory, the EPA could in theory impose a wide range of restrictions including, for example, prohibiting or limiting the amount manufactured or distributed.[101,361] As discussed above, however, the procedural and substantive requirements imposed on the EPA under the law mean it would find it difficult to regulate the nanoscale substance under this authority, which it has used only five times since the statute was enacted in 1976.[362] In addition, the EPA could, in theory, seize the nanoscale substance or products containing it if it determined that it was an "imminently hazardous" chemical. Again, the agency does not regularly use this authority and would be required to file a civil action in district court to do so.[110]

Finally, if it is considered an existing chemical, the EPA could review the hypothetical nanoscale substance using its authority to regulate "significant new uses" of existing chemicals—if it had already issued, prior to manufacture of the nanoscale substance, a chemical-specific SNUR or a SNUR that applied more broadly to certain categories of nanoscale substances. Neither of these situations applies to our hypothetical nanoscale materials. If, however the hypothetical nanoscale substance is considered a new chemical, the manufacturer would be required to file a PMN that contains information about the chemical, including "reasonably ascertainable" information about known environmental and health effects, its expected uses, and expected exposure.[363]

REACH

Under REACH, the nanoscale material could, in theory, be regulated through either the restriction or authorization process. The substance would only be subject to the authorization process if it is specifically included in Annex XIV because it is a CMR (category 1 or 2), a PBT, a vPvB, or a chemical identified from scientific evidence as causing equivalent probable serious effects to humans or the environment.[364] Whether the manufacturer would ultimately be allowed to manufacture the nanoscale substance could depend on several factors, including the availability of safer substitutes. The substance still could be manufactured if the manufacturer demonstrates that it is adequately controlled, but this would not be permitted

if it is a PBT, a vPvB, or a CMR substance for which a safe level could not be defined. Such a substance could only be manufactured for a specific use if there are no substitutes for that use and its socioeconomic benefits outweigh the risks. Furthermore, SVHCs are "fed into the authorization system as resources allow."[364] Thus, even if the nanoscale substance is a SVHC, it may not immediately be subject to regulatory action under REACH and could be placed on the market with controls determined to be adequate by the manufacturer until a decision is made through the authorization process.[365]

In addition, either a Member State or the ECHA could propose restrictions on the nanoscale substance, as discussed above. However, this process requires a demonstration of "an unacceptable risk to health or the environment" that must be addressed at an EU-wide level and, in most cases, only can be imposed through a multistage process.[366]

8.5 Conclusion

In summary, the TSCA and REACH differ considerably in their approaches to regulation of chemicals generally and nanoscale materials in particular, including differences in policies, authorities, and requirements. Nevertheless, many factors will influence the extent and manner to which these differences in approach result in disparate regulatory actions. These factors include implementation resources, interpretation of regulatory authorities, subsequent legislative reforms, and the extent to which regulators coordinate and share information at this critical juncture in the regulation of nanoscale materials.

Endnotes

1. As nanotechnologies lead to entirely new methods in mechanical, electrical and bioengineering, they are often compared to other new technologies with broad societal impacts. For example, Christine Peterson compares nanotechnology to the industrial revolution in the eighteenth and early nineteenth centuries Peterson (2000). Similarly, participants in a recent forum hosted by the U.S. Government Accountability Office (GAO) described nanomanufacturing as a "future megatrend" that may "match or outstrip the digital revolution in terms of economic importance and societal impact" US Government Accountability Office (2014, p. 17).
2. A reproduction of the lecture can be found on the homepage of Zyvex, a molecular nanotechnology company, available at http://www.zyvex.com/nanotech/feynman.html (accessed 21.12.14.).
3. Throughout this chapter, we refer to intentionally created nanomaterials (also referred to as engineered or manufactured nanomaterials), rather than incidental ones (e.g., car exhaust emissions) or those occurring naturally.
4. The International Council on Nanotechnology (ICON) provides a useful overview of the relevant toxicological literature, updated through September, 2014, available at http://icon.rice.edu/virtualjournal.cfm (accessed 21.12.14.).
5. Breggin et al. (2009).
6. The Royal Society and the Royal Academy of Engineering (2004).
7. Lövestam et al. (2010, pp. 12–20) (collecting definitions of relevant terms).
8. For ISO terminology and definitions for nano-objects, see ISO (2010) and other technical specifications issued by TC229. However, these definitions are not universally accepted (Roco, 2011).

