RECOMMENDATIONS FOR ADDRESSING POTENTIAL HEALTH RISKS FROM NANOMATERIALS IN CALIFORNIA

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Chapter 1: Introduction to Nanomaterials

1.1 General Introduction and Background

Once just an ambitious goal, nanotechnology is both common and a rapidly growing economic sector today. Nanotechnology is the manipulation of matter and the creation of new materials on an extremely small scale. Due to their small size, nanomaterials have unique physical and chemical properties, which in turn yield unique functionalities. Indeed, the promise and potential of nanotechnology are so great that its development has been described as the next Industrial Revolution.

However, the very same properties that yield these unique functionalities also raise concerns about the potential health and environmental implications of engineered nanotechnology materials and their applications. Notably, there are large gaps in our knowledge of the current and potential human exposures to and the toxicity of these novel materials, particularly in their production and use in other products. Nanomaterials also present new challenges to the policy and risk-assessment process, in part because there is no clear answer to where they fit within current regulatory and policy guidance and frameworks.

California has been and will continue to be a leader in the development of both new technologies and science-based policy solutions to prevent harmful exposures to environmental chemicals. With nanotechnology's potential to transform industrial society, the policy tools to address the potential health risks from exposure to nanomaterials also require transformation. To facilitate this effort, California's Office of Environmental Health Hazard Assessment (OEHHA) contracted with the University of California, San Francisco to prepare this report, which provides the State of California an overview of nanotechnology materials, potential exposures, and human-health risks and proposes a range of policy options for addressing potential health hazards and risks from nanotechnology.

Many reports have already been written on the subject of nanotechnology. One common theme emerging from these works is the need for more information on exposure, toxicology, and human health, coupled with a call for an information-gathering mechanism, whether voluntary or required. This report draws upon these predecessors and expands on their conclusions to determine the best course of action for California.

Chapter 1 briefly describes nanomaterials, applications, and current policy approaches to nanotechnology. **Chapter 2** provides a qualitative and quantitative look at "lessons learned" from past pollutants and how to use environmental policy to inform future decisions affecting human health. **Chapter 3** summarizes major findings in toxicology and environmental-health research and characterizes human exposures to nanotechnology materials. Finally, **Chapter 4** considers current regulatory frameworks at the state, federal, and international levels; highlights relevant programs in California; and offers policy recommendations for improving approaches to addressing health risks from nanotechnology. This report focuses on human exposures and health risks. While ecological risks are an additional concern that also informs human health risks, they are generally outside the scope of this report.

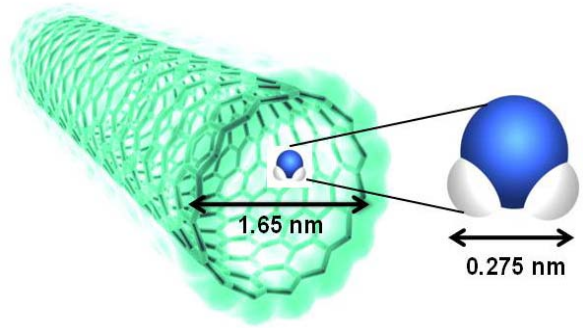
1.2 Definitions

The prefix **nano** refers to the number 10^{-9}, so a nanometer (nm) is 10^{-9} meters. The term **nanoparticles** refers to materials that have structures in the range of approximately 1–100 nm in one or more dimensions (length, width, or depth). While 100 nm is not necessarily a strict cut-

off point, all nanoparticles derive their unique properties from their small size. Nanoparticles are so small that they cannot be seen with a regular light microscope, requiring other techniques, such as electron microscopy, to image them. Figures 1 and 2 illustrate the relative size of nanoparticles.

FIGURE 1: Two examples of the relative size of nanoparticles. Figure adapted from the National Nanotechnology Initiative [1].

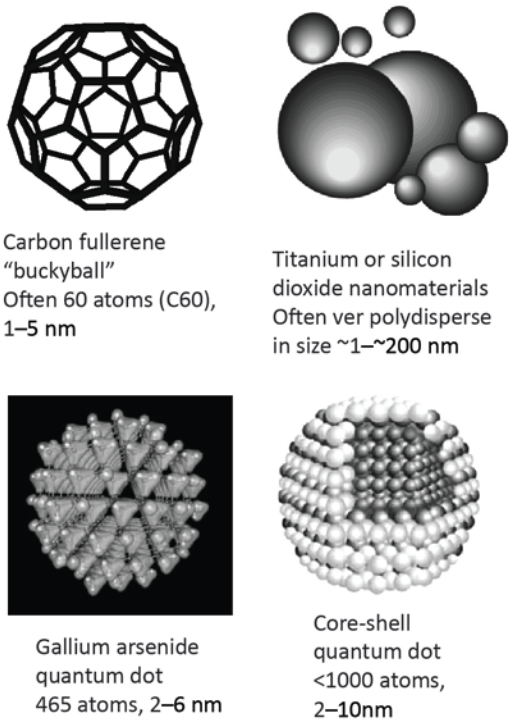
FIGURE 2: A carbon nanotube and a water molecule, drawn to scale. Single-walled carbon nanotubes can vary in diameter from about 1–10 nm.



Nanomaterials are functional or useful substances that contain one or more nanoparticles or materials with nanoscale structure that confers unique functionality. Nanomaterials can range from simple nanometer-scale particles, such as silver and gold used in basic research, to components of large, macro-scaled products, such as composite carbon-fiber bicycle frames. Examples of nanomaterials include fullerene compounds ("buckyballs"), which are made of carbon and shaped like soccer balls; nano-sized titanium dioxide (TiO_2) or zinc oxide (ZnO), which are used in sunscreens and cosmetics; and fluorescent quantum dots (QDs), which contain transition metals such as zinc and cadmium. For an illustration of the foregoing examples, see Figure 3, which shows the number of atoms, size, and relative shape of each. For comparison, environmental contaminants such as polychlorinated biphenyls (PCBs) and dioxin molecules are approximately 1 nm across.

The field of **nanotechnology** involves the development and control of materials and devices on the nanoscale, together with the tools to image and manipulate these materials and devices. Because it is neither industry- nor application-specific, the term "nanotechnology" applies to a wide array of materials and products, ranging from novel uses of conventional materials to completely new products based upon molecular self-assembly. This report focuses mainly on the intentional design and manufacture of nanomaterials. It does not address naturally occurring sources such as sea spray or volcanic ash or particles that are inadvertently generated from fossil-fuel combustion.

FIGURE 3: Schematic figures of various types of nanoparticles. Images from the US Environmental Protection Agency's Nanotechnology White Paper [2].

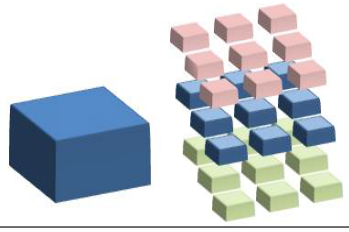


1.3 Unique Properties of Nanoparticles—Why Size Matters

The extremely small scale of nanoparticles confers special properties that the same material would not possess either in larger bulk form or at the smaller molecular level. One example is reactivity. The surface-area-to-volume ratio of nanoparticles is vastly higher than the material in bulk form. As a result, many more atoms are on the surface and available for reactions, as illustrated in Figure 4. Thus, one gram of nanosilver is much more reactive than a one-gram piece of bulk silver.

In addition to high surface area creating more reactivity, the small size of nanoparticles can also affect their electronic properties (e.g., resistivity and conductivity), optical properties (e.g., fluorescence and resonance), and chemical reactivity (e.g., photoreactivity). For example, certain carbon-based nanotubes can behave like semiconductors or conduct electrons as efficiently as metals, depending on their diameter and the arrangement of the atoms forming them. Unique optical properties can also arise at the nanoscale, as materials interact with electromagnetic radiation in novel ways. For some nanoscale materials, quantum effects begin to dominate behavior, leading to unusual phenomena such as particles that fluoresce in different colors depending on their exact size. For example, crystalline structure and size regulate titanium-dioxide particles' UV-reactivity properties in self-cleaning translucent coatings.

FIGURE 4: An illustration of how the ratio of surface area to volume changes as particles get smaller. There are many more molecules at the surface of the particle available for reacting, and this phenomenon is even more dramatic at the nanoscale.



Side length (per cube)	3	1
Volume	27	27
Surface Area	54	164

Many reports on nanotechnology suggest that nanomaterials qualify as new materials based on their unique, size-based properties and applications. A "New Materials" classification would require the industry to provide more toxicological and exposure-assessment information to the US Environmental Protection Agency (US EPA) before registration and could subject nanomaterials to new rules and/or risk-assessment

processes [2-5]. USEPA's current regulatory approach is to decide whether nanomaterials would qualify as a new material on a case by case basis[6]. While technically the same base material, nanomaterials possess different properties that can affect their toxicity, so failure to consider their unique, size-based properties in the regulatory process illustrates the inadequacy of policy and regulatory frameworks, which have not always kept pace with scientific discovery, to address the risks. For example, from a toxicological perspective, some nanoparticles can cross cell membranes, while others can cause fibroid-like growths or oxidative stress that can have harmful biological effects [7]. Certain types of nanoparticles can also be aerosolized easily and inhaled into the alveolar region of the lungs [8], which may give rise to special risks for occupational, consumer, or environmental exposures. As discussed further in Section 1.6, regulatory approaches to dealing with this novel and rapidly emerging field are lacking and need to be crafted.

1.4 Current and Projected Applications of Nanotechnology in California, the United States, and Worldwide

1.4.1 Regional and Economic Impacts

The unprecedented scientific and engineering challenges associated with working at the nanometer level have brought together scientists from many disciplines, including chemistry, physics, biology, robotics, metrology, and computer science. Just as the science of nanotechnology draws on nearly every physical discipline, the ramifications and applications of nanotechnology affect nearly every industry.

California has three of the five leading centers of nanotechnology activities ("Nano Centers") in the US: San Jose, San Francisco, and Oakland, all shown in Figure 5. The other two—Boston and Middlesex-Essex—are in Massachusetts [9]. These Nano Centers include nanotech companies, universities, research laboratories, and various nongovernmental and industry organizations.

Because the State of California is clearly emerging as the domestic frontrunner in nanotechnology competition, it can serve as a model in the field for integrating effective risk management and economic and societal benefits. The development of a successful model for nanomaterials will require careful analysis and planning across multiple disciplines.

Outside of California and the US, the economic implications of nanotechnology are vast. Estimates are that by 2014, nanotechnology-enabled products will be worth $2.9 trillion [10], or 15% of the global market [4]. Nationally and worldwide, nanotechnology is a fast-growing and promise-filled sector of the economy.

FIGURE 5: Maps of Nano Centers in California. Figure 5A indicates the density of nanotechnology research and development. Figure 5B shows sectors and locations of academic, government, and private nanotechnology activities in the Bay Area. Maps are courtesy of the Project on Emerging Nanotechnologies.

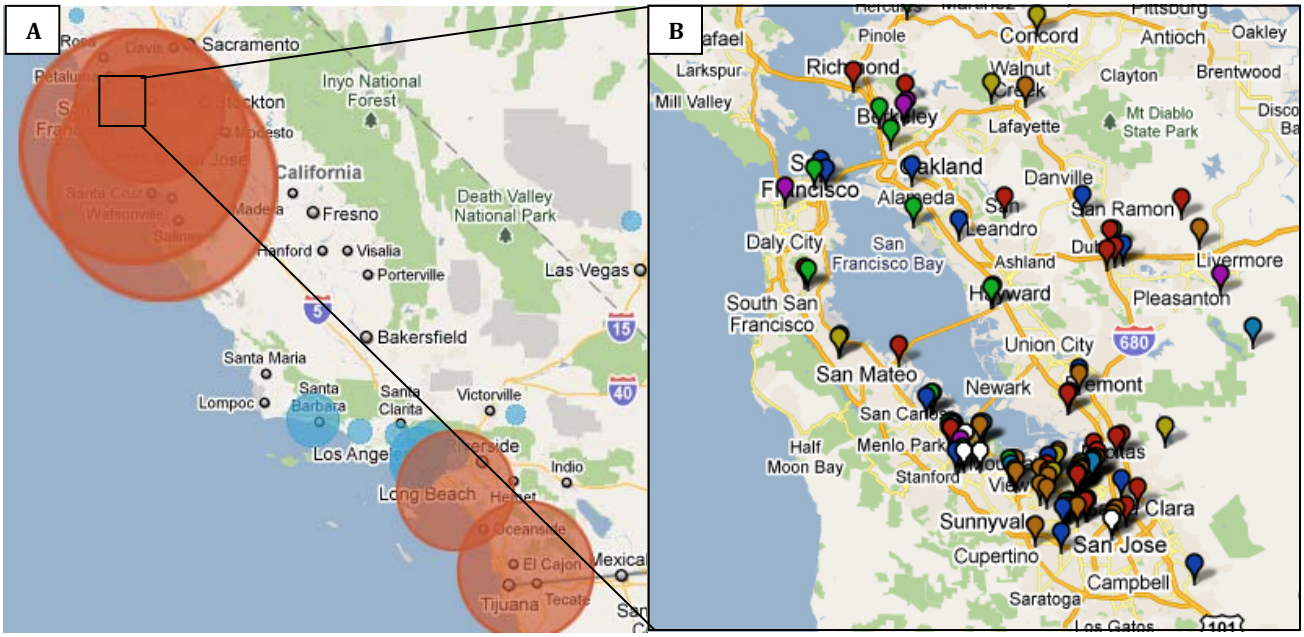


Figure 5B Legend

Academic and Government Research | Electronics | Energy and Environmental Applications | Imaging and Microscopy | Materials | Medicine and Health | Organizations | Tools and Instruments

1.4.2 Main Areas of Nanomaterial Use

Nanomaterials are already used in a wide variety of products and applications, as indicated in Table 1. Unfortunately, it is not currently possible to compile an authoritative inventory of all products that contain nanoparticles. This is because manufactured nanoparticles are typically not products in their own right; rather, they usually serve as raw materials, ingredients, or additives in existing products. Moreover, companies are generally not required to report which products contain nanoparticles or where they are sold. The most comprehensive inventory to date, compiled by the Woodrow Wilson Center's Project on Emerging Nanotechnologies (PEN) based on manufacturers' claims [11], listed more than 1,000 consumer products as of August 2009.

However, even this inventory provides only a low estimate of nanotechnology uses. First, given its focus on consumer products, it does not account for most business-to-business activity, such as the use of nanomaterials in fuel additives. Second, it relies on publicly available information that manufacturers have chosen to disclose.

According to the PEN inventory, the most common material now mentioned in product descriptions is silver (259 products). Carbon, which includes nanotubes and fullerenes, is the second most common (82 products), followed by titanium (including titanium dioxide) (50 products), silica (35 products), zinc (including zinc oxide) (30 products), and gold (27 products). Figure 6 shows the growing number of products added to the market each year that contain nanomaterials.

Current consumer-product use of nanomaterials includes many different applications. Examples include making sports equipment (e.g., tennis rackets, bicycles) lighter and stronger; coating clothing for a "lotus effect" or anti-staining properties; embedding nanoparticles in fabrics; and coating products for babies and children, including toys, for antimicrobial purposes. Notably, many household and personal-care products, such as food-storage containers, kitchen utensils, cosmetics, and dietary supplements, contain nanoparticles for their antibacterial, emulsion, and material properties. Furthermore, the area of "nanofoods" is growing, with scientists investigating the utility of nanoparticles for preservation, improving texture and color, increasing nutritional value, and sensing the likelihood for spoilage. Some of these uses are covered in the PEN inventory; many industrial-scale materials and environmental-remediation products are not.

The use of nanotechnology in the materials industry, which includes electronics, computers, coatings, communications, energy storage and conversion, and structural materials, is also substantial and growing rapidly. For example, electronics and computer chips now contain nanoscale circuitry, which makes possible the plethora of very small, portable devices on the market today. Paints, adhesives, and commercial coatings contain nanoparticles to aid emulsion properties such as spreadability and anti-separation. Ceramics and glass are coated for anti-fogging, anti-fouling, and self-cleaning purposes. In the energy sector, nanomaterials are proving useful as semi-conductors in solar cells and for energy transfer and storage in batteries. Still other applications include cerium dioxide as a diesel-fuel additive and some types of nanomaterials for environmental remediation of pollutants.

In the medical field, silver nanoparticles are used to coat medical instruments, such as catheters, for antibacterial purposes. Fluorescent quantum dots are in the research-and-development stage for advanced medical and diagnostic imaging, while the fields of drug delivery and targeted treatments have focused substantial resources on using various types of nanoparticles for drug carriers, detection, and specific biological interactions.

As this section illustrates, a wide range of nanomaterial products and applications already exists in society today. Many factors will determine nanomaterial use in the future, including consumer acceptance, regulatory structures, new information on human exposure and toxicity, and the overall benefit to society.

TABLE 1: Examples of nanomaterials in manufactured and consumer products worldwide and the estimated number of products known to contain nanomaterials*

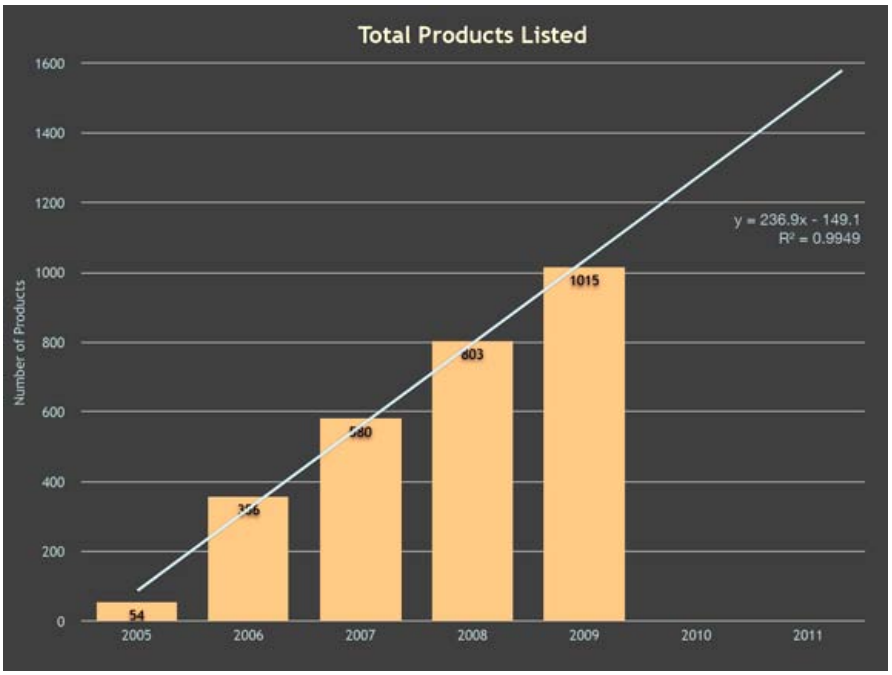
Category	Product type	Use of nanomaterial	Intended property	Number of products*
Electronics	Small portable devices	Metallic and inorganic connections, wires, circuit patterns	Electronic, optical	10
	Batteries	Connections, separation membranes, energy storage	Electrical, high surface area	5
	Computers	Storage, memory, displays	Electronic, optical	46
Household	Food storage	Mainly silver in storage materials or coatings; non-stick surfaces; sensing capabilities	Antibacterial, surface characteristics, special optical properties in sensing	80, 9**
	Kitchen utensils, food prep	Silver (antimicrobial); non-stick surfaces	Antibacterial, surface properties	37**
	Nanofoods	Capsules and micelles for fortification, nutritional benefits, and preservatives	Delivery, biocompatibility, antibacterial	17**
	Baby/children's products	Usually nanosilver coatings	Antibacterial	18
	Clothing, fabrics	Some silver, some fibers to create non-wetting surfaces	Anti-stain, "lotus effect"	115
Personal Care	Cosmetics	TiO_2 in sunscreens, mineral and other superfine particles for solution properties	Optical, emulsion/fluid Stabilization	160
	Dietary supplements, nutraceuticals	Dietary supplement additives or products (popular ones include silver ions or silver particles	Antimicrobial/antibacterial "cure-alls," absorption	44, 47**
Materials	Sporting goods	Carbon fibers and nanotubes as an integral part of physical structures	Material	81
	Coatings	Anti-fogging, anti-fouling, biological coatings	Anti-wetting/high surface area, antibacterial	51
	Paints	Fillers, pigments, and solution stabilizers (SiO_2 and TiO_2 particles)	Emulsion	7
	Energy generation, storage	Inorganic and metallic surfaces for batteries, solar panels, and other energy uses	Electrical, high surface area	< 10
Environment and Agriculture	Pollution prevention and remediation	Sensors, filtration, catalysis	Size, optical, electrical, high surface area, surface chemistry	≥ 34
	Fertilizers, pesticides	Nano-sized capsules and particles for better adherence and slow delivery	Surface properties, material	3+**
Medical	Drug delivery	Various polymeric (dendritic) or inorganic silicates as carriers for drugs or for isolated treatments	Biological compatibility, size, optical	†
	Detection, diagnostics, imaging	Inorganic QDs	Optical, fluorescent properties utilized for imaging & research	
	Tissue regeneration, growth, and repair	3-dimensional, porous, or fibrous nanoparticles to recreate cellular matrices	Biological compatibility, surface chemistry	

* As of August 2008, according to Woodrow Wilson Center's Project on Emerging Nanotechnologies [11].

** Friends of the Earth, *Out of the Laboratory and onto Our Plates: Nanotechnology in Food and Agriculture* (2008) [12].

† The Woodrow Wilson Center does not inventory medical products or devices. Aside from some antibacterial coatings for wound dressings and implements, there are very few, if any, nanomaterials currently in use for medical purposes, but this is a significant area of research.

FIGURE 6: Estimated number of products containing nanomaterials on the market, by year. Data from the Project on Emerging Nanotechnologies [11], which primarily covers consumer products based on voluntary industry reporting, by date of inventory update with regression analysis.



1.5 Potential for Exposure and Assessing the Risk of Nanotechnology

As discussed in the preceding section, the range of applications and uses of nanotechnology are vast and ever-expanding. In some applications, nanoparticles are fixed (e.g., attached to a surface or within a composite), while in others they are free or suspended in fluid. Both the degree to which nanoparticles are fixed in place as part of a material and the material's rate of release or degradation have a significant effect on potential health, safety, and environmental impacts.

Not all applications of nanotechnology have the same degree of exposure or risk; prospects for human exposure vary depending on many factors. For example, as Table 1 shows, consumer products—particularly personal-care and household products—could be a large source of exposure to nanoparticles given the high likelihood of contact for the general population. Exposure could also be significantly higher for workers who manufacture nanoparticles or of greater concern for vulnerable populations (e.g., the young, old, sick, and poor). It remains to be seen whether the main route of exposure for the general population is or will be the environment, direct use of consumer products, or some other means or combination thereof. For a discussion of exposure and toxicity with respect to specific types of nanomaterials, see Chapter 3.

Assessment of the risks posed by nanotechnology will require understanding the potential for exposure and subsequent potential health hazards. Furthermore, decisions about policy actions related to potential health risks may need to weigh the importance of various uses. For example, the antibacterial properties of silver nanoparticles can protect the most vulnerable from infections in

hospital situations, but embedding the same particles in sport socks to reduce odor can have toxic effects on fish and other aquatic life in wastewater-treatment effluent areas by leaching into the wash cycle. This comparison highlights the need to balance the consumer benefit carefully with the potential for exposure and adverse effects. While this report does not focus on the ecological impacts of nanotechnology, contaminants in the environment can become an exposure problem for humans and should also be considered.

1.6 Current Policy Approaches to Nanotechnology

While there is a wave of interest among both international, federal, and state authorities and nongovernmental organizations (NGOs) in ensuring the safe and appropriate use of nanotechnology, few plans are actually in place. This section provides a brief overview of governmental and nongovernmental concerns about gaps in policies to address potential health hazards from nanotechnology and proposed approaches to address these gaps through existing or new policy structures.

1.6.1 Brief Review of Governmental and Nongovernmental Analyses

Many governmental and nongovernmental entities have recently produced in-depth reports on nanotechnology. Governmental analyses include reports from Australia (AUS) [3], Canada (CAN) [13], the European Union (EU) [14], the United Kingdom (UK) [15], US EPA, and the US National Institute for Occupational Safety and Health (NIOSH) [2, 16]. NGO efforts include PEN's large number of reports, data, inventory, and analysis [4, 5, 17-29]; Friends of the Earth's (FoE) report on nanotechnology in food and agriculture [12]; and a framework Environmental Defense co-authored with DuPont for the responsible development of new nanomaterials [30]. For a summary of the main conclusions of these reports, see Table 2.

TABLE 2: Summary of main conclusions from governmental and nongovernmental reports on nanotechnology. For a more detailed discussion, see Chapter 4 and references [2-5, 13, 14, 17, 19, 21, 23, 26-29, 31].

Conclusions	Governmental reports	Nongovernmental reports
• No government entity has specific regulations for the management of nanotechnology or nanomaterials. • Existing regulations are weak and inadequate to deal with this area.	AUS, CAN, EU	FoE* PEN** 2, 3, 5, 7, 9, 10, 13, 14
• Large data gaps exist, including with respect to toxicity, exposure routes, health effects, bioaccumulative properties, and environmental fate.	AUS, CAN, EU, UK, US	FoE, PEN 2, 7, 9, 10, 13, 15
• A need exists for regulators to continue to research, identify, and monitor specific causes for concern.	AUS, CAN, EU, UK, US	FoE, PEN 3, 5, 9, 13
• A need exists for nano-specific research to fill data gaps.	AUS, CAN, EU, UK, US	PEN 2, 9, 10, 13, 15
• A need exists for better coordination and communication among agencies, governments, and NGOs.	AUS, CAN, UK, US	PEN 2, 3, 7, 9, 10, 13, 14
• New methods of risk assessment, such as use of predictive toxicology, may be needed, but use of traditional methods of toxicity testing to fill in data gaps should also continue. • New laws or regulations may be required to cover nanomaterials fully, but existing measures can and should be strengthened for all chemicals.	CAN, EU, UK	FoE, PEN 2, 3, 7, 9, 14, 15
• Prioritization and standardization of characterization methods are critical.	CAN, EU, UK	
* Friends of the Earth, *Out of the Laboratory and onto Our Plates: Nanotechnology in Food and Agriculture* (2008) [12] ** Project on Emerging Nanotechnologies series of reports, by volume number [11].		

While the reports vary in terms of their specific recommendations, all call for more information on nanotechnology exposure and toxicity and for some type of information-gathering mechanism, whether voluntary or required. Several of the governmental reports, and many of the nongovernmental reports, conclude that the existing regulatory structure is inadequate to address potential health risks from nanotechnology.

Most of the reports also agree on the need for more training of government scientists and university and graduate students in health and safety chemical-hygiene operating procedures. Finally, most agree on the need to expand the training of young scientists to "next-generation" technologies such as green chemistry and green engineering design [2, 5, 19], including incorporating toxicity implications into the design of new chemicals or materials.

The EU report, which focuses on the appropriateness of the risk-assessment process with respect to nanotechnology, emphasizes the need for standardization of methods, coordinated efforts among stakeholders, and better sources of information [14]. The Canadian report calls for use of the precautionary principle. In contrast, most US reports call for some combination of using existing law, such as the Toxic Substances Control Act (TSCA) or the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and creating a new government entity or oversight committee specifically for nanotechnology. Notably, such a course of action would also require overhauling or reorganizing current regulations.

1.6.2 Examples of Policy Efforts to Address Nanotechnology

There are several examples of reporting requirements on the state, municipal, and federal levels. On the state level, in 2009, the California Department of Toxic Substances Control (DTSC) asked manufacturers and importers of carbon nanotubes to provide information that could be used to determine if the nanomaterial poses a threat to public health and the environment. The DTSC gained authorization in 2006 to request such data from manufacturers and has exercised that right to obtain more information about nanotechnology. On Jan. 22, 2009, it sent notices to more than two dozen private and public facilities, including government labs and universities, giving them a year to submit toxicity data, identify the analytical tools used to monitor the substance in the workplace and environment, and outline their safeguards for protecting workers [32]. For a discussion of the results of DTSC's information requests, see Section 4.6.2.

At the local level, the city of Berkeley, California, adopted a material disclosure ordinance in 2007 requiring facilities that produce or handle manufactured nanoscale materials to submit a yearly report. While the ordinance does not contain detailed reporting requirements, it directs facilities to report both the types of nanoparticles and nanomaterials they work or might work with and their procedures for handling these particles and materials. While no company was known to manufacture nanoparticles in Berkeley at the time of adoption, PEN has highlighted the ordinance in a report outlining possibilities for state and local entities to manage the risks and benefits of nanotechnology [25].

On the federal level, a 2009 US EPA report [33] investigating the effectiveness of the agency's voluntary reporting program concluded that a very low percentage of companies have submitted any information and that only four companies have reported toxicity or health information. As a result, US EPA is considering its options for firmer action or decisions in the future.

In addition, in October and November 2008 [34, 35], US EPA clarified its stance on carbon nanotubes by defining them as a unique product aside from graphite or other allotropes of carbon

and stating that carbon nanotubes may be considered new chemicals under TSCA. This "New Material" classification triggers requirements for separate Material Safety Data Sheet (MSDS) information and integration into the TSCA process (which requires pre-manufacturing notices).

In Canada, the government moved to implement a new program in 2009 that requires manufacturers of nanomaterials to provide physical, chemical, and toxicity data about nanoproducts produced in more than one-kilogram quantities [36]. Two government agencies, Health Canada and Environment Canada, plan to use the data to develop new risk assessments and further regulation.

1.6.3 National Research Council Reports

In 2009, the National Research Council (NRC), the research arm of the US National Academy of Sciences (NAS), released a report analyzing the National Nanotechnology Initiative's (NNI) 2008 strategic plan for effectiveness, readiness, and appropriateness [37]. The NNI is a multi-agency federal program created in 2001 to coordinate nanotechnology research and development in the US. While commending the NNI's efforts to collaborate and avoid duplicative research, the NRC found that its strategic plan lacked a vision and overall goals. It also found that the NNI had not identified a sound research strategy to investigate nanotechnology and its effects on human health and the environment, much less developed a cohesive plan to address issues that might arise. The report concluded that "There remains an urgent need for the nation to build on the current research base related to the EHS [environmental health and safety] implications of nanotechnology . . . by developing a national strategic plan for nanotechnology-related environmental, health, and safety research."

Since the NRC report, the NNI has sought to address various shortcomings and recommendations. A recent report from the President's Council of Advisors on Science and Technology commends the NNI for improving its EHS research funding and for releasing a cross-agency EHS research strategy but also contains many recommendations for improvement, including developing clear principles to support identification of plausible risks and fostering changes to enable the NNI to better embrace environmental health and safety issues [38].

There are some specific federal agencies that are active on the issue of evaluating nanotechnology's potential risks. NIOSH, an agency within the Centers for Disease Control and Prevention, has a strategic plan and research goals to partner with both the public and private sector in the US and abroad to understand the impact of worker exposure to nanomaterials [16]. In addition, the National Toxicology Program is involved in the Nanotechnology Environmental and Health Implications Working Group within the NNI and receives some funding through the NIH's investment in environmental-health research on nanomaterials [39-41]. However, a more cogent, organized, inter-agency effort is needed to adequately protect human health and the environment.

There is also growing concern about the adequacy of evaluation of scientific information in a public-policy context, particularly in regard to risk assessment. The NRC released three reports in 2007 and 2008 that address deficiencies in the environmental-health assessment process and call for significant changes in the decision-making process to incorporate the latest scientific findings and approaches for addressing data gaps in an efficient and transparent manner. A brief summary of these reports follows, as their findings are highly relevant to assessing health risks from nanotechnology:

1. **Science and Decisions: Advancing Risk Assessment (2008)** [42] calls for an overhaul of

traditional risk assessment. The report's recommendations include using default assumptions, integrating the most current science into their development, and creating a unified approach to dose-response for cancer and non-cancer assessments that considers background exposures and vulnerable populations. The report also recommends improving the utility of risk assessment by including initial problem formulation and scoping as well as upfront identification of risk-management options.

2. **Phthalates and Cumulative Risk Assessment: The Tasks Ahead (2008)** [43] concludes that sufficient data exist to consider phthalates and other anti-androgenic compounds (chemicals that disrupt the male hormonal system) as behaving the same toxicologically and thus to warrant use of a cumulative approach when making risk-assessment decisions. In essence, this means that if exposure to different chemicals increases the risk of the same adverse health outcome, it is appropriate for risk assessment to include all of the chemicals. Several different approaches are presented using dose-addition methods.

3. **Toxicity Testing in the 21st Century: A Vision and a Strategy (2007)** [44] describes how new advances in molecular and cell biology and other fields could make toxicity testing faster, less expensive, less reliant on whole-animal testing, and more relevant to human exposure. The report highlights the cumbersome nature of current toxicity testing; how it has resulted in expensive, patchwork approaches; and how, as our understanding of biology expands, we can use that knowledge to create more efficient and reliable toxicity tests.

1.6.4 Opportunities in California

In light of identified gaps in the current policy structure to address potential health risks from nanotechnology [37], and given the changing field of chemicals policy in California, now is an appropriate time to consider new policy approaches to nanotechnology. California has often been at the forefront of innovative policies and regulations to address policy gaps.

California recently passed two important bills, AB 1879 and SB 509, together called the California Green Chemistry Initiative. They outline ambitious goals: expanding pollution-prevention and product-stewardship programs; developing a workforce-education and -training program; creating an online product-ingredient network and a "toxics clearinghouse" database of chemical toxicity and hazards; accelerating the quest for safer products, and moving towards a cradle-to-cradle (rather than cradle-to-grave) economy by leveraging market forces to produce products that are "benign by design." Both bills were structured to give various state offices the authority to implement the general goals listed above. At this time, the language is such that it would be possible to include nanotechnology within the scope of the implementation of the legislation, providing an opportunity to leverage existing law.

The emergence of nanotechnology presents many challenges, including its rapid growth as a sector in California's economy; its use in a wide array of industries, materials, applications, and products; and its unique toxicological risks. The remainder of this report reviews past experiences with policy approaches to addressing potential health risks from chemical exposures, identifies lessons for developing new approaches for nanotechnology, summarizes the main exposure and toxicological risks of nanomaterials, and identifies policy highlights from previous reports. The report concludes with a blueprint for how California can take advantage of this exciting new technology while ensuring the health and safety of its residents.

Chapter 2: Learning from Past Policy Experiences in Managing Chemicals

2.1 Introduction

Numerous engineered nanomaterials and nano-enabled products have already entered or are being developed for the marketplace. As discussed in Chapter 1, California leads the US in terms of the number of nanotechnology companies, and the economic growth of this industry is expected to be substantial in the coming years. Simultaneously, scientific and policy communities are continuing to frame and debate methodologies for assessing hazard and risk characteristics from nanotechnology. The goal of this report is to inform future approaches for evaluating or managing potential hazards from manufactured nanomaterials. As part of this process, it is important to reflect on what we have learned from policy approaches to manufactured and mined chemicals during the past 40 years. This recent history offers valuable lessons to help shape future approaches so they better anticipate, evaluate, and prevent potential hazards from the manufacture and use of nanomaterials.

This chapter focuses on several case studies that demonstrate key concepts that have emerged from past policy experiences. These case studies share a common theme: that the availability or consideration of additional information would have enabled the identification of potential hazards and appropriate intervention or mitigation strategies *before* public health consequences occurred. In many cases, enough information existed to cause concern, but no action was taken for other reasons, whether social, cultural, economic, or political. Each example reviews the case study history, illustrates the lessons, and discusses its relevance for future policy efforts in new technology areas.

The chapter ends with a summary of lessons from past experiences and consideration of their relevance to nanomaterials and nanotechnology policy.

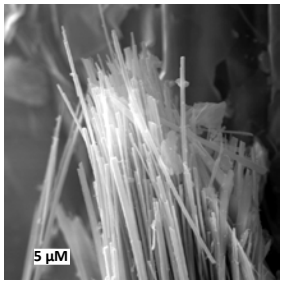
2.2 Key Concepts and Case Studies

2.2.1 Mass-Based Dosimetry

Historically, chemical hazard assessments have relied on mass-based dose metrics to describe harmful levels of exposure. Such metrics are typically expressed as mass per body weight, for example, milligrams of chemical per kilogram of body weight (mg/kg). Mass-based dose metrics assume that the critical factor determining toxicity of a substance is the concentration (or mass) of exposure. This assumption may seem simple and obvious but is often the source of misunderstanding. It is based on the *response* being related to the *dose* with first, a *molecular interaction* occurring between the chemical and the biological system, and second, a *degree of response related to the concentration* of active agent [45].