9. The Joint Research Centre of the European Commission noted that "representatives from science, industry and regulatory bodies concerned with subjects of nanotechnology, currently lack, and strongly need, a common definition for the term 'nanomaterial." Lövestam et al. (2010, p. 10). Similarly, participants in a forum organized by the U.S. Government Accountability Office indicated that "the current lack of a unified system to describe nanomaterials—including naming conventions, definitions, and standards [is] a possible limitation on innovation efforts." US GAO (2014, p. 34).
10. Subcommittee on Nanoscale Science Engineering and Technology (2014, p. 1).
11. While 100 nanometers is a commonly used cut-off point for defining nanomaterials, it is important to note that from a regulatory point of view it is the unique chemical and physical properties of nanomaterials that are of primary interest, and that these properties extend to materials above 100 nanometers, in some cases up to 300 nanometers.
12. The International Organization for Standardization (ISO, 2010). These definitions are broad enough to encompass a range of more specific materials, including nanoparticles, nanostructures, and nanoscale substances (ISO, 2008). Further distinctions can be made between naturally occurring nanomaterials and (deliberately) manufactured nanomaterials (the latter being of primary concern in the context of this chapter) and between transitive and nontransitive nanomaterials, with the former exhibiting "size-related intensive properties that differ significantly from that observed in fine particles or bulk materials," whereas the latter do not. When using the term *nanomaterials*, this chapter implicitly refers to deliberately manufactured transitive nanomaterials.
13. For an additional consensus-based definition of nanotechnology, see also ASTM (2012).
14. Roco (2004, 2011).
15. US Environmental Protection Agency (2007a).
16. Davies (2009) and Rodemeyer (2009).
17. Roco (2011, p. xlix).
18. Lux (2008, p. 9).
19. Klein (2007) and Lane and Kalil (2005).
20. Federal nanotechnology funding for research and development has leveled off in the United States in recent years but is approaching a cumulative $20 billion, whereas private funding was estimated at $24 billion in 2012. See US GAO (2014, pp. 5–6).
21. Roco and Bainbridge (2001, p. 3) and Lux Research (2008).
22. Lux Research (2014) and Whitman (2014).
23. See, for example, Berger (2007).
24. The U.S. Government Accountability Office recently profiled the impact of nanotechnologies across four sectors, including semiconductors, battery-powered vehicles, concrete, and medicine, noting rapid past economic growth and potential for future expansion in key areas. See US GAO (2014, pp. 79–98).
25. Project on Emerging Nanotechnologies (2014).
26. Owing to delays driven by the difficulty of assessing developments in novel technologies, the time it takes for the USPTO to reach a decision increased from an average of 33 months in 1985 to 47 months in 2005 (Lux, 2008).
27. Chen et al. (2008).
28. US GAO (2012). Examples of recent EHS research initiatives include commitments by the U.S. EPA and U.S. National Science Foundation to distribute up to $32 million to support research on safer chemical design, US EPA (2012a), and by the U.S. EPA and the US Consumer Products Safety Commission to collaborate on a worldwide research effort to assess the potential impacts on nanomaterials on human health and the environment. See US Environmental Protection Agency (2012b).
29. Klein (2007).
30. Service (2008).
31. International Council on Nanotechnology (2008).
32. US Government Accountability Office (2014, pp. 6–7).
33. See, for example, Sargent et al. (2013), Takagi et al. (2008), and Poland et al. (2008).
34. National Institute for Occupational Safety and Health (2013).
35. US Government Accountability Office (2014, p. 7).
36. See, e.g., Scientific Committee on Emerging and Newly Identified Health Risks (2009).

37. Maynard (2008, p. 3) and Youtie et al. (2008).
38. EPA (2007a).
39. Other federal agencies, notably including the U.S. Food and Drug Administration (FDA) and the Consumer Product Safety Commission also regulate nanomaterials under other legislation. For a discussion of additional regulatory authorities, see Breggin et al. (2009, pp. 16–18); Carolyne Hathaway et al., Toxic Substances Control Act Deskbook (ELI, 2012).
40. EPA (2011, p. 2).
41. Breggin and Pendergrass (2007), http://www.nanotechproject.org/file_download/files/NanoEnd-of-Life_Pen10.pdf (accessed 14.01.15.).
42. Breggin and Porter (2008), http://www.nanotechproject.org/process/files/6088/brief2_eli_2_5_08.pdf (accessed 14.01.15.).
43. Breggin and Porter (2008), http://www.nanotechproject.org/process/files/6088/brief2_eli_2_5_08.pdf (accessed 14.01.15.).
    2014-09-16/html/2014-22062.htm (accessed 28.01.15.).
44. 15 U.S.C. § 2601.
45. Davies (2006).
46. Applegate (2008, p. 723).
47. GAO (2009a, pp. 22–24).
48. GAO (2006).
49. See also Sachs (2009) (characterizing the statute as the 'lapdog of US environmental law').
50. See also Committee on Environment and Public Works, U.S. Senate (2008) (statement of Jim Gulliford).
51. EPA, Essential Principles for Reform of Chemicals Management Legislation, (n.d.), http://www.epa.gov/opptintr/existingchemicals/pubs/principles.html (accessed 14.01.15.).
52. EPA, Enhancing EPA's Chemical Management Program, (n.d.), http://www.epa.gov/opptintr/existingchemicals/pubs/enhanchems.html (accessed 14.01.15.).
53. GAO (2013, pp. 13–249).
54. The Environment Council of the State, Resolutions, http://www.ecos.org/section/policy/resolution (accessed 28.01.15.).
55. See also Richard A. Denison, Ten Essential Elements in TSCA Reform (2009) http://www.edf.org/sites/default/files/9279_Denison_10_Elements_TSCA_Reform_0.pdf (accessed 28.01.15.).
56. See also Committee on Environment and Public Works, U.S. Senate (2006) (statement of Michael Wall).
57. American Chemistry Council (2009).
58. 15 U.S.C. § 2604(a); see also 15 U.S.C. § 2602(7), (11) (defining covered entities).
59. 15 U.S.C. § 2604(a)(2)(A)–(D). These criteria include, but are not limited to, 'the extent to which a use changes the type or form of exposure of human beings or the environment' and 'the extent to which a use increases the magnitude and duration of exposure of human beings or the environment'. In issuing a chemical-specific SNUR, the EPA may rely on its generic SNUR regulations, which set out categories of significant new uses, such as "any manner or method of manufacturing, importing, or processing associated with any use of the substance" without establishing a worker protection programme that includes, for example, certain personal protective equipment. See e.g., 40 C.F.R. § 721.63.
60. Duvall and Wyatt (2009, p. 7).
61. SNURs for new chemicals can be issued using expedited rulemaking procedures in some cases that do not require full notice and comment rulemaking procedures. See US GPO, http://www.gpo.gov/fdsys/granule/FR-1995-03-29/95-7710 (accessed 30.01.15.).
62. 40 C.F.R. § 721.25.
63. 15 U.S.C. § 2604(d).
64. 15 U.S.C. § 2604(b).
65. GAO (2005, p. 11).
66. GAO (2005, pp. 12–15) (discussing the merits and weaknesses of the EPA's approach); see also Committee on Energy and Commerce, US House of Representatives (2009) (J.C. Davies stating "[u]nder the best of

circumstances structure–activity relationship analysis has limitations, but it is useless when there are no similar chemicals with known risks, as is the case with nanomaterials"). See also GAO 2013 Annual Report, (August 2013) http://www.gao.gov/assets/660/653604.pdf (accessed 30.01.15.).

67. 40 C.F.R. § 723.50.
68. Applies when 10,000 kilograms or less of the substance will be manufactured or imported each year.
69. 40 C.F.R. § 720.36; see also 15 U.S.C. § 2604(h)(3).
70. GAO (2007, p. 8).
71. See e.g. 40 C.F.R. § 720.50(a) (test data submission requirement).
72. 15 U.S.C. § 2604(f) (providing authority to EPA to issue a proposed rule, a proposed order, or apply for a judicial injunction).
73. 15 U.S.C. § 2604(f)(2).
74. 15 U.S.C. § 2604(e)(1)(A).
75. Bergeson and Hester (2008, p. 18).
76. Bergeson and Hester (2008, p. 18). The EPA explains that "most Section 5(e) Orders require the PMN submitter to develop and submit to EPA certain toxicity or fate tests before exceeding a specified production volume ("test trigger") designed to allow sales of the chemical to generate enough revenue to pay for the testing. Exposure-based section 5(e) Orders consist primarily of a requirement to conduct triggered testing (plus recordkeeping and "risk notification" in case the test data indicates a risk.) Risk-based TSCA section 5(e) Orders, depending on the type of concerns identified by EPA for a given PMN substance, typically also require exposure controls such as gloves, goggles, respirators, specified disposal technologies or restrictions on releases to water, and hazard communication such as material safety data sheets (MSDS), labels, and training." EPA, Possible Outcomes of a PMN Review, http://www.epa.gov/oppt/newchems/pubs/possible.htm (accessed 02.03.15.).
77. EPA, Chemical Categories Reports, http://www.epa.gov/oppt/newchems/pubs/chemcat.htm (accessed 02.03.15.).
78. EPA (2010b).
79. EPA (2010).
80. More recently, James Alwood, Program Manager for the Chemical Control Division, Office of Pollution Control and Toxics, U.S. Environmental Protection Agency, indicated that the EPA does not take action on 85–90% of new chemicals. Alwood et al. (2014), http://www.awma.org/events-webinars/~/conferences/conferences-detail-view/webinar--regulation-of-nanotechnology---practical-information-for-industry--researchers-and-other-stakeholders (on file with authors—accessed 14.01.15.).
81. EPA (2008a, pp. 2–3).
82. EPA (2009a, p. 18).
83. EPA (2008e, pp. 64946–64947).
84. See e.g., Denison (2008a) (concluding that the EPA's recent statement "flies in the face of nano-science, which makes clear that a nanomaterial's properties are dictated at least as much by its physical characteristics as by its chemical structure'); See also Bergeson and Hester (2008, pp. 22–28) (emphasizing the alternative authorities available to the EPA to regulate nanomaterials that are not considered "new" chemicals, most notably its authority to regulate significant new uses of existing chemicals).
85. EPA (2010d).
86. In 2010, the EPA compiled a generic list of structural characteristics, entitled "Material Characterization of Carbon Nanotubes for Molecular Identity (MI) Determination & Nomenclature." The system classifies carbon nanotubes by primary molecular identity (MI) features, such as weight, wall or tube number, type of wall or tube ends, tube length, wall or tube width, ring size and connectivity, hexagonal array orientation, and alignment of long axis. Carbon nanotubes can be further classified by secondary MI features, including deformities, ring hybridization, and agglomeration—Alwood (2014), http://www.awma.org/events-webinars/~/conferences/conferences-detail-view/webinar--regulation-of-nanotechnology---practical-information-for-industry--researchers-and-other-stakeholders (on file with authors--accessed 14.01.15.).
87. Other relevant information includes the method of manufacturing the nanotube, the surface treatment used, its purity, and it uses. Bergeson (2013).