A significant limitation of mass-based dose metrics is that they do not account for other characteristics of materials that may influence toxicity, such as shape, surface area, and reactivity. When health effects related to these characteristics do not correlate with effects related to mass, additional metrics may be needed to more accurately describe harmful levels of exposure. In the case of nanomaterials, mass-based metrics may be much less important than other metrics such as size or surface chemistry in determining the severity of outcomes after exposure.

FIGURE 7: Asbestos fibers. Image from the U.S. Geological Survey, scale bar = 5 µm [46].



The history of asbestos illustrates the importance of considering metrics other than mass or concentration when assessing toxicity. The fire-proofing properties of asbestos have been known since the time of the ancient Greeks. Its use grew quickly during the Industrial Revolution, when the fibers were first used in new materials such as insulation and filters, and increased dramatically in the early twentieth century after the development of modern mining techniques and the discovery of new sources. Asbestos is now estimated to be in more than 3,000 consumer products [47].

Asbestos toxicity cannot be evaluated accurately using mass-based dosimetry because the toxicity of asbestos fibers is primarily related to their shape: specifically, their aspect ratio (a measurement of the length of a particle compared to its width). For an image of asbestos fibers, see Figure 7.

While the toxicity of asbestos materials can be related to some extent to their composition or contamination by other materials, shape is more influential in determining overall risk. Materials with high aspect ratios—characterized by long, thin fibers— are not easily expelled by the lungs, lodge in the alveolar regions, and can result in chronic inflammation as the immune system attacks the lodged fibers. The lungs protect themselves from these fibers by forming scar tissue around the irritation.

Scar-tissue growth may lead to uncontrolled cell division or the interaction of fibers with single cells, causing disruption of their reproduction and genetic material. Either or both of these mechanisms can lead to cancer [48]. Evidence shows that longer, straighter fibers are more difficult to expel than some of the shorter varieties and that these longer types of asbestos cause higher incidences of lung disease and cancer [49].

As the example of asbestos shows, it is important to be aware of properties other than mass that may affect hazard or risk characterization. Some nanomaterials are shaped like asbestos fibers and exhibit similar toxicity profiles, suggesting the need for nontraditional dose metrics. Indeed, in the case of nanomaterials, mass-based metrics may be much less important than other metrics such as size or surface chemistry in determining the severity of outcomes after exposure.

2.2.2 Health Tracking

Asbestos also illustrates the importance of health tracking. Asbestos was once hailed as a “magic mineral” because of its superior material properties with regard to heat, chemical, and electrical resistance. Despite the fact that many miners and factory workers suffered from lung problems and other adverse health effects that were documented in the early 1900s, the use of asbestos was not regulated in the US until the 1970s. Given the number of people estimated to have contracted asbestos-related diseases, key lessons to prevent future harm include the need for: 1) regular monitoring of worker populations exposed to materials that could be harmful, followed by careful documentation; 2) identification of early warning signs of affected workers, including those from doctors’ observations; and 3) alerting the appropriate risk assessors, agencies, and/or policymakers.

2.2.3 Persistence and Bioaccumulation

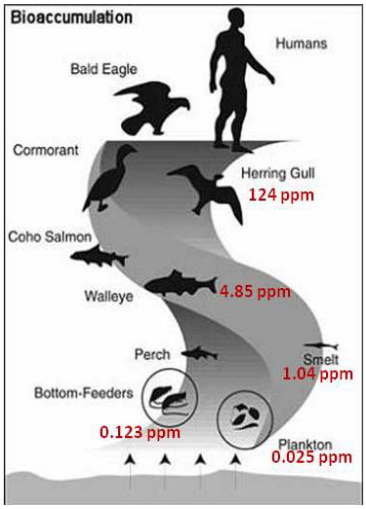
Persistent chemicals are compounds that endure in the environment and bioaccumulate in food chains [50]. Many of these compounds contain halogen atoms (e.g., chlorine, bromine, fluorine) that form very stable molecular structures, so they biodegrade or metabolize only very slowly. Moreover, persistent chemicals present two critical concerns: they transfer relatively easily among air, water, and land; and they span regulatory, geographical, and generational boundaries.

Persistent chemicals have been widely used in manufacturing processes and consumer products such as electronics, pesticides, and furniture for many years. Long-term stability is an important feature of these molecules and one of the reasons they have been used so ubiquitously. Examples of persistent chemicals include brominated flame-retardant compounds such as polybrominated diphenyl ethers (PBDEs); organochlorine pesticides such as dichlorodiphenyltrichloroethane (DDT); polychlorinated biphenyls (PCBs); and perfluorinated compounds, such as perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), which are used in a wide range of nonstick coatings and food applications. Unfortunately, the very longevity that has made these compounds desirable has also led to the unintended consequences of their accumulation in the environment and biomagnification in aquatic and animal life, with the highest concentrations occurring in species at the top of the food chain, such as humans.

Figure 8 illustrates bioaccumulation of PCBs in a freshwater ecosystem food chain. Levels of PCB contamination can increase from 0.025 parts per million (ppm) in plankton to 1.04 ppm in small fish and up to 124 ppm in bird eggs, a nearly 10,000-fold increase in concentration [51]. PCBs can affect the thickness of bird eggshells, causing the eggs to be crushed before hatching. The effects of PCBs in the food chain were discovered only after bird populations began to decline precipitously.

Our history with persistent, bioaccumulative compounds tends to be cyclical. In many cases, we identify their persistence and adverse health effects only after introducing millions of pounds of chemicals into the environment. We then implement use restrictions and bans, but because of the chemicals' environmental persistence, these policy decisions do not protect against exposure and the potential for adverse health effects until decades later. Moreover, because persistent, bioaccumulative compounds eventually end up in food sources, decisions made decades ago still limit our opportunities for healthy and nutritive food systems today. For example, fish are high in important nutrients, and dieticians recommend eating fish for brain development. However, the contamination of the fish supply by PCBs and other persistent, bioaccumulative compounds has extensively limited our ability to consume this important source of nutrition.

FIGURE 8: A diagram of a food chain and PCB levels. The concentration of PCBs increases as higher-level organisms uptake lower-level food sources. Image from GreenFacts.org; data (added in red) from the US Environmental Protection Agency's Great Lakes monitoring office [52].



As the field of nanotechnology advances and expands, a critical feature of future policy approaches should be the consideration of the potential persistence and bioaccumulative properties of nanomaterials. As our history with chemicals such as PCBs shows, introducing nanomaterials with such properties will eventually lead to the accumulation of exogenous compounds in our bodies and risk unanticipated consequences that could reverberate for many years.

2.2.4 Fate, Transport, and Transformation in the Environment and Biological Systems

One example of chemicals that transform and disperse in the environment over the course of their lifetime is brominated flame retardants, such as PBDEs. PBDEs are manufactured primarily in three forms—deca-BDE, octa-BDE, and penta-BDE—which differ in the number of bromine atoms attached to the molecule (10, 8, and 5, respectively). Penta-and octa-BDEs were banned in California in 2003 and phased out voluntarily in the US in 2004 [53] due to concerns over their toxicity to the neurological system. The ban and voluntary phase-out did not include deca-BDE because it was not clear these molecules, which are larger, were stable in the environment (i.e., that they did not transform into octa- or penta-BDE) and not taken up as easily by the body. However, as we learned years later, deca-BDE can degrade into the more toxic octa- and penta- versions [54, 55], and recent evidence suggests that animals and humans have higher deca-BDE body burdens than previously thought [56, 57]. Making policy decisions based on incomplete knowledge of the degradation pathways and fate of deca-BDE therefore resulted in continued exposure to the more toxic octa- and penta-BDEs.

As the example of deca-BDE shows, policy decisions based on incomplete or inaccurate information can have significant consequences. In the case of nanomaterials and nanoparticles, there is emerging evidence that their properties and mobility change as they are transported from their sources through the environment and biological systems. Understanding the degradation pathways, transport and transformation mechanisms, and fate of nanomaterials after their release into the environment, as well as their interaction with existing pollutants, will therefore be important to fully evaluating their potential to influence human health.

2.2.5 Environmentally Relevant Detection Capacity

In order to follow the fate, transport, and transformation of chemicals and other manufactured or mined materials in the environment, we need appropriate and up-to-date monitoring technologies that are sensitive and specific. We also need centralized databases to collect monitoring results so that interested parties such as academics, health organizations, and governments can access the data.

The story of perchlorate, an inhibitor of thyroid hormone production, reveals the importance of being able to measure low-level concentrations of chemicals in the environment. Perchlorate has been used in large amounts for many years, mainly as an oxidizer in solid rocket-fuel propellants but also in the manufacture of fireworks, flares, paints, and other products. Its main use today is for rocket fuel and missiles by the US Department of Defense and NASA [58]. Perchlorate was also used in the 1940s and 50s in high doses as a medical treatment for hyperthyroidism, but recent science indicates that perchlorate has adverse effects on human thyroid function at low doses [59, 60].

Perchlorate is very persistent and mobile in both surface and ground water. It has also been detected in the food supply in fruits, vegetables, dairy products, meat, and breast milk, so in areas

where perchlorate contamination of groundwater is already near or above the safe limit, populations can be exposed to potentially harmful levels.

Notably, manufacturing and waste-disposal practices have introduced substantial amounts of perchlorate into water systems in many states in the US. For example, in 1997, more than 1000 pounds of perchlorate were entering Lake Mead, the largest reservoir in the US, each day through contaminated groundwater [58]. Despite the large volume, this contamination went undetected for decades because, until the late 1990s, only very high concentrations of perchlorate—400 parts per billion (ppb) or more—could be detected using then-available technologies.

The first reported detection of perchlorate in California groundwater was in 1964, and levels were found to be as high as 18,000 ppb [61]. In the late 1970s, perchlorate was detected near Superfund sites in the state, and further studies found adverse health risks from exposure to perchlorate [62]. This prompted the development, in 1997, of an analytic method with a lower detection limit of 4 ppb [62]. Only after the development and use of methods that could detect lower levels of perchlorate did we learn that perchlorate contamination was widespread in water supplies, the food supply, and people. Subsequently, health-based action limits and reference doses were established, all of which corresponded to drinking water concentrations in the range of 4–25 ppb. Thus, only after decades of perchlorate use and disposal did we have the methodological capacity to detect exposures of public-health significance and awareness of the need for mitigation to protect public health.

As new nanomaterials are developed and introduced, we must simultaneously take appropriate measures to ensure that detection and monitoring technologies are capable of identifying low-level, environmentally relevant contaminations.

2.2.6 Susceptible Populations

Environmental chemicals can increase the risk of a broad spectrum of effects that depend not only on the dose and route of exposure but also on the susceptibility of the individual to the compound. Age, gender, genotype, and disease status can influence susceptibility to disorders, anatomic abnormalities, and diseases from exposures. Yet, in many cases, estimated doses for *de minimis* risk are based on a healthy, 70-kg adult.

The use of such an adult as a model has proved problematic with regard to populations including children and the elderly. For example, the elderly may be at special risk from exposures to environmental chemicals, as their immune systems are often in a state of decline. Also, we know that children are not small adults; they have different behaviors, metabolism, and responses to infectious and environmental challenges. From fetal development through childhood, there are many important windows of development during which humans are particularly susceptible to chemical exposures.

Exposures to exogenous chemicals during critical windows of susceptibility—especially prior to conception and during pregnancy—may result in adverse effects with lifelong and even intergenerational health impacts [63]. Two examples from the 1950s highlight the unique sensitivity of fetuses to chemical exposures. First, pregnant women who ate fish contaminated with high levels of mercury gave birth to children with debilitating neurological and reproductive problems. Second, pregnant women who took therapeutic doses of a morning-sickness drug called thalidomide without experiencing any side effects themselves gave birth to babies with severe limb deformities. Then, in the early 1970s, we found out from our experience with diethylstilbestrol (DES) that chemicals can damage the development of offspring in less visible but equally damaging ways.

DES, which was given to pregnant women in the US from 1938 to 1971 to prevent pregnancy complications, was assumed to be safe for the fetus. However, prenatal exposure to DES caused reproductive abnormalities in the adult offspring of women who took it [63]. It also increased the risk of male and female reproductive-tract problems in the grandchildren of women who received the drug [64].

In the case of nanomaterials, there is emerging evidence that certain types of plastic nanoparticles can cross the placental barrier, subjecting fetuses to unknown exposure and risk [65].

When developing recommendations for identifying hazards and risks from nanomaterials, the foregoing case studies show that evaluating the toxicity of chemicals requires considering unique susceptibilities, including those that occur during developmental time periods.

2.3. Summary and Conclusions

A 2008 commentary in the journal *Nature Nanotechnology* opens with the observation that "history is littered with examples of promising technologies that never fulfilled their true potential and/or caused untold damage because early warnings about safety problems were ignored. The nanotechnology community stands to benefit by learning lessons from this history" [66]. The commentary goes on to compare examples from a 2001 report by the European Environment Agency (EEA) [67] to the current state of nanotechnology and concludes that "we are doing some things right, but we are still in danger of repeating old, and potentially costly mistakes."

The EEA report, *Late Lessons from Early Warnings*, outlines many examples of contaminants and other hazards that exhibited early warning signs and summarizes what we can learn from these examples in "12 Late Lessons." It provides a historical account of specific cases and treats them as learning opportunities for chemical policy reform. For a summary of the report's conclusions, see Box 1.

BOX 1: Conclusions from the European Environment Agency's *Late Lessons* report for improving future chemicals policy [67]

1. Acknowledge and respond to ignorance, uncertainty, and risk in technology appraisal and public policy-making.
2. Provide adequate long-term environmental and health monitoring and research into early warnings.
3. Identify and reduce "blind spots" and gaps in scientific knowledge.
4. Identify and reduce interdisciplinary obstacles to learning.
5. Ensure that real-world conditions are adequately accounted for in regulatory appraisals.
6. Systematically scrutinize claimed justifications and benefits alongside potential risks.
7. Evaluate a range of alternatives for meeting needs alongside the option under appraisal, and promote more robust, diverse, and adaptable technologies to minimize the costs of surprises and maximize the benefits of innovation.
8. Ensure use of "lay" and local knowledge, as well as relevant specialist expertise in appraisals.
9. Take full account of the assumptions and values of different social groups.
10. Maintain the regulatory independence of interested parties while retaining an inclusive approach to information and opinion gathering.
11. Identify and reduce institutional obstacles to learning and action.
12. Avoid "paralysis by analysis" by acting to reduce potential harm when there are reasonable grounds for concern.

2.3.1 Lessons for Nanomaterials

1. **Consider all characteristics that may affect toxicity, as traditional mass-based dose models are not sufficient. New traits or properties are needed.**
   Evaluating the hazards posed by nanomaterials may require consideration of different properties than those traditionally used to assess toxicity. More specific toxicology endpoints are discussed in the next chapter, but current evidence suggests that the very same aspects that give nanomaterials their superior properties, such as surface charge, aspect ratio, size, purity, and reactivity, may be more important than mass or vapor pressure when determining hazard characteristics. Metrics such as particle counts per volume and surface area are emerging as more useful properties in describing toxicity for small particles, including nanomaterials.

2. **Heed early health warnings.**
   Paying close attention to groups such as workers, manufacturers, and end users and tracking their health will provide indicators of potential harmful exposures from nanomaterials.

3. **Identify persistent and/or bioaccumulative materials early, as build-up of exogenous chemicals is usually detrimental in some way.**
   We need more information on persistence and biointeractions of nanomaterials to know if they will accumulate in the environment or our bodies. We know some nanoparticles are made of very stable and persistent compounds, which can make them causes for concern. For example, carbon nanotubes and metal oxides are very stable and do not change their physical properties very easily. Further evaluation of their fate and transport through the environment and what future exposures might be important will enhance our understanding of how their structure may contribute to persistence and bioaccumulation. Further efforts to identify properties that are predictive of persistence and bioaccumulation are an important area of focus. Because we are challenged by gaps in our ability to measure and identify how nanomaterials move through the environment and into people, a focus on evaluating representative nanomaterials will help inform approaches addressing similar materials.

4. **Ascertain fate, transport, and adverse pollutant interactions.**
   Understanding the degradation pathways, breakdown products, transport mechanisms (both in the environment and in our bodies), final destinations, and fate of nanomaterials after their release into the environment is important to protecting human health and the environment. There is growing evidence that nanomaterials can degrade and thus that their toxicity and exposure profiles can change throughout their life cycle. They may also serve as carriers of other pollutants due to their high surface area.

5. **Develop detection and monitoring technologies for measuring nanomaterials.**
   The availability of tools and technologies to measure nanomaterials in the environmental chain should be on par with that of manufactured nanomaterials so we can have knowledge of their location and end fate. However, the development of technologies to detect the presence of nanomaterials in different environments and media has not kept pace with the rate of nanotechnological innovation in a way that would prevent unintentional exposures.

6. **Consider susceptible populations.**
   Hazard characterization of nanomaterials should consider potential unique or enhanced susceptibilities, such as developmental life stage. It should also take into account the higher exposure of certain populations, such as workers in manufacturing, researchers, and perhaps even groups such as firefighters and remediation

workers, as the use of nanomaterials grows in different types of products (e.g., paints and coatings). Care should also be taken with materials that may disproportionately affect vulnerable populations such as infants, children, workers, and the elderly.

2.4 Conclusions

As much as we can learn from history, no list of "past lessons" is guaranteed to include all aspects of potential exposure or health risks. The ability to anticipate potential problems, act quickly, and avoid overly restrictive definitions or language will enable more flexible policy and thus facilitate responses to changing exposure or toxicity possibilities.

Nanomaterials are still relatively new to the marketplace, so a prime opportunity exists now to develop and implement effective health protections that will guide the development of the nanotechnology industry.

Chapter 3: Exposure Potential and Toxicity of Nanomaterials

3.1 Introduction

Nanomaterials are used in more than a thousand consumer products, and their use is expected to increase dramatically over time. Yet many uncertainties exist with regard to how and how much people are exposed to nanomaterials and the potential health hazards posed by such exposure. This chapter highlights the current science on exposures to and health hazards of nanomaterials, emphasizing properties that are likely to influence their toxicity and identifying critical knowledge gaps. The information presented forms the basis of the policy recommendations in Chapter 4.