88. Alwood et al. (2014), http://www.awma.org/events-webinars/~/conferences/conferences-detail-view/webinar--regulation-of-nanotechnology---practical-information-for-industry--researchers-and-other-stakeholders (on file with authors—accessed 14.01.15.). (Stating that as of October 2014 EPA had received 160 new chemical notices for nanomaterials since 2005).
89. EPA, Control of Nanoscale Materials under the Toxic Substances Control Act (April 2010), http://www.epa.gov/opptintr/nano/ (accessed 16.01.15.); EPA (2009a, p. 23).
90. Alwood et al. (2014) (on file with authors), http://www.awma.org/events-webinars/~/conferences/conferences-detail-view/webinar--regulation-of-nanotechnology---practical-information-for-industry--researchers-and-other-stakeholders
91. EPA, Significant New Use Rule; Chemical-Specific SNUR to Extend Provisions of Section 5(e) Orders, Federal Register (2010), http://federalregister.gov/r/2070-AB27 (accessed 16.01.15.).
92. Alwood et al. (2014), http://www.awma.org/events-webinars/~/conferences/conferences-detail-view/webinar--regulation-of-nanotechnology---practical-information-for-industry--researchers-and-other-stakeholders (on file with authors--accessed 14.01.15.). See e.g., 40 C.F.R. § 721.10287.
93. GAO (2005, Cover Page) (according to the Government Accountability Office, 'TSCA prohibits the disclosure of confidential business information, and chemical companies claim much of the data submitted as confidential. Although EPA has the authority to evaluate the appropriateness of these confidentiality claims, EPA states that it does not have the resources to challenge large numbers of claims'); see also http://nanotech.lawbc.com/2013/02/articles/united-states/federal/epa-proposes-snurs-for-37-chemical-substances-including-14-nanomaterials/.
94. GAO (2005, p. 32).
95. EPA (2009a, p. 23).
96. The EPA separately has indicated that the exemptions are under the low-release, low-exposure exemption. See also EPA (2009b) (according to the EPA, the "exemption is intended to encourage companies to develop manufacturing, processing, use, and disposal techniques which minimize exposures to workers, consumers, the general public, and the environment").
97. Denison (2005, p. 4); see also Nanosafe, Efficiency of Fibrous Filter and Personal Protective Equipments Against Nanoaerosol*s*, (January 2008) http://www.nanosafe.org/home/liblocal/docs/Dissemination%20report/DR1_s.pdf (accessed 16.01.15.).
98. EPA (2009a, p. 10).
99. EPA, Report No. 12-P-0162: EPA Needs to Manage Nanomaterial Risks More Effectively, (2011, pp. 11, 16), http://www.epa.gov/oig/reports/2012/20121229-12-P-0162.pdf (accessed 28.01.15.).
100. 15 U.S.C. § 2605(a). See also TSCA Chemical Substances Inventory, http://catalog.data.gov/dataset/tsca-inventory (accessed 16.01.15.). (There are approximately 83,000 chemical substances on the Inventory at this time).
101. 15 U.S.C. § 2605(a).
102. Although the standard for imposing requirements differs with respect to new and existing chemicals, the types of requirements that can be imposed are similar and include, for example, prohibiting or limiting the amount of manufacturing, processing, or distribution of the chemical; requiring any article containing the chemical to be labeled or accompanied by warnings and instructions; regulating the manner or method of commercial use; and directing manufacturers or processors to give notice of unreasonable risk of injury to distributors.
103. § 2605(c).
104. 15 U.S.C. § 2605(c)(1)(C), (D).
105. GAO (2005, pp. 58–60). http://www.gao.gov/assets/660/653276.pdf.
106. 15 U.S.C. § 2618(c).
107. See *Corrosion Proof Fittings v. Envtl. Prot. Agency* 947 F.2d 1201 (5th Cir. 1991); see also GAO (2007, p. 20) (stating that "the court found that EPA … failed to show that the control action it chose was the least burdensome reasonable regulation required to adequately protect human health or the environment. … the proper course of action for EPA, after an initial showing of product danger, would have been to consider

the costs and benefits of each regulatory option available under Section 6, starting with the less restrictive options, such as product labeling, and working up through a partial ban to a complete ban").

108. GAO (2013, p. 21). http://www.gao.gov/assets/660/653276.pdf.
109. GAO (2013, Introduction). http://www.gao.gov/assets/660/653276.pdf.
110. 15 U.S.C. § 2606(a).
111. 15 U.S.C. § 2606(f).
112. GAO (2010), http://www.gao.gov/new.items/d10549.pdf.
113. Fed. Reg. (58 FR 51735) http://www.reginfo.gov/public/jsp/Utilities/EO_12866.pdf.
114. OMB, Nanoscale Materials; Significant New Use Rule (SNUR), RIN: 2070-AJ67, (2010). http://www.reginfo.gov/public/do/eAgendaViewRule?pubId=201010&RIN=2070-AJ67&operation=OPERATION_PRINT_RULE (accessed 16.01.15.).
115. Environmental Defense Fund, A hint of movement in the Super Slo-Mo that is nanoregulation at EPA under TSCA, (2014), http://blogs.edf.org/health/2014/10/08/a-hint-of-movement-in-the-super-slo-mo-that-is-nanoregulation-at-epa-under-tsca/#more-3987 (accessed 16.01.15.).
116. OMB, Chemical Substances When Manufactured or Processed as Nanoscale Materials; TSCA Reporting and Recordkeeping, (2014) http://www.reginfo.gov/public/do/eAgendaViewRule?pubId=201410&RIN=2070-AJ54 (accessed 16.01.15.).
117. See also: Bergeson & Campbell PC, Nano and Other Emerging Technologies Blog (n.d.) (http://nanotech.lawbc.com/articles/united-states/federal/ (accessed 16.01.15.).
118. 15 U.S.C. § 2603(a); see also *Chem. Mfrs. Ass'n v.US Envtl. Prot. Agency* 859 F.2d 977, 984 (D.C. Cir.1988) (upholding EPA's test rule).
119. 15 USC § 2603(a)(1)(A)(i), (B)(i); see also Denison (2008b) (explaining: "[i]n virtually all cases where it has issued test rules for conventional chemicals, EPA has relied on making the second, exposure-based finding. For nanomaterials, however, making such a finding may prove much more difficult …. These values are virtually astronomically high for most nanomaterials").
120. 15 USC § 2603(a)(1)(A)(ii), (B)(ii).
121. 15 U.S.C. § 2603 (a)(1)(A)(iii), (B)(iii).
122. GAO (2007, p. 20).
123. GAO (2013). http://www.gao.gov/assets/660/653276.pdf.
124. EPA (2009c) (under the HPV program, "companies are 'challenged' to make health and environmental effects data publicly available on chemicals produced or imported in the United States in the greatest quantities").
125. See EPA, Nanoscale Materials Stewardship Program, http://www.epa.gov/oppt/nano/stewardship.htm (accessed 15.01.15.).
126. See EPA, Nanoscale Material Stewardship Program: Interim Report (January 2009), http://www.epa.gov/opptintr/nano/nmsp-interim-report-final.pdf (accessed 16.01.15.). Listing participating companies and trade associations and the nanoscale materials covered by the reporting.
127. EPA (2009a, p. 9).
128. EPA (2008b).
129. See e.g., Denison (2009b).
130. General Services Administration, View Rule, Multiwall Carbon Nanotubes, available at http://www.reginfo.gov/public/do/eAgendaViewRule?pubId=200904&RIN=2070-AJ47 (accessed 23.01.15.).
131. OMB, Nanoscale Materials; Test Rule for Certain Nanoscale Materials, RIN: 2070-AJ47, (2010) http://www.reginfo.gov/public/do/eAgendaViewRule?pubId=201010&RIN=2070-AJ47 (accessed 16.01.15.).
132. A nongovernmental organization expert theorized that the EPA decided not to pursue a proposed test rule because of the "quagmire" the other proposed nanomaterial—related rules had experienced. See also: Dennison Richard, A hint of movement in the Super Slo-Mo that is nanoregulation at EPA under TSCA, (2014) http://blogs.edf.org/health/2014/10/08/a-hint-of-movement-in-the-super-slo-mo-that-is-nanoregulation-at-epa-under-tsca/#more-3987 (accessed 16.01.15.).
133. 15 U.S.C. § 2607(c).

134. 15 U.S.C. § 2607(e).
135. EPA, Claims of Confidentiality of Certain Chemical Identities Submitted under Section 8(e) of the Toxic Substances Control Act (January 2010), http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-1013-0001 (accessed 30.01.15.).
136. See Environmental Defense Fund (2007, p. 22) (addressing the small manufacturer exemption).
137. 15 U.S.C.§ 2607(a); see also EPA (2009d) (explaining that "Section 8(a) regulations can be tailored to meet unique information needs (e.g., via chemical-specific rules) or information can be obtained via use of 'model' or standardized reporting rules,' such as the 'Preliminary Assessment Information Rule' (or PAIR), which requires producers and importers of a listed chemical to report certain site-specific information on a two page form").
138. 40 C.F.R. § 710.52. (2010).
139. GAO (2013, p. 14). http://www.gao.gov/assets/660/653276.pdf.
140. EPA, Proposed Modification to IUR Rule Fact Sheet (July 2010), http://www.epa.gov/cdr/pubs/Fact%20Sheet_IUR%20ModificationsFinalRule_8-11-11.pdf (accessed 23.01.15.).
141. 15 U.S.C. § 2607(d); see also GAO (2007, p. 10).
142. 15 U.S.C. § 2610(c); see also Greenwood (2009, p. 10039) (noting that EPA has 'virtually ignored' its subpoena power under Section 11).
143. GAO (2013, p. 15). http://www.gao.gov/assets/660/653276.pdf.
144. See e.g., EPA, 8(e) and FYI Submissions Received October 2008, http://www.epa.gov/oppt/nano/nmsp-interim-report-final.pdf (accessed 23.01.150).
145. See also Denison, Nanotechnology Notes Blog, Environmental Defense, *Yes, Virginia, Inhaled Carbon Nanotubes Do Cause Lung Granulomas* (October 31, 2008) http://blogs.edf.org/nanotechnology/2008/10/31/yes-virginia-inhaled-carbon-nanotubes-do-cause-lung-granulomas/ (accessed 16.01.15.).
146. EPA, Nanoscale Materials Stewardship Program (January 2009,) http://www.epa.gov/oppt/nano/nmsp-interim-report-final.pdf (accessed 23.01.15.).See also: EPA, TSCA Sect. 8: Substantial Risk Notifications and FYI Submissions (2008), http://www.epa.gov/oppt/tsca8e/pubs/8emonthlyreports/2008/8eoct2008.html (accessed 23.01.15.).
147. Denison Richard, A hint of movement in the Super Slo-Mo that is nanoregulation at EPA under TSCA, (2014) http://blogs.edf.org/health/2014/10/08/a-hint-of-movement-in-the-super-slo-mo-that-is-nanoregulation-at-epa-under-tsca/#more-3987 (accessed 16.01.15.). Attributing OMB delay to industry pushback but mostly resistance from within the Obama administration from those promoting nanomaterials who were concerned that even mild regulation could stigmatize nanomaterials.
148. OMB, Chemical Substances When Manufactured or Processed as Nanoscale Materials; TSCA Reporting and Recordkeeping Requirements, RIN: 2070-AJ54, (2014) http://www.reginfo.gov/public/do/eAgendaViewRule?pubId=201410&RIN=2070-AJ54 (accessed 16.01.15.).
149. Bergeson, Campbell, EPA Fall 2014 Regulatory Agenda Includes Item Concerning TSCA Section 8(a) Rule for Nanoscale Materials, (2014), http://nanotech.lawbc.com/articles/united-states/federal/ (accessed 30.01.15.).
150. EPA, EPA Needs to Manage Nanomaterial Risks More Effectively, Report No. 12-P-0162, (2011) http://www.epa.gov/oig/reports/2012/20121229-12-P-0162.pdf (accessed 16.01.15.).
151. See e.g., 40 C.F.R. §§ 704.7, 707.75, 710.58, 712.15, 716.55, 717.19, 720.80, 720.85; 720.87, 720.90, 720.95, 790.7 (EPA has issued numerous regulations that implement the statutory requirements and processes that must be used by manufacturers in making CBI claims and the procedures EPA must follow if it seeks to disclose CBI).
152. 15 U.S.C. § 2613.
153. 40 C.F.R. §§ 707.70, 707.75; see also GAO (2005, pp. 13–15).
154. GAO (2005, p. 32) and GAO (2007, p. 8).
155. Chatham House (2009).
156. GAO (2007, pp. 41–42).
157. Denison (2007, p. VII–1). (Footnote omitted.)
158. Grad (1973, p. 4B59); see also American Chemistry Council (2007).