This chapter starts with an overview of risk-assessment and risk-management processes, followed by a discussion of hazard and exposure considerations in assessing potential health effects. Next, it provides an overview of the physical and chemical characteristics that may be important for evaluating and characterizing the hazard and exposure potential of nanomaterials. It then reviews several types of nanomaterials, including carbon, elemental metals, metal oxides, quantum dots, and dendrimers, discussing emerging trends in *in vivo* and *in vitro* nanotoxicity testing. It then presents key current scientific findings about exposure routes and the fate and transport of nanomaterials within cells and the body. As the science on the potential toxicity of nanomaterials is continually evolving and thus difficult to capture, we highlight available information and do not attempt an exhaustive review. The chapter concludes by identifying key knowledge gaps.

3.1.1 Risk-Assessment and Risk-Management Basics

Quantitative **risk assessment**, as practiced in the US, is the process used to characterize the potential adverse health effects of exposure to environmental hazards. The process begins with **hazard identification**, which entails using the results of scientific research to describe the characteristics of a chemical or substance and determine whether it has the potential to cause or contribute to adverse health effects. For example, evidence from studies of exposed animals that later develop cancers can be used to identify carcinogens or cancer hazards. The second step of the process is **dose-response analysis**, the aim of which is to determine quantitatively the risk of health hazard over a known dose or concentration range of exposure to a particular chemical. The third step is an **exposure assessment**, which describes the potential ways human populations are exposed to the chemical or substance as well as what is known about current levels of exposure.

The last step of the risk-assessment process is to integrate the hazard identification, dose-response analysis, and exposure assessment into a **risk characterization** that describes both the health-hazard risks that different populations may face given current exposure potentials or levels and the uncertainties of the overall assessment. Risk is a function of health hazard, exposure, and host susceptibility or sensitivity factors. For example, a potentially very hazardous material might be used relatively safely with appropriate safety precautions that preclude exposure. Conversely, a lower-risk material with ubiquitous exposures in the population could result in a high number of adverse health events. Therefore, it is necessary to describe both health hazard and exposure in order to understand risk, which is accomplished through the risk-characterization step.

The information and conclusions produced by a risk assessment feed into policy decisions and the making of regulations through the **risk-management process**. Risk management takes both the risk assessment and other considerations (e.g., public health, economics, and politics) into account to reach decisions about mitigating or preventing exposure.

In 2008, the National Academy of Sciences (NAS) released an updated framework for risk assessment [42]. Notably, the framework includes a problem-formulation and -scoping step in which the problem and options for risk management prior to conducting a risk assessment are defined. It then follows the recommendations to modernize current approaches to quantitative risk assessment. Finally, it includes more opportunities for stakeholder involvement throughout the process.

Risk assessors within government agencies develop and provide risk characterizations using available dose-response information and exposure assessment as inputs in the regulatory and decision-making process. When the available scientific information is limited or nonexistent, this can lead to large uncertainties in risk characterization and contribute to difficulties in decision-making. For example, many decisions include scenarios with potential for increased hazard to children, but information on the specific exposure levels and greater susceptibility of children is often not available. In such cases, agencies necessarily use assumptions and default inferences to fill in for missing information—an action NAS considers scientifically appropriate [42].

In the case of nanomaterials, there are many knowledge gaps, so both qualititative and quantitative default inferences are needed to characterize hazards and risks. Almost all of the nanotoxicity studies done to date have addressed acute exposures only. Very few studies—and often none in the case of many nanoparticles—have investigated sub-chronic or chronic exposures or multi-generational or reproductive outcomes.

3.1.2 Hazard and Exposure Considerations

The overall goal of exposure and toxicity-testing research is to provide the information base for risk assessments, which seek to understand the exposure and response of biological systems to exogenous substances such as nanomaterials. The complexity of exposure and hazard scenarios requires robust and comprehensive toxicological-testing strategies informed by life-cycle and case-study assessments.

Exposure research must take several factors into account. Exposures can be acute (short or intermittent and at high concentration) or chronic (moderately low-level over longer periods of time), and they can occur from contact with a variety of media, such as air, water, and soil. Furthermore, once a chemical enters the body, its effects might be local to the site of contact or more systemic, affecting other tissues, and it might be rapidly excreted or sequestered over long periods of time in certain parts of the body (e.g., fat). Moreover, exposures and resulting increased risks can be influenced by intrinsic and extrinsic factors such as age, disease status, sex, and other exposures.

Both toxicological testing and risk-assessment processes have been time-consuming and resource intensive, resulting in calls for broader, more efficient, and more expeditious evaluations. Some of the difficulties stem from reliance on chronic endpoints from whole-animal studies. Methods under development for both areas use information on biological events that occur earlier in the disease process and may result in more rapid and predictive results. Recent scientific advances providing an increased understanding of early biological perturbations in the exposure-to-disease continuum

may facilitate the use of other models such as tissue culture [68].

The development of new approaches to toxicity testing coincides with an increased need to evaluate the potential human-health risks from the growing volume of nanomaterials in use. For a list of research needs, outlined in 2006 by the Nanotechnology Environmental and Health Implications Working Group, see Box 2 [69]. Commonalities between the older and newer paradigms for testing chemicals include identifying chemical properties and using testing strategies—whether whole-animal studies or the newer toxicity-pathway tests—to explore the key areas identified in Box 2. Key elements of a toxicity screening strategy and exposure assessment should include:
1) physicochemical characterization of nanomaterials; 2) *in vitro* assays (cellular and noncellular); 3) *in vivo* studies; and
4) environmental and aquatic toxicology studies.
The evaluation of these elements is used to assess whether exposures to nanomaterials and by-products associated with their applications can increase the risk of adverse health effects such as developmental, pulmonary, neurological, cardiovascular, and carcinogenic effects [70].

Critical information in determining such toxicities includes the capacity for macromolecular perturbations, potential for unintended carriage of toxic molecules, location of particles in the body after exposure, agglomeration state, and chemical composition [71]. Currently, however, there is no systematic study or reporting of this information for any specific nanomaterial.

Some nanomaterial reports and studies have called for unification of research goals or a central government agency in charge of coordinating nanotoxicity data, research goals, information, and funding. The US does have a nano-specific program called the National Nanotechnology Initiative (NNI), but, as discussed in Chapter 1, a recent review by the National Research Council (NRC) identified many shortcomings in the program [37]. In its executive summary, the NRC said "NNI (2008) does not have the essential elements of a research strategy—it does not present a vision, contain a clear set of goals, have a plan of action for how the goals are to be achieved, or describe mechanisms to review and evaluate funded research and assess whether progress has been achieved in the context of what we know about the potential EHS [environmental health and safety] risks posed by nanotechnology" [37].

BOX 2: Research needs identified by the Nanotechnology Environmental and Health Implications Working Group for human-health assessment of nanomaterials

- Understand the absorption and transport of nanomaterials throughout the human body.
- Develop methods to quantify and characterize exposure to nanomaterials and to characterize nanomaterials in biological matrices.
- Identify or develop appropriate *in vitro* and *in vivo* assays/models to predict *in vivo* human responses to exposure to nanomaterials.
- Understand the relationship between the properties of nanomaterials and uptake via the respiratory tract, digestive tract, eyes, and skin and assess body burden.
- Determine the mechanism of interaction between nanomaterials and the body at the molecular, cellular, and tissue levels

One of the challenges for assessing risks from nanomaterials, as further discussed in this chapter, is there is little direct information to use in hazard assessment and only a limited foundation for making inferences. The challenge for government agencies, given existing laws, is to determine how to use available information to make informed decisions. There are some emerging resources, including the National Library of Medicine's Hazardous Substances Databank and materials from the Organisation for Economic Co-operation and Development's (OECD) Working Party on Manufactured Nanomaterials.

3.1.3 Nanomaterial Characterization

Chemical characterization, including physicochemical properties, can provide insights into the exposures and hazards of chemicals. Traditionally, properties such as molecular structure, vapor pressure, solubility, and partition coefficients have been reported and considered in assessing hazard and exposure potential (see Table 3). For example, the octanol-water partition coefficient (K_{ow}) can reflect a chemical's ability to cross cell membranes.

Nanoparticles are a new class of materials and macromolecular structures that retain some properties of traditional small-molecule chemicals. However, they have additional physicochemical properties and characteristics that are important for understanding their exposure and hazard potentials. The same characteristics that give nanomaterials their unique properties, such as size, aspect ratio, surface charge, and reactivity, may also be important determinants of exposure and hazard. For example, some nanoparticles are similar in size to strands of DNA and proteins and can pass through cell membranes. Because of their high surface-area-to-volume ratio, they can be very reactive and can interact with cells differently than the same chemical constituent in bulk or at the molecular level.

Much of the discussion regarding hazard evaluation of nanomaterials has focused on identifying the key physicochemical properties of nanomaterials that can be used to guide initial evaluations of hazard and exposure potential. While identifying these properties for laboratory-generated nanoparticles is important for developing a fundamental understanding of nanoparticle behavior, given that the method of synthesis and matrix effects can alter the properties of nanomaterials, end-use products should be tested as well.

The first column of Table 3 lists properties of chemicals and materials that are typically reported in material safety data sheets and considered in exposure and toxicity determinations. The second column lists properties and characteristics that may be important for understanding the hazard and exposure potential not just for nanomaterials but also for conventional chemicals. The third column lists additional properties and characteristics particular to nanomaterials that may be important for understanding their hazard and exposure potential.

Primary properties, such as those listed in the first column, are intrinsic properties that are inherent to a chemical or substance. Secondary properties are characteristics that are not defined in simple units or that may change depending on the chemical environment. Properties related to size and surface chemistry are emerging as critical indicators of certain important toxicities and have been linked to cancer, reproductive harm, and respiratory fibrosis.

Table 4 highlights some specific properties that may affect the toxicity of general classes of nanomaterials. For example, inhalation of carbon nanotubes causes inflammation of the lungs due to the nanotubes' size and shape distribution and can lead to asbestos-like outcomes. For a more extensive discussion of the properties and nanomaterials highlighted in Table 4, see sections 3.2 and 3.4.

TABLE 3: Properties and characteristics that may affect hazard or exposure potential

Primary physicochemical measurements typically described for conventional chemicals	Secondary properties for both conventional chemicals and nanomaterials	Additional information needed for nanomaterials and other ultrafine and small particles
• Molecular weight • Chemical structure • Boiling point • Melting point • Vapor pressure • Density • Vapor density • Water solubility • Other solubilities • LogK_{ow} • Henry's Law constant • OH reaction rate constant • K_{oc}	• Persistence and/or bioaccumulation • Identity/purity of contaminants (manufacturing by-products) • Reactivity • Bioavailability • Lipophilicity • Biodegradability • Particle size, length, diameter, surface-area-to-volume ratio • Generation of oxidative species	• Size and shape distribution • Surface treatments of particles (e.g., charge, functionalization) • Crystal structure • Carrier role/capacity • Form of nanomaterial (e.g., dry powder, wet slurry, aqueous solution) • Method of synthesis (gas or liquid when generated) • Agglomeration capacity

TABLE 4: Examples of properties that may affect the toxicity of various classes of nanomaterials

Property or type of information	Nanomaterial	Property's influence on toxicity	Reference
Size (width, length, aspect ratio, surface-area-to-volume ratio)	TiO_2	Smaller particles create more inflammation when inhaled and are retained in the lungs longer.	[72]
	Gold, silver	Smaller particles are associated with more cell toxicity.	[73, 74]
	QDs	Very small particles (< 5.5 nm) are easily excreted through renal pathways; larger particles remain in the body longer.	[75, 76]
	Carbon nanotubes	When inhaled, carbon nanotubes that have larger aspect ratios are more inflammatory to pulmonary tissues.	[8, 77, 78]
	Silver	Smaller particles generate more reactive oxygen species in cell cultures.	[73, 79]
Surface properties (functionalization, charge)	Gold, metal oxides	Positively charged particles are more toxic to whole animals (zebrafish); higher positive charges are more cytotoxic.	[73, 80]
Stability and reactivity	QDs	Surface modifications can degrade, exposing toxic chemicals in the core.	[81, 82]
	QDs, carbon nanotubes and/or fullerenes	Ability to accumulate in the body and extreme long-term stability lead to biopersistence.	[76, 83]
	TiO_2	Particle surface reactivity, as measured using a vitamin C yellowing assay, determines toxicity when inhaled.	[84]

3.2 Important Emerging Determinants of Hazard

As outlined in Table 4, four properties are emerging as important determinants of hazard and exposure potential across various types of nanomaterials: size, surface properties, stability, and reactivity. Subsections 3.2.1–3.2.3 describe these properties and how they may influence exposure and hazard.

Size, surface properties, stability, and reactivity are not the only properties that may affect toxicity. Other characteristics, including those listed in the third column of Table 3, also warrant consideration in risk-assessment decisions. Reporting of all properties is important, even if the effect or property is not currently known to be predictive of toxicity. But while other properties may emerge as important, this report highlights size, surface properties, stability, and reactivity because these

four properties have been identified in the scientific literature as key traits to consider in assessing nanomaterial toxicity.

3.2.1 Size

Size is characterized by measurement of the width (diameter), length, and aspect ratio of nanoparticles. Surface-area-to-volume ratio, which increases dramatically as particles get smaller, is also an important property to identify as more surface area results in higher reactivity.

Nanoparticles range widely in their dimensions, from approximately 1–100 nm or more. Because there are also many biologically active compounds, such as proteins, DNA, and cellular organelles, in this size range, a nanoparticle's specific size greatly influences where it can be transported or accumulate. Size can also affect the generation of reactive oxygen species in cells [73, 79, 85], pulmonary expulsion of particles [8, 77, 86, 87], excretion of particles through normal biological pathways [75, 76], and the potential for crossing barriers and biodistribution (i.e., where and how quickly particles travel in the body) [72, 88, 89].

There is no general trend (e.g., smaller is worse) in how size affects the toxicity of nanoparticles, as it depends on the specific endpoint measured or the type of nanomaterial. Particles this small can, and often do, aggregate to form larger clusters. These "agglomerates" are typically larger than nano-sized and are often of lower toxicity [90]. Agglomeration greatly depends on surface chemistries, the medium in which nanoparticles are suspended, and interactions with biological components in tissues and cells with which they might come into contact.

Aspect ratio is the ratio of a nanoparticle's length to width. Longer, thinner structures or fibers are typically more toxic to the respiratory system than shorter, wider particles [8, 78]. The high respiratory toxicity of asbestos fibers is an example of toxicity linked to aspect ratio and biopersistence [48, 78, 90]. Nanomaterials with high aspect ratios, such as carbon nanotubes, are harder for the lungs to expel and may lead to health effects similar to those from asbestos, including inflammation of the lungs and possibly cancer [78, 86].

Surface-area-to-volume ratio is a size characteristic that has been observed to exhibit a better correlation to toxicity than particle width in the case of inhaled titanium-dioxide particles and carbonaceous particles (e.g., carbon nanotubes) [91-93]. Further study will enhance our understanding of the use of this ratio as an indicator of toxicity.

3.2.2 Surface Properties

Some nanoparticles have other chemical molecules attached to their surface, usually termed "surface modifications" or "surface functionalization." Functionalization refers to any surface modification of a nanomaterial. It includes molecules such as surfactants or other long-chain groups to stabilize nanoparticles; biologically relevant modifications; surface charges stabilized by soluble salts; and other modifications that are not the original, core constituent of nanoparticles themselves. Surface functionalizations serve a wide variety of purposes. Examples include making nanoparticles biologically active, making them water soluble, or preventing agglomeration. The specific chemistry and functionalization of the surface play a large role in the ultimate fate and reactivity of nanoparticles.

Other nanomaterials, such as metals, can have intrinsic properties on their surface, such as a positive or negative charge that affects how the surface interacts with its surroundings. Indeed, electrostatic charge is one surface property that can give nanoparticles better performance characteristics. The behavior of charged particles depends on the charge status (positive or negative), the relative size of the charge (+1, +2, +3, etc.), and the charge or polarity of the surrounding environment. In general, charged particles

decrease cell viability compared to neutral particles, with both positively and negatively charged particles implicated in differing adverse outcomes. For example, in zebrafish embryos, positively charged nanoparticles contributed to significantly higher toxicity and morbidity than negatively charged or neutral particles [80].

3.2.3 Stability and Reactivity

Stability is the retention of all original surface properties, functionalization, and size. In other words, a stable nanomaterial has the ability to retain all intended properties and not to degrade over time, expose other portions of the nanomaterial, or be chemically altered into a new compound. In some contexts, stability can refer both to the stability of the suspended solution and its agglomeration capacity, the likelihood of nanoparticles clumping together either before or after environmental release. Agglomerates of particles often become large enough to reduce some of the “nano" effects, but understanding or predicting how and to what extent this may happen is difficult.

Some nanomaterials are comprised of an inner core of toxic materials surrounded by a protective and biologically neutral surface coating, the stability of which is critical to preventing toxic effects. Unstable surface chemistries can cause protective outer coatings to erode, exposing potentially more toxic cores. Quantum dots contain heavy metals such as cadmium, selenium, and lead in their central core; a second layer or shell of metal-containing salts; and typically a final layer of functionalization to render them more amenable to user applications. If the layer of functionalization degrades, the toxic metals in the inner layers can be released into the body or the environment.

The ability to persist for very long periods of time can influence toxicity and other adverse environmental impacts. Very stable substances tend to persist and can accumulate in the environment and biological systems. For example, some quantum dots are highly stable, giving them the potential to persist or bioaccumulate. There is evidence that quantum dots larger than 5.5 nm are retained in the body much longer than smaller particles [75] and that they can build up in organs [76]. Carbon nanotubes are another example of highly stable materials that do not degrade in the environment or by normal biological mechanisms [83]. As discussed in Chapter 2, bioaccumulation is a trait that needs special attention when assessing the risk of any chemical or metal.

Reactivity can have different meanings, but in this report it refers to the ability to cause reactive oxygen species (ROS) to occur in biological systems. Generation of ROS can lead to adverse biological outcomes by overwhelming the antioxidant defense capacity of cells and causing disruptions in the equilibrium of their redox potential. The specific composition, size, surface area, and surface chemistry of nanoparticles all affect their ability to generate ROS.