159. See Committee on Energy and Commerce, US House of Representatives (2009) (statement of Cal Dooley).
160. EPA, TSCA Inventory Update Reporting Modifications (August 2010), http://www.tsgusa.com/tsgnews_inventoryamendment.htm (accessed 16.01.15.).
161. EPA, TSCA Inventory Update Reporting Modifications (August 2010).
162. EPA, Claims of Confidentiality of Certain Chemical Identities Submitted under Section 8(e) of the Toxic Substances Control Act (January 2010), http://www.gpo.gov/fdsys/pkg/FR-2010-01-21/pdf/2010-1105.pdf (accessed 23.01.15.).
163. GAO (2013, pp. 24–25) http://www.gao.gov/assets/660/653276.pdf; See also http://www.eenews.net/greenwire/stories/1060004790/search?keyword=tsca.
164. 7 U.S.C. § 136(u); see also EPA, About Pesticides, http://www.epa.gov/pesticides/about/index.htm (accessed 12.11.10.).
165. EPA (2007a, p. 66).
166. 7 U.S.C. § 136a(a).
167. 40 C.F.R. § 152.50; see also 7 U.S.C. § 136d(a)(2).
168. EPA (2007c).
169. EPA (2009f).
170. American Bar Association (2006, p. 5); see also Davies (2007, p. 26) (stating that "[i]n contrast to TSCA, it is clear that in almost every case a nanopesticide will be considered 'new' and will have to go through the FIFRA registration process… However, EPA probably will need to make some changes in the data it requires to be submitted for registration, and perhaps it will need to modify or add to other regulations to deal with nanopesticides….").
171. 7 U.S.C. § 136a(c)(5)(C)–(D).
172. In addition, EPA must determine that the pesticide's 'composition is such as to warrant the proposed claims for it,' and 'its labeling and other material required to be submitted comply with the requirements' of FIFRA. See U.S.C. § 136a(c)(5)(A)–(B).
173. U.S.C. § 136(bb).
174. 40 C.F.R. §§ 152.160–75; see also EPA, Restricted and Cancelled Uses, http://www.epa.gov/pesticides/regulating/restricted.htm (accessed 12.11.10.); Schierow (2008b).
175. Schierow (2008b); see also EPA, Setting Tolerances for Pesticide Residues in Food, http://www.epa.gov/pesticides/factsheets/stprf.htm#registration (accessed 12.11.10.).
176. 7 U.S.C. § 136a(c)(7)(C).
177. 845 F. Supp. 2d 174 (D.D.C. 2012).
178. See EPA, US EPA Fines Southern California Technology Company $208,000 for 'Nano Coating' Pesticide Claims on Computer Peripherals (March 5, 2008). http://yosemite.epa.gov/opa/admpress.nsf/dc57b08b5acd42bc852573c90044a9c4/16a190492f2f25d585257403005c2851!OpenDocument (accessed 12.11.10.).
179. http://yosemite.epa.gov/opa/admpress.nsf/2dd7f669225439b78525735900400c31/cc8bf8d3f4c6f5f385257d3200642a61!opendocument (accessed 25.02.15.).
180. International Center for Technology Assessment (2008) can be found at http://www.centerforfoodsafety.org/files/cta_nano-silver-petition__final_5_1_08.pdf (accessed 03.03.15.).
181. International Center for Technology Assessment (2008).
182. EPA, Petition for Rulemaking Requesting EPA Regulate Nanoscale Silver Products as Pesticides, http://www.epa.gov/EPA-PEST/2008/November/Day-19/p27204.htm (accessed 12.11.10.).
183. http://www.centerforfoodsafety.org/press-releases/3664/nonprofits-sue-epa-for-failure-to-regulate-novel-pesticide-products-created-with-nanotechnology (accessed 26.02.15.).
184. Center for Food Safety v. McCarthy, No.14-cv-2131 (D.D.C. filed December 16, 2014) http://www.centerforfoodsafety.org/files/2014-12-16-dkt-1--pls--complaint_78869.pdf (accessed 26.02.15.).
185. EPA (2012).
186. Bergeson (2012).
187. EPA, Nanomaterial Case Study: Nanoscale Silver Disinfectant Spray (External Review Draft) (September 2010), http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=226723#Download (accessed 19.11.10.).

188. EPA, Office of Pesticide Programs, Pesticide Registration (PR) Notice 2013-1, Silver Task Force North America (May 1, 2013).
189. "EPA Proposes Registration of Nanosilver Pesticide Product" (August 27, 2013), available at http://www.epa.gov/oppfead1/cb/csb_page/updates/2013/nanosilver.html (accessed 26.02.15.).
190. http://www.epa.gov/pesticides/ppdc/2010/dec2010/session5-nano.pdf (accessed 25.02.15.) see also Bergeson & Campbell, P.C., OPP Considering Labeling of Nanopesticides (September 2010), http://www.lawbc.com/news/2010/09/opp-considering-labeling-of-nanopesticides/ (accessed 19.11.10.).
191. McLain (2010), http://www.lawbc.com/news/docs/2010/09/EPA-McLain-Nanopesticide-Regulation.pdf (accessed 19.11.10.).
192. Notice, Pesticide Product Registrations; Conditional Approval, 77 Fed. Reg. 10,515 (February 22, 2012).
193. *Natural Resources Defense Council v. EPA*, No. 12-70268 (9th Cir. 2013).
194. 7 U.S.C. § 136d(a)(2); see also EPA, Adverse Effects Reporting: FIFRA 6(a)(2), http://www.epa.gov/pesticides/fifra6a2/ (accessed 12.11.10.).
195. Bergeson and Hester (2008, pp. 36–37).
196. 7 U.S.C. § 136d(b).
197. 7 U.S.C. § 136d(c).
198. 7 U.S.C. § 136c.
199. 7 U.S.C. § 136o.
200. Labeling of Pesticide Products and Devices for Export; Clarification of Requirements, 78 Fed. Reg. 4073 (January18, 2013) (to be codified at 40 C.F.R. pts. 9 and 168) (final rule).
201. 7U.S.C. § 136o; see also EPA (2007c).
202. 7 U.S.C. § 136h(a); see also 40 CFR §§ 158.33 (c),161.33 (for each item, the submitter must cite the applicable portion of FIFRA on which the claim of confidentiality is based); 40 CFR § 172.46(d) (claims of confidentiality in experimental use permit notifications must be accompanied by "comments substantiating the claim and explaining why the submitter believes that the information should not be disclosed").
203. 7 U.S.C. § 136h(b); see also 7 U.S.C. § 136h(c) (outlining the process EPA must follow prior to release of CBI).
204. 7 U.S.C. § 136h(d)(1) (stating "[a]ll information concerning the objectives, methodology, results, or significance of any test or experiment performed on or with a registered or previously registered pesticide … and any information concerning the effects of such pesticide on any organism or the behavior of such pesticide in the environment … shall be available for disclosure to the public").
205. 7 U.S.C. § 136h(d)(1).
206. 7 U.S.C. § 136h(d)(2).
207. 40 C.F.R. § 168.75 (regulations on the export of unregistered pesticides permit sharing of information claimed as CBI in 'purchaser acknowledgment statements' with the government of the importing country).
208. 40 C.F.R. § 158.33(c)(4).
209. European Commission (2006).
210. See e.g., EurActiv, *EU environment legislation 'slow or incomplete', says review* (July 3, 2008), http://www.allvoices.com/news/786312/s/12946975-eu-environment-legislation-slow-or-incomplete-says-review (accessed 12.11.10.).
211. European Commission (2006); Regulation (EC) 1272/2008 of the European Parliament and of the Council.
212. The subsequent discussion focuses mainly on REACH, but the REACH and CLP regulations need to be seen as complementary in creating the overall framework for chemicals regulation in the EU.
213. The use of substances in applications covered by certain other legislations, such as cosmetics, pharmaceuticals or food, is excluded from certain REACH provisions.
214. European Commission (2006, art. 1(1)). See also Environment Directorate-General (DG Environment), REACH, http://ec.europa.eu/environment/chemicals/reach/reach_intro.htm (accessed 12.11.10.).
215. European Commission (2006, art. 1(3))('[the] provisions [of this regulation] are underpinned by the precautionary principle').

216. REACH applies to substances that are "manufactured, imported, used as intermediates or placed on the market, either on their own, in preparations or in articles, unless they are radioactive, subject to customs supervision, or are non-isolated intermediates" European Commission (2007b, p. 6). Exceptions include waste, substances necessary for defence purposes, polymers, substances covered by other specific legislation, such as those in food, medicinal products and biocides, and a few other substances that are either considered to be safe or inappropriate/unnecessary to register such as oxygen, glass or coal. Polymers may be subject to registration "once a practicable and cost-effective way" to manage them has been established EU Press Release (2007).
217. REACH imposes certain requirements on downstream users to consider the safety of their uses of substances and apply appropriate risk management measures. REACH also contains requirements for sharing of information relating to environmental, health, safety and risk management measures down and up the supply chain. A detailed description of these requirements is beyond the scope of the chapter.
218. Registered under their respective EINECS (European Inventory of Existing Commercial Chemical Substances) number.
219. Registered under their respective ELINCS (European List of Notified Chemical Substances) number.
220. The testing requirement for new substances applied to quantities of over ten kilograms. Exceptions existed only for so-called "priority substances," that is, substances that were produced in very high volumes.
221. One of the important motivations behind the creation of REACH was the perception that the system of differentiating between new and existing chemicals "did not produce sufficient information about the effects of the majority of existing chemicals on human health and the environment" European Commission (2007b).
222. http://echa.europa.eu/regulations/reach/registration/registration-statistics;jsessionid=8BA5E29373BB04E2BAEA441FD4C7BF23.live1 (accessed 26.02.15.).
223. *See also* European Commission Joint Research Centre, European Chemical Substances Information System (ESIS), http://ecb.jrc.ec.europa.eu/esis/ (accessed 12.11.10.).
224. Geert Dancet and Christel Musset, Presentation: 2013 REACH Registration deadline results, 3 June 2013. http://echa.europa.eu/documents/10162/13126357/reach_2013_presentation_en.pdf (accessed 26.10.14.).
225. http://ec.europa.eu/environment/chemicals/nanotech/reach-clp/ripon_en.htm (accessed 26.10.14.).
226. European Commission (2006b, art. 1(3)).
227. The terms "substance," "preparation," and "article" have a very specific meaning in the context of REACH. "Substance" refers to "a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition." "Preparation" refers to "a mixture or solution composed of two or more substances," and "article" refers to "an object which during production is given a special shape, surface or design which determines its function to a greater degree than does its chemical composition." In line with common usage and secondary literature on REACH by the European Commission, including 'REACH in Brief', European Commission (2007c), references to "chemical substances" in this text acknowledge the above definition of a "substance" in the REACH context.
228. European Commission (2007b, p. 7).
229. Denison (2007. pp. IV-27 to IV-29) (noting that REACH allows for registrants to adapt standard testing regimes, including use of alternative methods of testing, and to waive higher-tier testing requirements without any independent evaluation of appropriateness, unless the substance is later selected by the ECHA or a member state for evaluation—prior to which time it may be manufactured).
230. European Commission (2008i, art. 5); see also European Chemicals Agency (2009a).
231. In an official publication on REACH titled *Questions and Answers on REACH*, the European Commission explains that "the [Chemical Safety Report] should also generically cover consumer use of substances as such, in preparations and in articles (e.g. plastics, textiles and toys) and subsequent waste handling" European Commission (2007b).
232. European Commission (2006b, art. 7(1)).