Table 4 provides examples of how size, surface properties, and stability and reactivity can influence the toxicity of different types of nanomaterials. How these properties influence toxicity may vary not only by the type of nanomaterial but also by conditions such as exposure routes, end uses, and disposal methods. To understand nanomaterial risk, the relationships between properties and hazard and exposure potentials need to be described. For example, do nanomaterials change structure or properties throughout their life cycle (e.g., pure metal nanoparticles such as silver or iron turning into an oxide)? Changes to nanomaterials during their life cycle may alter their potential health hazards and should be assessed to fully understand possible hazards and risks.

3.3 Measurable Adverse Effects

Several types of measurable health-related effects are commonly observed in studies of exposures to nanomaterials. This section highlights three effects that are also emerging as pathways by which nanoparticles may increase the risk of adverse effects: impaired phagocyte formation, ROS generation, and granuloma formation. When determining appropriate toxicity assays to use for assessing nanomaterial hazards, these are measurable endpoints that might be considered.

1. **Impaired phagocyte formation**. Phagocytes are phagocytic cells (white blood cells) that form protective coatings around small foreign particles. If the ability to form phagocytes is compromised, contaminants can cause inflammation. Significant and prolonged inflammation has been linked to cancer development and progression, so reduced ability to form phagocytes as a result of nanoparticle exposure could be a risk factor for cancer as well as other adverse health effects.

2. **Reactive oxygen species (ROS) generation**. Reactive oxygen species naturally occur in biology and are important parts of some cell-signaling processes. However, if too many ROS occur, they can damage cells by creating oxidative stress and harming organelles or by causing disruptions in the equilibrium of the redox potential of cells. Excessive ROS generation in cells has been associated with cardiovascular disease, programmed cell death, and premature aging. Cells typically respond to ROS-induced damage or the overproduction of ROS with enzymes or antioxidants. Since so many different types of nanoparticles have been implicated in ROS generation, it is an important pathway to assess.

3. **Granuloma formation**. Granulomas are groups of immune cells generated to remove substances the body perceives as foreign. The presence of granulomas typically indicates an immune response to an irritation or perturbation. Granuloma presence in the lungs is an early indication of asbestosis and lung cancer, and inhaling nanoparticles may also generate precursors to granulomas [8, 78, 87, 94, 95].

3.4 Types of Nanomaterials and Toxicity Highlights

This section describes several types of nanomaterials and underscores emerging trends in *in vivo* and *in vitro* nanotoxicity testing, highlighting toxicity results that raise concerns and illustrating the potential for adverse health effects. As with other sections of this report, it is not an exhaustive review.

The field of **nanotoxicology** is relatively new. While groups such as OECD[1] have sought to create standards and methodologies for the field, there are currently no federally or state-recognized standard procedures, assays, or methods, nor is there any coordinated, systematic approach to the types of toxicity tests conducted, materials assessed, or endpoints identified. The limited toxicity data that do exist provide some indication of hazard potential, but much more research is needed to fully understand the characteristics and hazard potential of nanomaterials.

In addition to the various cellular-level studies that have been done, current health and safety investigations of nanomaterials focus mainly on the following three areas: routes of exposure and the resulting potential deposition or accumulation in biological systems; translocation (biokinetics); and adverse effects or biological deposition in target organs beyond the initial site of exposure, such as the kidneys, brain, heart, and liver [75, 96, 97].

[1] For information on OECD's efforts, see http://www.oecd.org/department/0,3355,en_2649_37015404_1_1_1_1_1,00.html.

Furthermore, most studies using whole animals have focused only on inhalation or intratracheal instillation exposures. [87, 98-102]. There are only limited studies of workers who may be highly exposed for short periods of time. Therefore, there are very few studies on low-level systemic toxicities (e.g., sub-chronic or chronic exposures, multi-generational or reproductive outcomes) or multiple exposure routes (e.g., inhalation and ingestion). A few studies in rats using both nano-sized and micron-sized exhaust particles have evaluated deposition in or impacts on the function of reproductive organs [103, 104]. However, the paucity of data and, in some cases, conflicting results on toxicity make it difficult to generalize how the physicochemical properties discussed earlier in this chapter relate to biological activity and toxic potential [80].

3.4.1 Carbon-Based

Carbon-based nanomaterials are made of anywhere from sixty to hundreds of carbon atoms. The majority are in the form of nanotubes or fullerenes ("buckyballs," shown directly above). While all carbon-based nanomaterials are made of pure or mostly pure carbon, nanotubes and buckyballs such as C_{60} have very different chemical and physical properties and thus exhibit differing toxicities.

Carbon-based nanoparticles have a wide range of uses and properties. They are currently included in more than 80 consumer products [11], and their frequency of use is second only to silver nanoparticles. Moreover, many carbon-based nanomaterials are integrated into a matrix that comprises the product (e.g., a bicycle frame), making this an area of particular interest.

Exposure to workers and, ultimately, the general population via air emissions from manufacturing is beginning to emerge as an issue of concern and is an area of extensive ongoing research, mainly through the US National Institute for Occupational Safety and Health (NIOSH). Workers who manufacture these products are likely to be at greatest risk; indeed, manufacturing facilities seem to be the locations of highest exposure potential in general, with inhalation being the main route of exposure, although dermal exposures occur with dermal irritation as a secondary effect. The primary concern for workers is inhalation of long (high aspect ratio) nanotubes. It appears unlikely that carbon-based nanoparticles are released from consumer products and inhaled by the general population to any great extent, but as use of nanomaterials continues to grow unchecked and unregulated in these products, it will be difficult to know to what extent the particles are safely incorporated. In addition, over the lifespan of these products, exposures may occur through normal wear or grinding of composite materials. Moreover, there could be environmental releases of carbon nanotubes associated with manufacturing.

The wide-ranging quality of carbon nanomaterials—some are combustion-formed; some are highly pure and crystalline in structure—leads to substantial variation in performance and makes it difficult to treat carbon-based nanomaterials as a class. Significantly, differences in purity can lead to varying toxicities. For example, higher levels of impurities in carbon nanotubes have been observed to have more adverse health effects than pure carbon-based nanotubes [8].

Table 5 highlights toxicity studies of carbon-based nanomaterials. To date, whole-animal studies of such nanomaterials have focused primarily on effects on the respiratory system, the site of contact for inhalation exposure. But there have also been many studies focusing on *in vitro* effects, with results depending on the specific material studied or endpoint measured. In general, these studies show that carbon-based nanomaterials tend to

cause lower cell proliferation, lower cell viability, and cell death in a dose-dependent manner.

Perhaps most notably, a 2006 review by Lam et al. [8] emphasizes the rodent evidence that exposure to carbon nanotubes may cause adverse effects including pulmonary inflammation, microscopic nodules, fibrosis, and other toxicological changes in the lungs. These results indicate potential human risk and the pressing need for further study. Furthermore, a more recent study by Poland et al. using carbon nanotubes of varying sizes and shapes found that exposure to longer fibers produced far more lung inflammation than shorter tangled or bundled fibers (see Figure 9) [78]. The fibers were of similar diameter (both in the range of 15–100 nm) but different lengths (1–20 μm vs. 20–100 μm), and the study used nanoparticulate carbon black as a short-fiber control and long-fiber asbestos as a long-fiber control.

While a number of studies have evaluated the respiratory toxicology of carbon nanotubes, few have addressed possible systemic effects. Studies indicating that certain particles have the ability to enter the brain through the nasal cavity [105-107] highlight the need for careful study of possible systemic effects. Recent studies have also provided evidence of vascular effects following pulmonary deposition of carbon nanotubes [108].

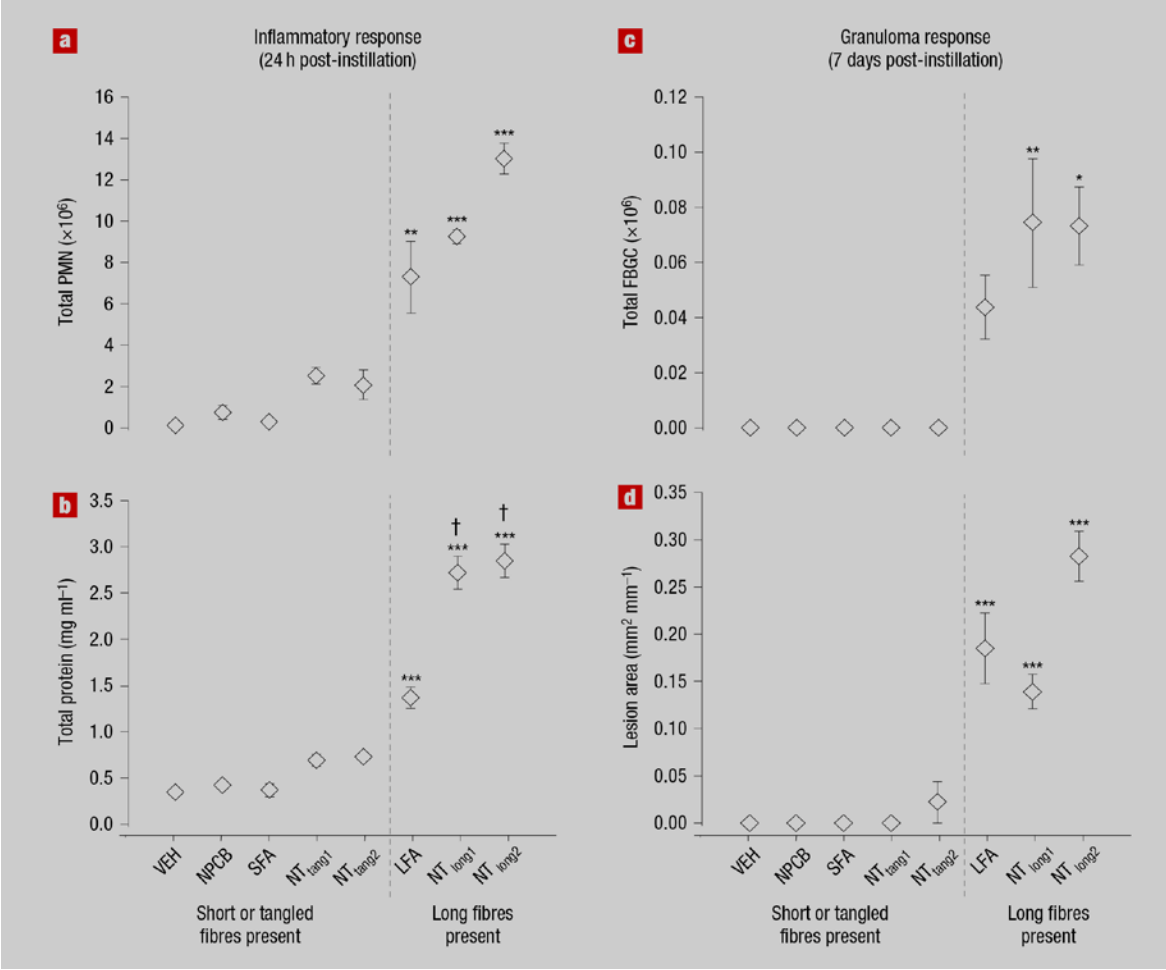
TABLE 5: Examples of findings from toxicity studies of carbon-based nanomaterials

Test	Organism	Nanomaterial	Findings	Reference
Cell studies: *in vitro*	Bacterial cells	Single-walled carbon nanotubes (SWCNTs)	• Oxidative stress, cell death in time- and dose-dependent manner	Shvedova et al. 2003 [109]
	Animal cells	SWCNTs, multi-walled carbon nanotubes (MWCNTs), quartz, C_{60}	• Cytotoxicity dependent on material • Changes in cell structure • Ability to produce phagocytes reduced in dose-dependent manner	Jia et al. 2005 [110]
	Human cells	Various types of SWCNTs and MWCNTs, carbon black, fullerenes.	• Decreased cell viability • General toxicity in dose-dependent or purity-based manner	Cui et al. 2005 [111], Bottini 2006 [112], Magrez et al. 2006 [85]
Whole body studies: *in vivo* intratracheal instillation or intraperitoneal injections	Rats	Quartz, SWCNTs, other carbon particles	• Pulmonary inflammation • Granuloma formation	Warheit et al. 2004 [102]
	Mice	Carbon nanotubes	• General decline in health • Granuloma formation • Bronchial inflammation	Lam et al. 2004 [87] Lam et al. 2006 [8] (review)
	Mice	Various sizes and shapes of carbon nanotubes	• Asbestos-like, length-dependent pathogenic behavior	Poland et al. 2008 [78]

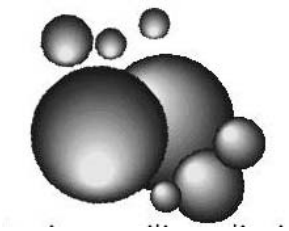
FIGURE 9: Effect of acute exposure to carbon particles of various sizes in the lungs of mice. Figure from Poland et al. 2008 study exposing mice intraperitoneally to various solutions of short or tangled carbon nanofibers (left side of graphs) or longer fibers (right side of graphs) [78].

Graphs (a) and (b) show the short-term (24-hour) inflammatory response to pathogenic particles, with polymorphonuclear leukocyte (PMN) and protein exudation.

Graphs (c) and (d) show the longer-term (7-day) inflammation, indicated by granuloma formation and foreign giant body cell (FGBC) formation. Only the samples containing long fibers caused significant toxicity of these endpoints, which are indicators of adverse effects.



3.4.2 METAL-BASED



The metal-based category of nanomaterials covers two major areas: **elemental metals** such as silver (Ag), gold (Au), and iron (Fe, sometimes referred to as "ferrous"); and **metal oxides** such as titanium dioxide (TiO_2), zinc oxide (ZnO), iron oxide (Fe_2O_3 or Fe_3O_4), and silica (SiO_2). There are a few other forms of metal-based nanomaterials, but the vast majority of products containing metal-based nanomaterials fall into one of these two categories.

3.4.2.1 Elemental Metals

Pure silver and gold particles comprise the majority of this class of nanomaterials. Most are spherical, but some are in rods or other shapes.

Silver nanomaterials are used in more consumer products than any other class of nanomaterials. Silver's antibacterial properties have been known for centuries [23], and, when nano-sized, silver can be easily integrated into polymers, fabrics, coatings, and other materials with the purpose of rendering them bacteria-resistant. Nanosilver has also been integrated into dietary supplements for oral ingestion, allegedly to cure a range of ills.

Most of the procedures to integrate silver particles into fabric or other matrices do not bind the silver through molecular or chemical bonds; rather, they are non-specifically bound to the surface of threads or polymers, which makes them susceptible to dislodging and coming out of the original matrix. For example, nanosilver-coated socks leach out silver particles during both normal wear and wash cycles [113-115]. Furthermore, in some cases, silver nanoparticles are not bound at all—for instance, in special washing machines that inject solutions of silver nanoparticles into the wash cycle—and subsequently enter wastewater and the environment. The potential therefore appears to exist for cumulative environmental exposure to silver.

Gold nanoparticles are found in cosmetics and dietary supplements and are used as a colloidal stabilizer in fluids such as paint and lubricating oil. Many uses involve direct ingestion, skin application, or food contact, indicating that gold might be a material with a large exposure profile. Gold nanoparticles are also used in medical applications, cell biology, and diagnostics, which are more controlled-use situations.

Findings related to potential human and environmental toxicity for gold, silver, and other elemental-metal nanoparticles are summarized in Table 6. For example, nanosilver's bactericidal properties have the potential to disrupt bacterial colonies at wastewater treatment facilities, which could result in increases in other contaminants that these colonies typically filter out. Moreover, many silver compounds are bioaccumulative, especially in aquatic species. Silver nanoparticles are also highly toxic to various aquatic species that form the basis of the food chain, especially during their early life stages.

Silver can also cross blood-organ barriers and accumulate in the liver, kidneys, and subcutaneous regions, and chronic exposure can lead to argyria, a graying of the skin and/or eyes. Humans can absorb silver through inhalation, oral, and dermal (through broken skin) routes [116]. Therefore, it is possible that use of silver nanomaterials could cause overexposure to silver itself. Some areas, especially near modern photochemical processing plants, already have high levels of silver contamination in water sources [117]. Silver is not a substance that is typically monitored, however, so current research and monitoring protocols would not identify increases either in environmental contamination or human exposure.

TABLE 6: Examples of findings from toxicity studies of elemental-metal nanomaterials

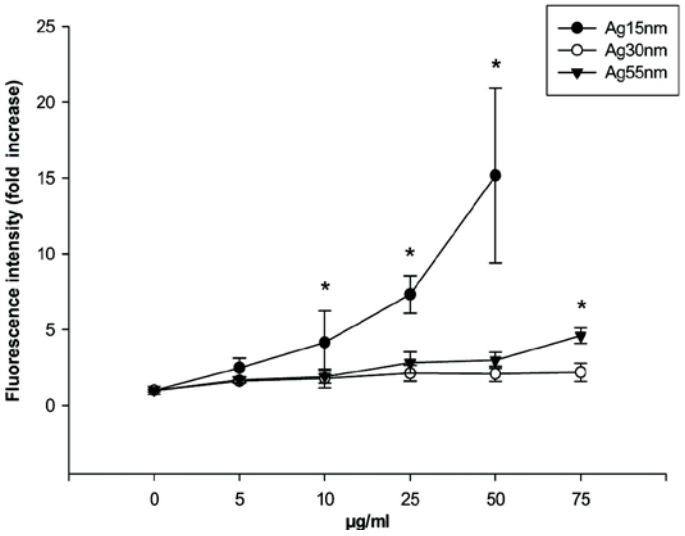
Test	Organism	Nanomaterial	Findings	Reference
Cell studies	Soil microbes	Silver ions	• Decreased microbe nitrogenation of soils	Throback 2007 [118]
	Human cells	Gold nanorods and particles	• Varying surface charges increased cell uptake	Hauck et al. 2008 [119]
		Gold	• Positively charged particles more toxic to cells	Goodman et al. 2004 [120]
		Silver	• Smaller particles increased ROS generation	Carlson et al. 2008 [73]
Whole animal	Zebrafish	Gold particles	• Positively charged particles more toxic than neutral particles to zebrafish embryos	Harper et al. 2008 [80]
	Daphnia, zebrafish, algae	Copper, silver, nickel, and cobalt	• Silver and copper nanoparticles more toxic to all species • Toxicity of other metal particles varied by composition and species	Griffitt et al. 2008 [121]
Reviews	Medicinal applications	Gold	• Skin irritant and cytotoxic effects	Panyala et al. 2009 [122]

The main properties of concern for metallic nanomaterials seem to be size, surface charge, and the ability to form metal ions with associated antibacterial properties. Size is an important property, raising concerns on both ends. Larger particles tend to bioaccumulate more, as particles less than ~5 nm can be excreted through the kidneys [75] [75]. But, as seen in Figure 10, smaller particles (15 nm) generate more ROS than larger particles (30 or 50 nm) *in vitro* [73]. In addition, a recent review of metallic nanoparticles' toxicity factors suggests that the oxidation potential and oxidation state of metals can change and are critical to understanding the potential toxicity of various materials [123].