233. A supplier of such articles "shall provide the recipient […] with sufficient information […] to allow safe use of the article including, as a minimum, the name of that substance." European Commission (2006b, art. 33(1)).
234. European Commission (2006b, art. 7(2)–(3)). See also European Chemicals Agency (ECHA), *Guidance Fact Sheet: Requirements for Substances in Articles* (2008), http://echa.europa.eu/doc/reach/echa_08_gf_03_articles_en_20080801.pdf (accessed 12.11.10.).
235. Decisions of whether a risk to human health or the environment exists and whether this risk is "acceptable" or "unacceptable" are taken in "comitology" procedures, discussed further in footnote 168, where the Commission chairs a committee consisting of representatives of the competent authorities of the Member States. Scientific support can be provided by the ECHA and may draw on EHS data collected through REACH.
236. European Commission (2006b, Annex VI(5), (6)). See also European Commission (2007c, p. 7).
237. However, classification and labeling obligations as outlined in the "Dangerous Substances" Directive (67/548/EEC) are not subject to the respective volume threshold. See Commission Directive 2001/59/EC.
238. European Commission (2006b, Annex I). Annex I further states that such a safety assessment "shall be based on a comparison of the potential adverse effects of a substance with the known or reasonably foreseeable exposure of man and/or the environment to that substance taking into account implemented and recommended risk management measures and operational conditions."
239. European Commission (2006b, recital (70)).
240. Annex 1 of REACH on the "General Provisions for Assessing Substances and Preparing Chemical Safety Reports' provides specific guidelines to all four areas of safety assessment" see European Commission (2006b, Annex I).
241. European Commission (2006b, art. 14(5)).
242. The costs for such joint registrations are shared among all registrants. Manufacturers and importers may opt out of the joint registration, however, if they face excessive costs by doing so, if they disagree with the lead registrant on the content of the registration, or if the disclosure of confidential information may lead to "substantial commercial damage" European Commission (2007c, p. 8). As noted, to facilitate the coordination of such joint registrations, the ECHA has created the Substance Information Exchange Forum (SIEF) for use in the pre-registration phase. ECHA, SIEF, http://echa.europa.eu/sief_en.asp (accessed 12.11.10.).
243. Nanotechnology Now (2014).
244. Council of Europe Parliamentary Assembly (2013).
245. European Commission (2014).
246. European Commission (2006b, art. 10(a)(xi)).
247. European Commission (2006b, art. 118(a)(xi)).
248. European Commission (2006b, art. 119(2)(a)(xi)).
249. European Commission (2006b, art. 119(1)).
250. European Commission (2006b, art. 120(a)(xi)).
251. European Commission (2007b, pp. 11–12).
252. European Commission (2007c, p. 12).
253. ECHA website, http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan (accessed 26.10.14.).
254. European Commission (2006, art. 91).
255. Decisions related to the following can be appealed to the Board: PPORD exemptions, rejections of incomplete registrations, data sharing with potential registrants and SIEF members, and dossier and substance evaluations.
256. European Commission (2007c, p. 18).
257. If included in Annex XIV, specific *uses* of substances may, however, be exempted from authorization requirements if, for example, "sufficient controls established by other legislation are already in place."

258. This describes the process whereby committees consisting of representatives from member states enter a dialogue with the Commission to "assist" it in implementing legislation. In some cases, the European Parliament also has the right to scrutinize and oppose measures proposed by the Commission. See also Europa Glossary on Comitology, http://europa.eu/scadplus/glossary/comitology_en.htm (accessed 12.11.10.).
259. ECHA, Guidance on inclusion of substances in Annex XIV 22–27, (August 2008) http://guidance.echa.europa.eu/docs/guidance_document/annex_xiv_en.pdf (accessed 12.11.100).
260. European Commission (2007c, p. 13).
261. European Commission (2007d).
262. The Commission has explained that "banning will not occur by default and a decision on such applications will always be taken by the Commission….[w]here the time limit for a decision has been exceeded, article 56(1) (d) provisions apply—i.e., can be placed on the market until a decision is taken."
263. European Commission (2006b, art. 68).
264. Most of the Guidance Documents already have been prepared, including guidance to aid local authorities in prioritizing substances for authorization. See European Chemicals Agency, *Guidance on inclusion of substances in Annex XIV* (August 2008), http://guidance.echa.europa.eu/docs/guidance_document/annex_xiv_en.pdf?vers=12_08_08 (accessed 12.11.10.); European Chemicals Agency, *Guidance on inclusion of substances in Annex XV* (June 2007), http://guidance.echa.europa.eu/docs/guidance_document/restriction_en.pdf?vers=19_09_08 (accessed 12.11.10.).
265. The EC states that this document will "strive for making [socio-economic analysis or] SEA outputs as comprehensive, consistent and user-friendly for the SEA committee as possibly taking into account the broad range of chemicals, uses, alternatives, etc. to be analysed and the various parties and processes to be covered by the guidance" European Commission (2008b).
266. European Commission (2008b).
267. Topics of additional documents under the implementation project include, but are not limited to, downstream user requirements, substances in articles, and substance identity.
268. See European Commission, REACH Implementation Project 4: Guidance Documents for Authorities, http://ec.europa.eu/environment/chemicals/reach/preparing/rip_4_en.htm (accessed 12.11.10.).
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270. http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32013R0284; http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32013R0283.
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