In cell studies, surface charge appears to affect both gold, and sliver nanoparticle toxicity, as seen in Figures 10 and 11.[73, 80] For example, exposing zebrafish embryos to positively charged particles caused 2–5 times higher morbidity compared to similarly sized neutral or negatively charged particles [80]. In addition, in E. coli cell cultures, higher positive charges led to higher cytotoxicity [119].

The few whole-animal studies of silver and gold nanoparticles show little toxicity to the animals, but there are more gaps in data and available information than conclusive studies. The extent to which silver nanoparticles are converted to silver ions that can react to form other silver compounds with higher toxicity is also unclear.

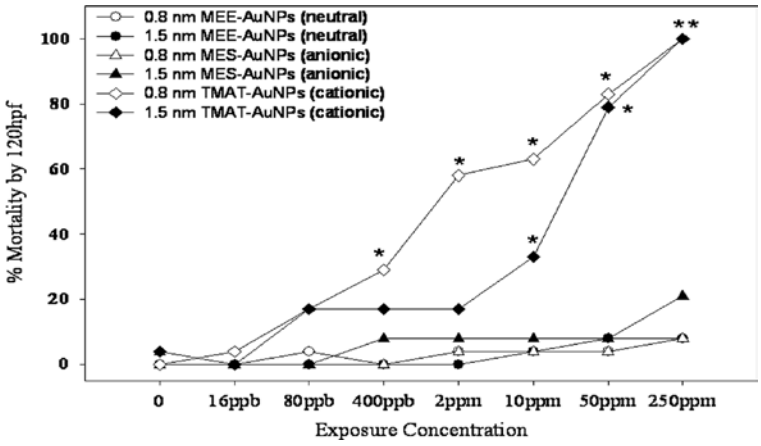
FIGURE 10: Effect of silver nanoparticle size on generation of reactive oxygen species (ROS) in macrophages. Smaller nanoparticles cause more ROS generation. Graph from Carlson et al. 2008 [73].



The fluorescence intensity of a fluorescent dye was assessed. Increase in fluorescence of the dye indicates higher concentration of oxidative species.

Asterisks (*) indicate a statistically significant difference compared to controls ($p < 0.05$).

FIGURE 11: Mortality of embryonic zebrafish increases with surface charge and dose. Graph from Harper et al. 2008 [80].



Cumulative percent mortality of embryonic zebrafish exposed to 0.8 nm (open symbols) or 1.5 nm (solid symbols) gold nanoparticles with various surface charges. Positively charged particles caused significantly higher mortality. Asterisks (*) indicate a statistically significant difference compared to controls ($p < 0.05$).

3.4.2.2 Metal Oxides

Metal oxides are molecules that contain at least one oxygen atom and a metal. Metal oxides occur in nature (e.g., iron oxide, or rust) and are also used widely in consumer products. For example, nano-sized cerium oxides are often used as catalysts for many petrochemical and other synthesis processes, as their extremely high surface area makes them good substrates for catalytic activity. Because there is always a supply of oxygen in our environment, molecules that are not fully oxidized tend to become more so as time goes on and to become quite stable (e.g., rust). This stability can decrease biological reactivity, which may also decrease potential toxicity, but may increase the ability to bioaccumulate.

Titanium dioxide is a white powder that varies in particle size and is used widely in paints, coatings, and dyes for pigmentation and solution-stabilization properties. It also possesses some antimicrobial properties in water and is used in some anti-fouling agents. Its white/opaque properties also make it a useful sunscreen because it physically blocks the harmful rays of light. Traditionally, micron-scale particles have been used in sunscreen, but nano-sized particles are increasingly popular because their small size makes them transparent to visible light, making the sunscreen invisible on the skin, but opaque to UV rays. Because sunscreens are so widely used, there is widespread human exposure to titanium-dioxide nanoparticles.

Table 7 gives examples of findings from toxicity studies of metal oxides. Like carbon and some metals, nano-sized metal oxides can demonstrate toxicity in the form of ROS generation and irritation in cell-culture experiments and inhalation studies. ROS can lead to protein and DNA damage [125, 129, 131]. For example, a recent review by the International Agency for Research on Cancer (IARC) found sufficient evidence in rat studies to suggest titanium dioxide might be carcinogenic to humans (group 2B on its rating scale)[129]. The IARC cited increased lung tumors in rats exposed via inhalation to nanoparticles, as well as similar symptoms in people who work in dusty places, as sufficient evidence for possible carcinogenic effects. Interestingly, some nano-sized metal oxides actually scavenge oxygen and prevent excessive ROS damage [132].

TABLE 7: Examples of findings from toxicity studies of metal oxides

Test	Organism	Nanomaterial	Findings	Reference
Cell study	Mouse fibroblast cells	TiO_2	• Cell death • ROS formation and oxidative stress • Decreased viability and cell function	Jin et al. 2008 [124]
	E. coli cell culture	ZnO	• Increased cell permeability and internalization of particles, leading to death	Brayner 2006 [125]
	E. coli cell culture	Compared all metal oxides: Zn, Cu, Al, La, Fe, Sn, and Ti	• Cationic surface charge determined cell toxicity; higher-charged particles were more toxic. • Identity of metal less important	Hu et al. 2009 [126]
Tissue study	Human, pig, and rat skin	TiO_2 and ZnO	• Insoluble nanoparticles of TiO_2 & ZnO do not generally penetrate healthy skin.	Nohynek et al. 2007 [127] (review, contains many references)
Whole animal	Mice	TiO_2 aerosols	• Subacute exposure showed inflammatory response.	Grassian et al. 2007 [128]
	Various rodents, inhalation and injection	TiO_2	• Inhalation studies showed increased lung tumors; injection studies did not show tumors.	IARC, summary and evaluation of TiO_2, [129]
	Rats, inhalation and injection	MnO, Fe_2O_3	• Inhaling MnO ultrafine particles and nanoparticles resulted in translocation into the olfactory bulb (brain). • Iron oxides did not translocate to a large extent.	Elder et al. 2006 [105] Petri-Fink et al. 2007 [130]

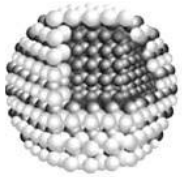
Given the wide use of metal-oxide nanoparticles in sunscreen and cosmetics, one focus of recent research is on determining whether these materials are absorbed through the skin. Current evidence indicates that there is little dermal penetration. In a review of dermal-application studies of nanomaterials, Nohnyek et al. [127] report that: 1) in 15 studies, no nanoparticles were shown to cross the skin barrier in living-tissue experiments; and 2) in experiments using pieces of skin from humans or other mammals separate from the larger epidermal system, sometimes up to 1% of the nanoparticles penetrated a few strata of the epidermis, but not the entire tissue. Nohnyek concluded that there is no current risk posed by the use of nano-sized zinc or titanium dioxide in cosmetics and sunscreens. However, there have been no studies to date on compromised tissue such as sunburned skin. Accordingly, there are other groups, including Consumers Union, which publishes Consumer Reports, that do not believe nanomaterials have been proven safe and have called on the U.S. Food and Drug Administration (FDA) to test nanoparticles and require labeling for sunscreen and cosmetic use.

Consideration of other small particle research may help fill data gaps in our knowledge of nanomaterial toxicity. For example, the IARC has found talc possibly carcinogenic to humans based on studies of human use of talcum body powder on perineal areas [133]. Talc is a magnesium-silicate-based mineral compound that is used widely in consumer products, and its size ranges from about 2–100 µm (2,000–100,000 nm), depending on the application. The mechanism by which talc may cause cancer is unknown, and the findings of cancer are not definitive, but women who used talcum powder in perineal regions were more likely to suffer from ovarian cancer. While talc particles are, on average, larger than nanoparticles as traditionally defined, talcum powder may still contain particles that have similar properties to nanomaterials as well as some particles that are nano-sized.

In considering human exposure risks from nanomaterials, the Environmental Working Group (EWG) has estimated that the highest risk will likely be to workers exposed to large numbers of particles, possibly in the dry or aerosol form during manufacturing. EWG also identified a possible risk of inhalation exposure to consumers in spray forms of sunscreen and other powdered cosmetics [134].

As for worker exposure to titanium-dioxide particles, NIOSH reached two conclusions in a 2009 report [135]. First, the tumorigenic effects of TiO_2 exposure in rats do not appear to be either chemical-specific or a direct action of the chemical substance itself. Rather, they appear to be a function of particle size and surface area acting through a secondary genotoxic mechanism associated with persistent inflammation. Second, exposures to low concentrations of TiO_2 pose a negligible risk of lung cancer in workers.

3.4.3 Quantum Dots



Quantum dots (QDs) are nanomaterials with a more complicated molecular formula, typically containing 2–5 different elements in a core/shell structure. An example is a core of cadmium selenide (CdSe), surrounded by a thin shell of zinc sulfide (ZnS), which would be represented as CdSe/ZnS, along with its specific diameter. This hard central core and shell structure is the functional portion of the nanoparticle: the core always contains one or more heavy metals, such as cadmium, zinc, or lead, and the shell is most often functionalized further with other coatings or surface chemistries to enable suspension of the particle in various solvents and environments such as biological systems. While surface modifications increase particles' overall diameter, sometimes enough to restrict and/or control their movement within biological systems, without such modifications, most quantum dots

would be insoluble or incompatible in biological and other water-based systems. As mentioned earlier in this report, there are many types of quantum dots, and there are also many types of surface functionalizations that render them biologically active or amenable to other specific chemistries.

Quantum dots are currently used mainly in research for cell diagnostics[2] but are also being developed for medical imaging, solar cell materials, and "smart" labeling technologies that could be used to track and store information.

Quantum dots' interesting properties arise mainly from their specific size and shape, which cause the electrons confined within the particles to consistently absorb and emit specific wavelengths of light. Quantum dots have significant advantages over traditional molecular dyes due to these properties. First, quantum dots are much more stable than traditional molecular dyes, allowing them to be used in whole-animal assays without undergoing chemical reactions and losing their fluorescent nature [82]. Second, quantum dots greatly facilitate the use of multi-colored experiments. Most molecular dyes require a specific excitation wavelength in order to emit their corresponding color, which makes multi-colored experiments very difficult. Quantum dots, however, require only one wavelength of light for excitation; as shown in Figure 12, each particle emits a discrete wavelength, depending on its particular diameter, so multi-colored experiments can be conducted simply by using particles of different sizes. This capability is important for conducting complicated biological experiments that require tracking and/or imaging more than one biological system simultaneously.

Quantum-dot structures are almost always made with toxic heavy metals, including the known human carcinogens cadmium and selenium. Since heavy-metal ions are known cell toxicants, one important expected determinant of quantum-dot toxicity is the stability of the surface chemistry and its susceptibility to degradation. Other factors that can influence quantum-dot toxicity include size, concentration, photolytic stability, and the chemical and physical nature of their ultimate fate locations (e.g., air, water, land) [82].

FIGURE 12: Schematic of how one light source can be used to excite different-sized quantum dots that then emit specific, discrete colors depending on their size.

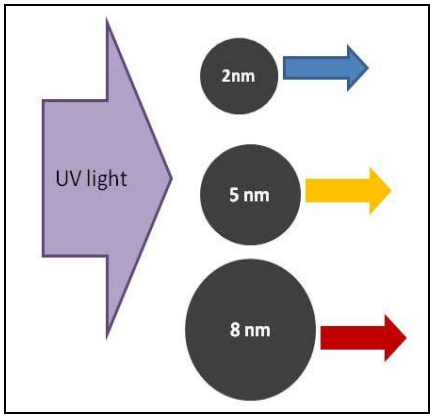


Table 8 highlights general conclusions from toxicity tests of quantum dots. In cell experiments, quantum dots are generally shown to be cytotoxic in *in vitro* experiments. Few experiments have been done to date on whole animals, so although these studies did not generally find an increased risk of adverse health effects from injections of various types of quantum dots, quantum dots were seen to accumulate in organs and other areas of rodent models such as the liver, spleen, and bone marrow [82]. With the increased usage of quantum dots for

[2] Cell diagnostics can refer to various types of uses but typically involve attaching a quantum dot to a biological structure of interest and monitoring its movement and interactions within the cell. Typically, such experiments are done with primary cells in culture dishes, but quantum dots are also being used increasingly in whole-body experiments to track larger-scale movement and behavior.

biological imaging and medical diagnostics, humans are likely to be exposed to higher levels of quantum dots than in the past. As quantum dots degrade, humans may also be exposed to the heavy metals in their cores. Due to the known toxic components in most quantum dots, the possibility of degradation in the environment, and the extent to which such degradation might occur, warrant investigation.

Situations may arise where increased or prolonged use might cause bioaccumulation in target organs, resulting in health decrements. For example, a mouse study of the chemical fate of CdTe quantum dots commonly used in medical technology found elemental cadmium increased in the kidneys of the mice, indicating that cadmium was being released from the inner core of the particle seen [136]. Cadmium is nephrotoxic in humans; and cytotoxicity generally was observed from chronic rather than acute exposures [82].

In general, quantum-dot toxicity studies have focused on cell-based assays, which are limited for determining whole-organism toxicity. Furthermore, the limited number of whole-organism studies on quantum dots has primarily focused on the biological fate of the particles and less on toxicity [137]. Accordingly, there are large data gaps on toxicity and limited data on biological fate, and a review by Pelley et al. suggests that the studies that do exist in both of these areas suffer from lack of standardization and too few endpoints measured [137].

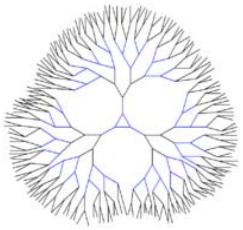
TABLE 8: Examples of toxicity studies of quantum dots

Test	Organism	Nanomaterial	Findings	Reference
Embryo development	Zebrafish embryos	CdSe/ZnS	• Toxicity dependent on various surface chemistries	King-Heiden et al. 2009 [138]
Cell study	Human breast-cancer cells	CdSe/CdS	• Cellular uptake dependent on surface chemistry • Cell viability dependent on concentration	Chang et al. 2006 [139]
	Various cell lines	QDs with various surface chemistries and compositions	• Cellular toxicity dependent on surface chemistries and size • Several studies demonstrate release of cadmium, a known toxicant.	Pelley et al. 2009 [137] (review)
Whole animal	Mice	QDs with various surface chemistries	• Studies with short-term exposures generally did not see toxicity. Toxicity was generally seen from studies of longer term exposure.	Hardman 2006 [82] (review)
	Mice	QDs of varying sizes	• QDs < 5.5 nm excreted via normal, renal/urinary routes • QDs > 6 nm have much longer half-lives in the blood and body tissues.	Choi 2007 [75]
	Mice	QDs of varying sizes and surface chemistries	• Can distribute throughout the system and accumulate in a variety of organs and tissues	Hardman 2006 [82] (review)

Overall, manufactured quantum dots cannot all be considered alike. Their absorption, distribution, metabolism, excretion, and toxicity depend on various factors including size; charge; concentration; outer coating material (functional groups); and oxidative, photolytic, and mechanical stability [82]. However, despite differences in their structure, studies show that quantum dots can

degrade and expose the heavy metals in their core, which gives them a shared property of containing a known toxic metal.

3.4.4 Dendrimers and Polymeric Nanomaterials



Like the other nanomaterial classes, the term "dendrimer" can refer to a large range of particles and materials, but it is usually used to refer to a branching-type bonding structure that radiates from a center position. Some dendrimers contain one or more metal nanoparticles, such as gold, in the center, with branching molecules surrounding the nanoparticle(s). Others are mainly polymeric—with a “soft,” flexible, branched molecular composition—and are typically highly biologically active or biocompatible.

Dendrimer nanomaterials are not currently in wide use in consumer products; their current primary use is in pharmaceutical and medical applications with development focused on drug delivery and diagnostics. Very specific particles or molecules can be attached to dendrimers and then dispatched to precise areas in various biological systems. Since the FDA handles most of the decisions regarding the safety of drugs and medical devices, this section addresses the exposure and toxicity of dendrimers only briefly.

In vitro tests suggest exposure to dendrimers lowers the viability of cell cultures. As in most nanomaterial experiments, toxicity depends on the specific structure; for dendrimers, the core structure and polymer structure have the largest impact on toxicity. Because of their polymeric nature, dendrimers can be thought of as “soft structure” and are normally not nearly as robust as "hard" nanomaterials that resist environmental degradation [140]. However, size and surface charge have been shown to regulate dendrimer biokinetics in animal studies [141].

Overall, given that most current dendrimer uses are highly specialized and controlled, their public-health risk profile is currently relatively low.

3.5 Exposure Routes

As discussed in the sections above, there are various ways humans might be exposed to different nanomaterials. Typically, the worker in the manufacturing process is considered to have the highest exposures, but there may be exceptions as uses and applications evolve over time. For example, as nanomaterials are more widely used in applications such as paints, coatings, and building materials, other groups of workers such as those in construction may be at risk of significant exposure.

Exposure to nanoparticles, similar to other industrial chemicals, can occur by inhalation, orally, or dermally. Moreover, the exposure route can influence the absorption and distribution of these particles in the body. In order to comprehensively understand exposures, we need to know where nanomaterials are located throughout their life cycle, which includes information about where they are manufactured and used. We also need to know how they move from their initial manufacture, to use and incorporation in products, and then to disposal. Finally, we need monitoring systems to measure nanomaterials in areas of concern, for example, air, water, and/or food. Such information and monitoring would provide a more complete picture of the potential for exposure and, where appropriate, a means to identify useful interventions. Unfortunately, however, we currently lack both the policy structure to require information from manufacturers and the technology to detect these materials accurately in mixed media. Accordingly, this section focuses on routes of exposure, which have been studied to a limited degree, and how they can influence toxicity.

1. **Inhalation:** Currently, the primary information on inhalation exposure comes from animal studies and from studies focusing on workplace exposures. The primary source of inhalation exposure in the occupational setting is from manufacturing processes that contain loose, dry forms of nanomaterials such as titanium dioxide or carbon nanotubes. Most studies have focused on respiratory effects from inhalation exposures; few have assessed other systemic toxicity. There is some evidence for asbestos-like response to carbon nanotubes of certain sizes, as discussed earlier in Section 3.2.1. Cardiac tissue damage may occur from these types of exposures as well [8, 142, 143]. Worker inhalation of ultrafine and small particles has also been associated with severe lung-related and other adverse health outcomes [95], indicating high risk to populations with high occupational exposures. While this example does not represent general-population exposure, it does highlight the need for appropriate worker interventions to prevent harmful exposures and gives insights about the potential health effects for non-occupational exposures.

2. **Oral:** Nanomaterials have been introduced intentionally into a number of products for oral consumption, including so-called "nutraceuticals," nanofoods, and nanoparticle solutions intended for drinking. Food and beverages can also be contaminated with nanoparticles used to coat the surfaces of some types of cookware, food storage containers, and baby products (via secondary routes of exposure through degradation and migration). In addition, as with other types of chemicals, children can be exposed via hand-to-mouth behavior from dust and surface depositions. Currently, the most likely route of non-workplace exposure to nanoparticles is oral ingestion. Gold, silver, or metal-based nanoparticles have the potential to bioaccumulate in organs such as the kidney and liver. If enough nanoparticles are released into the environment, the potential also exists for exposure through drinking water; however, there are currently no large-scale ongoing studies of fate and transport of these materials in the environment.

3. **Dermal:** The main dermal exposure route to nanoparticles is currently through consumer products that are directly applied to the skin. Various types of cosmetics and many sunscreen products contain nanoparticles for solution stability and spreadability. Smaller particles penetrate further into the dermal layers than larger particles [127, 144]. While there is currently very little evidence of nanoparticles migrating through healthy skin, broken or damaged skin may have the potential to allow some nanoparticles through. A recent review by Crosera et al. evaluating the dermal toxicity of nanoparticles stated, "there are limited data on carbon-based nanoparticles and very few data on other metal nanoparticles increasingly used in industry" [145]. Notably, there have been no studies on infant skin or significantly aged skin.

3.6 Biokinetics

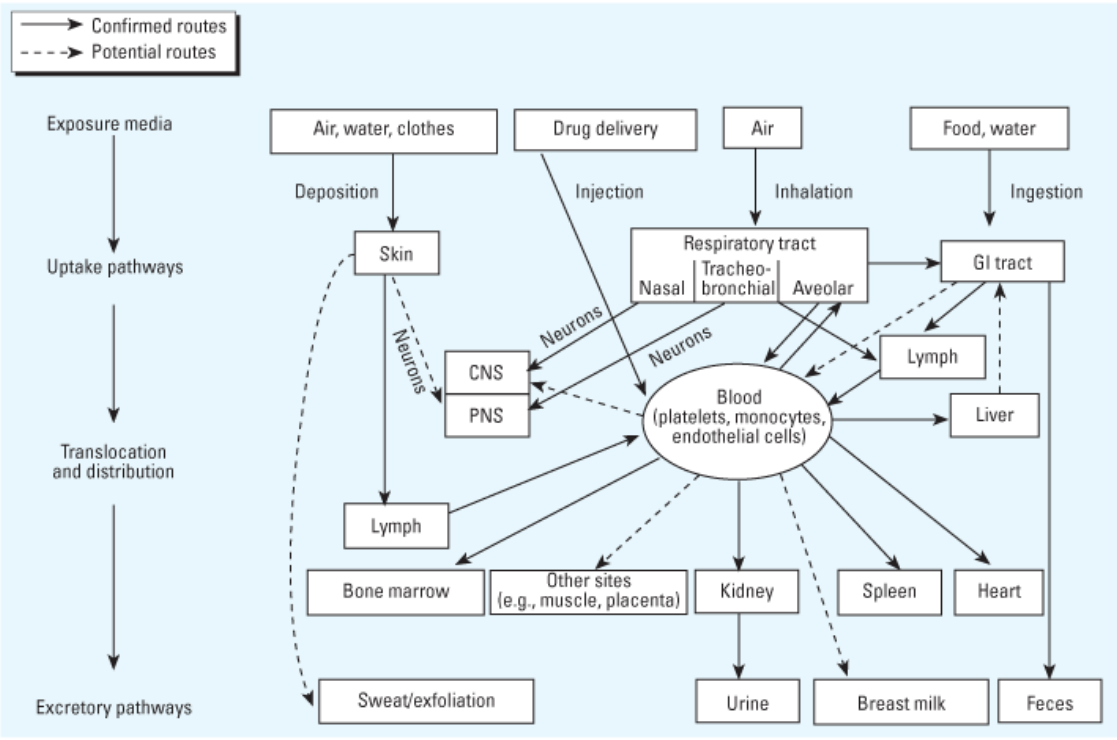
Biokinetics refers to the fate and transport of nanomaterials within cells, across membranes and barriers, and within larger biological systems such as organs or the whole body. For example, materials such as dendrimer-based nanoparticles can sometimes be degraded fully in the body and excreted with no accumulation. Other particles such as silver or gold slowly accumulate in filter organs such as the liver and kidneys, depending on particle size. Figure 13 outlines some confirmed and potential biokinetic routes of nanoparticles in humans and the environment. Translocation rates, areas of accumulation, retention times, and mechanistic pathways—all of which depend on the physicochemical characteristics of the surface and core of the nanomaterial—are largely unknown. Understanding biokinetics can inform both

potential target physiological systems and risks for nanomaterials.

Because of nanoparticles' size, cells interact with them differently than single molecules such as conventional chemicals. Nanoparticles are in similar size ranges as very large biologically active compounds, known as "macromolecules," such as large protein complexes, strands of DNA, and virus capsules. On the cellular level, the main route of nanoparticle entry into cells is called phagocytosis, a process represented schematically in Figure 14. In phagocytosis, the cell membrane surrounds a foreign object such as a nanoparticle, bacterium, or other large biological structure. The object is then transported to the inner portion of the cell, where naturally occurring particles such as bacteria are broken down into harmless parts and released. In the case of nanomaterials, however, depending on their composition, they may not be broken down by normal biological processes and may consequently accumulate in areas or irritate the cell to the point of death.

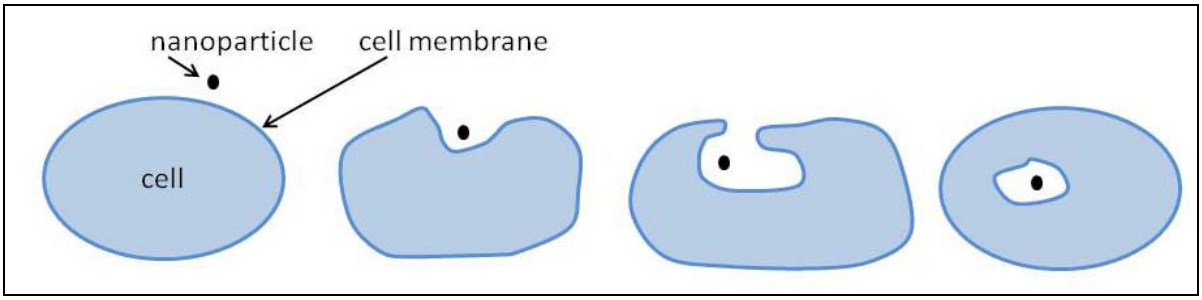
Notably, the small size of nanoparticles leads to a much higher rate of phagocytosis than for larger, micron-sized particles [146], such as 2.5- and 10-micron particles (the sizes defined in air pollution standards for particulate-level air pollution). Such micron-sized particles are typically not taken up or surrounded completely by cells because they are on a similar size scale as the cell itself and may irritate larger organs by frustrating phagocytosis. In addition, nanoparticles typically both persist and accumulate in specific organelles, or they react with cells, causing their surface chemistries to change. If this change causes exposure of toxic compounds in the nanoparticles, the result can be abnormal cell behavior and possibly cell death.

FIGURE 13: Biokinetics of nanoparticles in various environmental and biological systems. Figure from Oberdorster et al. 2005 [91].



Legend: PNS=peripheral nervous system, CNS=central nervous system.

FIGURE 14: Schematic of phagocytosis process (not drawn to scale). When phagocytes (and often other types of cells) encounter a foreign object, such as a nanoparticle or bacterium, they internalize the object by wrapping the cell membrane around it and forming a package to contain it.



Chemicals such as pesticides, nitrates, perchlorate, polychlorinated biphenyls (PCBs), and drugs are much smaller than nanoparticles (anywhere from 10–100x smaller, or about 0.1–1 nm) and can also be taken into cells. However, this occurs through very different processes because these chemicals are too small to trigger phagocytosis. Typically, a potentially toxic chemical is taken into a cell either via active transport (through specific channel proteins in the cell membrane) or directly through the membrane itself (if the chemical is small enough and has the right properties), which is approximately 4 nm thick. The implications of these different interactions are that nanomaterials are likely to elicit different cell responses than traditional small-molecule chemicals.

3.7 Challenges to Closing the Gap in Our Understanding of Potential Nanomaterial Health Risks

The biggest challenge in assessing potential health risks from nanomaterials is lack of data. This issue comes up in almost every chapter and every report on nanotechnology toxicity. Notwithstanding the toxicity experiments noted here, there are many more unknowns than knowns with regard to nanomaterial toxicity, including a dearth of longer-term and low-level exposure studies. The many knowledge gaps make it very difficult to quantitatively assess the potential risks of nanomaterials.

Some of the key research area needs to enhance our ability to understand potential health risks include the following:

1. **Biokinetics**: Understanding the fate, transport and distribution of nanomaterials in biological systems from the source (air, food, etc.) to the initial exposure route (inhalation, oral, dermal) to the internal distribution and destination of nanoparticles is important in determining whether local or systemic health effects are likely to occur. Aside from some of the medical-application and drug-delivery studies, our knowledge of nanomaterial biokinetics is fairly limited. The field of nanotoxicology needs to be defined in more detail (e.g. whether to focus on cellular-level transport, whole-body transport, or transport through the environment). A coordinated effort to communicate and disseminate results in a systematic way is also needed so that as more data gaps are addressed, further research goals can be prioritized. In

addition, understanding nanomaterials' interactions with the environment and co-pollutants will become increasingly important as use of these materials in various products grows and life-cycle-analysis processes improve.

2. **Basic toxicological research and standardized protocols and procedures**: In order to characterize health effects, basic toxicological characterization research must be performed, and, as this section of the report highlights, is an area in which only limited efforts have occurred to date. Furthermore, standardized protocols, assays, and test procedures need to be augmented and updated to assess the toxicity of nanomaterials. Traditional mass-based, dose-response toxicity tests may not address the specific properties that make nanomaterials different from traditional chemicals. While some traditional animal assays, such as the two-year bioassay, can be informative for nanotoxicity studies, other aspects of experimental design, such as sample preparation, surface chemistries, and exact manufacturing processes, vary and are not standardized. Accordingly, there is a need both to reevaluate and refine existing tests and to incorporate newer predictive methods and high-throughput screening assays. It is important to note that high-throughput assays are not necessarily ready to completely replace traditional toxicity tests for nanomaterials or environmental chemicals. Finally, a determination of which protocols generate the most useful information should be made in the near future in order to obtain reliable data.

3. **Detection of nanomaterials:** As discussed in Chapter 2, the ability to detect the presence of nanomaterials in the environment and biological systems is an area that needs more research and technological development. Current methods are costly, time-consuming, and resource intensive and do not take a holistic approach in that our ability to monitor is generally limited to specific products or a specific source such as manufacturing sites (point-source monitoring). Analytical methods are not yet fully developed to conduct the larger-scale biomonitoring that is possible for conventional chemicals.

In addition to data gaps, there are other factors that need to be considered in assessing potential health risks from nanomaterials. Two such factors, background or co-exposures and susceptibilities, have already been recommended for further integration into non-nanomaterial chemical risk assessments. As such, a more comprehensive chemical-assessment process might help eliminate the differences between nanotechnology and traditional chemical assessments.

1. **Background or co-exposures:** When evaluating risks from exposure to nanomaterials, multiple nanomaterial exposures as well as other background chemical exposures need to be considered. NAS recently recommended grouping materials with similar biological endpoints or outcomes for assessing risks, as co-exposures can enhance individual nanomaterial risks [43]. For example, many nanoparticles are known to create ROS in cell and animal models, which can lead to damage of cellular structures such as proteins, DNA, and fatty acids. As the use of nanoparticles in materials and consumer products grows, it will be important to consider all sources of exposure to ROS-generating chemicals and other chemicals that effect similar adverse health outcomes to accurately assess possible risks. Similarly, many nanoparticles have antimicrobial properties, and as their use increases in consumer products, we may have to include multiple sources in the exposure-assessment profiles.

2. **Susceptibilities:** Individual people and populations may have extrinsic or intrinsic susceptibility factors (such as age or pre-existing health conditions) that make them more or less likely to have a biological or health response to

exposure. Sufficient accounting for susceptibilities when interpreting studies that may be conducted in non-susceptible biological systems will be needed to ensure adequate characterization of risks.

Some of the difficulty in hazard identification is due to the interrelation of research gaps identified earlier in this section. For example, we cannot determine fate and transport very effectively without adequate detection methods. Similarly, we cannot identify toxicity traits without adequate testing protocols and standardized procedures. All of these factors need to be better understood and defined to develop an adequate picture of hazards.

3.8 Conclusions

To date, most toxicity studies of nanomaterials have been narrow in focus and material-specific and have generated data using *in vitro* toxicity testing with current limited ability to predict human toxicity. *In vivo* studies have typically focused on biokinetics, while *in vitro* cellular studies have examined various enzyme and protein pathways with ranges of results depending on the nanomaterial. There are few, if any, generational tests or comprehensive multi-endpoint studies and almost no information on reproductive effects.

Consequently, there are still large data gaps in our knowledge of nanoparticle toxicity. Some of these gaps are due to the lack of required testing and reporting for nanomaterials. While traditional toxicity tests may provide some useful information, they may not be appropriate to fully predict the possible health effects of nanomaterials—which, due to their size, interact with biological systems differently than most small-molecule chemicals. Moreover, although this report discusses various studies finding toxic effects of nanomaterials, the causes of the toxicity are mostly uncharacterized [147].

Finally, the diversity of nanomaterials presents a challenge to the risk-assessment process and regulatory structure. As discussed in this chapter, there is a large range of nanomaterials, as they are made of different substances, in different configurations, for various applications. A key threshold decision is whether to categorize nanomaterials into groups of materials that behave similarly or attempt case-by-case decision-making, which is notoriously slow and resource intensive.

Given this challenge, identifying properties that may be predictive of exposure and toxicity is an important area of focus. The main properties of nanomaterials that are emerging as important to toxicity are size, surface properties, stability, and reactivity. This set of properties may change as additional research fills knowledge gaps, but existing data suggest that we should characterize and record these properties to be able to compare results of future toxicity tests.

Ultimately, to understand the possible health effects of nanomaterials, most researchers agree on the need to collect information on material properties, improve material characterization techniques, require basic *in vivo* and *in vitro* toxicity testing, and monitor usage of these materials.

Chapter 4: Conclusions and Recommendations

4.1 Introduction

This chapter lays out general policy recommendations to address the potential health risks from nanotechnology, as well as recommendations developed specifically for California's Office of Environmental Health Hazard Assessment (OEHHA). The first section identifies traits for successful stewardship of nanotechnology policy. The second section reviews health-related policy recommendations from other nanotechnology reports. The third section reviews lessons learned from the past 40 years of chemicals policy, setting the stage for the policy recommendations in this report to address potential health risks from nanomaterials in California. The fourth section enumerates thirteen recommendations that can be achieved under the existing regulatory structure by OEHHA to address health risks from nanomaterials in four areas: characterizing nanomaterials; identifying sources and understanding exposure to nanomaterials; prioritizing and characterizing health effects; and communicating among government agencies, NGOs, and the public. The fifth section identifies relevant environmental programs in California that regulate or make recommendations on health and the environment and that could act to address nanomaterials. The sixth section sets forth specific recommendations for OEHHA to take action on nanomaterials using existing regulatory structures. The seventh section outlines broader recommendations that are required to ensure successful implementation of the recommendations in section four. Many of these are likely to require legislative changes. Finally, the chapter ends with some concluding remarks on the current opportunity and need to address nanomaterials.

4.2 Current Status of Health Policies for Addressing Nanomaterials in California

Table 9 summarizes responsible, health-protective policy traits for addressing potential health effects and risks from nanomaterials and where California stands in relation to these traits for nanomaterials. These traits have been identified in several nanotechnology reports (listed in Box 3). Understanding the current status of policies for nanomaterials in California and where it stands in relation to desirable policy is important to inform future recommendations on how to bridge current gaps in policies to address potential health risks from nanotechnology.

BOX 3: List of nanotechnology-related reports, arranged by publication year, that address health and safety aspects of nanomaterials

The Appropriateness of Existing Methodologies to Assess the Potential Risks Associated with Engineered and Adventitious Products of Nanotechnologies, 2006, Scientific Committee on Emerging and Newly Identified Health Risks, European Commission.

Managing the Effects of Nanotechnology, 2006, J. C. Davies, Project on Emerging Nanotechnologies, Woodrow Wilson Center PEN 2.

Nanotechnology: A Research Strategy for Addressing Risk, 2006, A. D. Maynard, Project on Emerging Nanotechnologies, Woodrow Wilson Center PEN 3.

Regulating the Products of Nanotechnology: Does FDA Have the Tools It Needs?, 2006, M. R. Taylor, Project on Emerging Nanotechnologies, Woodrow Wilson Center PEN 5.

EPA and Nanotechnology: Oversight for the 21st Century, 2007, J. C. Davies, Project on Emerging Nanotechnologies, Woodrow Wilson Center PEN 13.

Nanotechnology: A Report of the U.S. Food and Drug Administration Nanotechnology Task Force, 2007, U.S. FDA Nanotechnology Task Force.

Nanotechnology White Paper, 2007, U. S. Environmental Protection Agency, Office of the Science Advisor, Washington, D.C.

Thinking Big about Things Small: Creating an Effective Oversight System for Nanotechnology, 2007, M. Greenwood, Project on Emerging Nanotechnologies, Woodrow Wilson Center PEN 7.

Where Does the Nano Go? End-of-Life Regulation of Nanotechnologies, 2007, L. K. Breggin and J. Pendergrass, Project on Emerging Nanotechnologies, Woodrow Wilson Center PEN 10.

The Consumer Product Safety Commission and Nanotechnology, 2008, E. M. Felcher, Project on Emerging Nanotechnologies, Woodrow Wilson Center PEN 14.

Nanotechnology in New South Wales, Final Report, 2008, Legislative Council, Standing Committee on State Development, Sydney, Australia.

Nanotechnology Oversight, an Agenda for the Next Administration: Review of Federal Strategy for Nanotechnology-Related Environmental, Health and Safety Research, 2008*,* National Academy of Sciences.

Novel Materials in the Environment: The Case of Nanotechnology, 2008, Royal Commission on Environmental Pollution, London, UK.

Out of the Laboratory and onto Our Plates: Nanotechnology in Food and Agriculture, 2008, Friends of the Earth.

Silver Nanotechnologies and the Environment, 2008, S. N. Luoma, Project on Emerging Nanotechnologies, Woodrow Wilson Center PEN 15.

Small Is Different: A Science Perspective on the Regulatory Challenges of the Nanoscale, 2008, Council of Canadian Academies, Expert Panel on Nanotechnology, Ottawa, Canada.

Approaches to Safe Nanotechnology: Managing the Health and Safety Concerns Associated with Engineered Nanomaterials, 2009, U.S. National Institute for Occupational Health and Safety, Centers for Disease Control and Prevention.

TABLE 9: Traits of responsible, health-protective policy and where California stands with regard to each for nanomaterials.

Trait	**Current California policies**
Ensure wide availability of information on where, how, and in what amounts nanomaterials are used.	• Voluntary company disclosure on products (e.g., advertising and/or labeling) and voluntary data call-in are the only sources of publicly available data. • No official inventory of nanotechnology materials exists. One non-standardized inventory produced by the Project on Emerging Nanotechnologies at the Woodrow Wilson Center is available online.
Obtain a robust understanding of risk and hazard profiles.	• Only preliminary data exist on toxicity and occupational exposure. Very little to no data exist on potential adverse health effects from long-term or multi-generational exposures, or on exposures to humans and to the environment.
Maintain an open and transparent process for making science-based policy decisions, including good communication between researchers and decision-makers.	• Research to fill knowledge gaps is not coordinated among government and academic research labs. No organization has the lead role, and there is no database or communication network to share findings.
Support desirable business growth and economic incentives.	• California is a leader in nanotechnology research and development. Policies should not discourage responsible entrepreneurial ventures and business growth.
Include public education and input during risk-assessment and policy-making decision processes.	• The majority of the public know little to nothing about nanoscience. Those who have heard of it or are familiar with it generally have positive impressions.
Protect public health and the environment; do not add to the existing disease burden.	• No nanomaterials have specifically been evaluated with a risk-assessment process or regulated based on concerns of risks to public health. • Biomonitoring studies show that as chemicals are widely used, exposure occurs throughout the population.

4.3 Policy Recommendations from Other Nanotechnology Reports

This section compiles policy recommendations from prior reports on nanotechnology. As used here, the term "nanotechnology report" refers to a science-based governmental or nongovernmental organization (NGO) publication that addresses nanotechnology and health-related issues and the specific regulatory and/or policy issues that arise from nanomaterials' unique features. Many reports have been published, ranging in focus from the economic impacts of and regulatory policy options for nanotechnology to the possible health effects, specific applications, and properties of nanomaterials. The reports listed in Box 3 address policy and health implications specifically.

These reports identify shortcomings of existing regulatory structures, specifically in the areas of minimizing public-health risks and other problems related to nanotechnology health and safety policy. They also recommend solutions. Table 10 summarizes the shortcomings and solutions that are identified in multiple reports and that form the basis of several of the recommendations in Section 4.5.

Despite these shortcomings, some reports emphasize that existing public-health mandates provide the authority and flexibility to make certain decisions and act on current information without the need for legislative change, which can take years. These reports note that nanomaterials are already in extensive use in consumer products and that occupational and public-health exposures are ongoing. Thus, they stress the need to act now and work with existing policy and regulatory structure.

4.4 Lessons Learned from Past Chemical Policy Experiences

Chapter 2 presented lessons from past experiences in regulating chemicals that can inform current efforts to develop better approaches to environmental-health policy for nanomaterials. Table 11 provides a summary of these lessons and corresponding recommendations on how to apply them to improve policies on nanotechnology. The recommendations from Table 11 are integrated into the General Recommendations in Section 4.5.

TABLE 10: Summary of shortcomings and recommended solutions for nanotechnology policy from governmental and nongovernmental reports listed in Box 3.

Shortcoming	Recommended solutions
Existing regulations are weak and too limited to ensure adequate protection of public and occupational health from nanomaterial hazards and risks.	• Expand current regulatory and legal structures to adequately address nanomaterials. • In addition to traditional toxicity tests, consider using new toxicology and risk assessment methods, such as predictive toxicology, high throughput screening, and the use of upstream biological events as signals of chemical exposure, and/or promulgate new laws or regulations. • Standardize risk-relevant definitions, characterization techniques, and detection methods for nanomaterials.
There is very little, if any, government authority to specifically regulate or manage nanotechnology or nanomaterials.	• Some reports call for designating a centralized, lead organization to prioritize and coordinate research, data sharing, and risk assessment. Others recommend new regulations or building upon and improving existing regulatory structures. • Some reports recommend new regulations or building upon and improving existing regulatory and legal structures to adequately address authority for nanomaterials.
Large gaps exist in our understanding of the toxicity, exposure routes, health effects, bioaccumulative properties, environmental fate, and exposures to nanomaterials.	• Increase funding and support for targeted, nano-specific research to fill data gaps. • Obtain information from manufacturers and downstream users in order to build a database on properties, sources, and exposure routes. • Improve coordination and monitor communication among federal and state agencies, other countries' governments, and NGOs. • Implement environmental monitoring, biomonitoring, and reporting to understand the fate and transport of nanomaterials.

TABLE 11: Lessons from past chemical-policy experiences and subsequent recommended nanotechnology policies.

Lesson	Recommended Approaches
Traditional mass-based dose models are not always sufficient to characterize toxicity. Consideration of new traits and properties is needed.	• Define and collect information on additional properties and characteristics relevant for describing nanomaterials and integrate them into decision-making processes.
Heed early health and exposure warnings to identify potential health hazards	• Improve communication between clinicians, occupational health experts, and manufacturers on worker-health and general population health issues that may arise from exposure to nanomaterials.
Detection and monitoring of nanomaterials are integral to identifying potential health hazards.	• Identify and/or develop methods for monitoring nanomaterials in the environment and in humans. Use biomonitoring to better understand fate and transport and better inform future use and mitigation efforts.
Identify persistent and/or bioaccumulative materials early, as build-up of exogenous chemicals is usually detrimental in some way.	• Require reporting for nanomaterials of chemical properties used by REACH and US EPA to define persistent, bioaccumulative, and toxic (PBT) compounds. • For nanomaterials in the PBT category, integrate approaches for other PBTs, including phase-outs and toxicity testing. • Identify any additional properties unique to nanomaterials that can predict potential for PBT.
Better understand fate and transport of nanomaterials in our bodies and the environment and their interaction with other chemical pollutants.	• Support specific research to understand the life cycle of nanomaterials, with emphasis on understanding various applications (primary, secondary use in products, etc.).
Consider susceptible populations in risk assessment and decision-making.	• In the absence of data, use default adjustment values to account for susceptibilities or sensitivities of appropriate populations, such as children and pregnant women or populations that might have higher background exposures from other chemicals or stressors.

While Table 11 covers specific areas of focus for addressing nanomaterials, there is an overarching principle that has emerged for successful chemicals policy management: the need for sufficient information to understand potential exposures and health risks to inform decision-making. Notably, the current legal system does not require sufficient testing for either new or existing chemicals to adequately identify or manage potential health risks. Indeed, it does not require any testing at all for chemicals on the market prior to 1976. Accordingly, a broad range of government agencies, industries, and NGOs have called for modernizing the Toxic Substances Control Act (TSCA), the primary regulatory authority for governing manufactured chemicals, to test chemicals for their potential to adversely affect health [148-153].

4.5 Recommendations under existing Regulatory Authority

The two preceding sections cover common nanotechnology-policy recommendations made in other reports and recommendations based on lessons from past chemical-policy experiences. This section outlines thirteen recommendations focused on improving approaches for assessing potential health risks from nanomaterials that can be implemented by the state of California under its current regulatory structure. The recommendations are based on previous reports, lessons learned, and additional needs identified through the development of this report. Wherever possible, it also includes provisions for using resources appropriately in terms of funding, research goals, and information sharing.

The section is organized into four focus areas: characterizing nanomaterials for exposure potential and hazard identification; identifying sources of, and understanding exposure to, nanomaterials; prioritizing and characterizing health effects; and communicating among relevant government agencies, businesses, NGOs, and the public. Each subsection includes numbered, more specific recommendations and a brief discussion to illustrate their importance.

While some progress on addressing potential health risks from nanomaterials can be achieved from implementing these recommendations, it will be difficult to fully implement the recommendations in this section because of limitations in existing regulatory and legal structure both in California and the US. Thus, we provide a set of separate recommendations in section 4.8 and Table 14 that are likely to require legislative changes that would ensure successful implementation of the recommendations.

4.5.1 Characterizing Nanomaterials for Exposure Potential and Hazard Identification

1. Develop a definition of nanomaterials that can be used to identify them.

The first step in characterizing nanomaterials is to develop an agreed-upon definition that describes the difference between nanomaterials or nanoparticles and other small-molecule chemicals. It is important to have a standard definition that could be interpreted in the policy context to clarify which materials would be covered under regulatory approaches that are specific to nanomaterials. This definition needs to account for the diverse range of nanomaterials, which are made of different substances, have different configurations, and are used in various applications.

A European Commission review of current definitions used by different countries and nongovernmental organizations has noted that a wide range of definitions is available and that developing a harmonized definition that can be integrated into policy has been challenging [154]. For example, the Organisation for Economic Co-operation and Development (OECD) is developing a definition for nanomaterials that is slightly different than the definition of the European Union's (EU) Scientific Committee on Emerging and Newly Identified Health Risks [154]. Identifying and incorporating appropriate aspects of these frameworks and definitions is an important part of developing a working definition for the State of California.

2. Identify and define priority properties of nanomaterials for risk characterization and collect information about them for each nanomaterial, including:

- **"traditional" risk-assessment or hazard-identification properties**
- **"unique," nanomaterial-specific properties**

Many nanotechnology reports have called for identifying a new list of properties specific to nanomaterials in addition to those that are already used for manufactured chemicals, such as density, melting point, and vapor pressure. Such properties can be used to identify particular exposure or hazard characteristics. For example, as discussed in Chapter 3, four unique properties of nanomaterials have been associated with adverse outcomes in toxicological studies: size; surface functionality; stability; and reactivity. Submitting information on these properties to governing bodies in addition to the more "traditional" properties of chemical composition identified in Table 3 would help characterize potential exposures and hazards or risks. We recommend that this information be reported to or collected routinely by government agencies. Given that one of the challenges in collecting information on nanomaterials is the lack of standardized methods to test and describe these properties, however, this is an area that warrants further research.

3. Develop characteristics by which to define, describe, and group nanomaterials according to conventional or unique properties for risk management decisions.

Taking a case-by-case approach to evaluating nanomaterials for risk-management decisions can be slow and resource intensive. We therefore recommend addressing nanomaterials by groups or categories and defining groups using the conventional or unique properties for each nanomaterial and the values for each property. For example, for conventional chemicals, persistent and bioaccumulative chemicals can be identified by their half lives (persistence), their fish bioconcentration factor, and their octanol-water coefficient. Such values could also be used to group nanomaterials. Similarly, properties unique to nanomaterials can be used to identify and organize them. For example, nanomaterials that act similarly could be identified and grouped according to size, surface charge, specific components, or specific uses.

4.5.2 Identifying Sources of and Understanding Exposure to Nanomaterials

4. Establish a publicly accessible clearinghouse and inventory of nanomaterial sources and products.

A comprehensive inventory of nanomaterial sources and products is needed in order to understand where nanomaterials exist and in what quantities to inform potential exposures and risks. Information on sources should include information on both the manufacture of the nanomaterials (e.g., facility location and amount manufactured) and secondary uses of manufactured nanomaterials (e.g., integration into new products). Product information should specify whether nanomaterials are covalently bound to a larger matrix or used loosely or in solution as an active or primary ingredient, as this affects their exposure potential.

Creating a clearinghouse would enable a more systematic approach to recording, sharing, and accessing relevant information. Making the clearinghouse publicly available, while ensuring protection of confidential business information, would reduce redundancy in reporting and educate consumers. Coordinated efforts are also needed to communicate and disseminate results in an organized way so that, as data gaps are filled, the areas that still need to be addressed become apparent.

5. Identify and/or develop methods for monitoring nanomaterials in environmental media and through human biomonitoring.

6. Collect information on the fate and transport of nanomaterials, including through monitoring in environmental and biological media.

In order to characterize the risk of potential health effects from nanomaterials, we need to better understand the fate and transport of nanomaterials in the environment from their source (air, food, etc.) to the initial route of human contact (inhalation, oral, or dermal) to the internal distribution and destination of nanoparticles. Current knowledge in this area is limited, and current monitoring methods are costly, time-intensive, and resource intensive. Moreover, these methods do not take a comprehensive approach, in that we can usually monitor only small, specific sources such as manufacturing sites (point-source) or conduct monitoring in conjunction with use of a specific product. In addition, analytical methods are not fully developed to measure nanomaterials in various environmental and human biological media.

7. As for other chemicals, focus on identifying and addressing nanomaterials that are persistent, bioaccumulative, and toxic (PBT).

Past chemical-policy experience highlights the need to identify the potential for persistence and bioaccumulation of nanomaterials, as build-up of exogenous chemicals has often been found to be detrimental well after extensive release into the

environment and subsequent build-up in biological and human tissues. Current efforts to address PBTs should including identifying and characterizing nanomaterial.

4.5.3 Prioritizing and Characterizing Health Effects

8. **Use existing hazard traits from other chemicals and toxicological and environmental-health-related endpoints to assess potential adverse health outcomes from nanomaterial exposure.**

Since nanotechnology is still a relatively new field, there are few data available with which to make toxicity or risk decisions. In cases where nanoparticles are used in a free or loose form, we can draw on existing small-particle science, such as experiments on health risks from exposure to carbon black and particulate matter (PM), and use the knowledge to inform decisions about loose nanoparticles.

9. **Evaluate existing risk-assessment guidelines to determine whether they sufficiently cover nanomaterials, adjusting or incorporating nano-specific approaches as needed.**
   - **Use existing data to evaluate the guidelines**
   - **Consider applying an adjustment factor to address enhanced risk for nanomaterials that exhibit properties of concern.**

OEHHA and other government agencies that conduct risk assessment have already developed guidelines [155-157] for characterizing hazards and risks from conventional chemicals. These guidelines should be evaluated and, if needed, updated to incorporate considerations unique to nanomaterials. Two good opportunities for updating such guidance include assessing the need for additional adjustment factors and considering multiple exposures. Both have been recognized by the National Academy of Sciences (NAS) as important areas for modernizing risk assessment [42].

First, adjustment factors may be needed to address potentially enhanced and/or unique risks from particular types of nanomaterials. Default adjustment factors are used in quantitative risk assessment in situations where chemical-specific data are lacking, but underlying knowledge indicates a relationship between certain properties and increased risk from an individual chemical. For example, when US EPA assesses risk from pesticide exposures, it uses an additional factor of 10 in the risk assessment of noncancer effects to account for potential childhood sensitivity, unless specific data show this is not necessary. Similarly, adjustment factors could be used for individual nanomaterials in the absence of exact data when similar data indicates a need. Adjustment factors could likewise be used for individual nanomaterials. For example, if there are no data on the toxicity of the surface charge of a particular nanomaterial, and studies indicate that surface charge represents an additional risk, then development and use of an adjustment factor (e.g., 10x) for surface charge would be appropriate.

Another aspect that may warrant development of additional adjustment factors is whether the nanoparticles in question are being used in a primary or secondary form—that is, whether the particles are free or bound into a matrix. Loose particles or non-covalently bound particles can pose considerable inhalation risks and the risk from loose particles may be greater than for particles that are part of a larger product or matrix, which could necessitate the use of an adjustment factor when the risk assessment for loose particles is based on data for those that are bound.

Second, consideration of multiple exposures, whether from other nanomaterials or background chemicals, is also important for evaluating risks. The NAS recently recommended that chemicals that increase the risk of common adverse outcomes be considered as a group when assessing risks because co-exposures can enhance the risk that exposure to

any one chemical poses [42]. This principle should be applied when assessing risks from individual nanomaterials as well. For example, many nanoparticles are known to create reactive oxygen species (ROS) in cell and animal models, which can lead to damage in cellular structures such as proteins, DNA, and fatty acids, so considering them as a group for risk assessment would be appropriate. Other chemicals can also negatively impact cellular function and should be accounted for when assessing the risk from individual nanomaterials. Notably, considering the effects of multiple exposures will become increasingly pressing as exposures to nanoparticles grow with increased use in materials and consumer products.

10. Integrate nanomaterials into current efforts to modernize toxicity testing for risk assessment.

The NAS has called for new approaches to toxicity testing to increase the efficiency and pace of our understanding of the relationship between environmental chemical exposures and health [44]. As part of this effort, more emphasis should be placed on early indicators of harm along the toxicological pathway and their integration into decision-making. New toxicity assays in development, such as using zebrafish embryos, new types of cellular-based assays, and predictive modeling, need standardization and implementation to better assess nanomaterial safety. The results of these studies should be combined with the information gathered from traditional toxicity assays to develop a more accurate estimate of risk from exposure to nanomaterials. Efforts to address risks from nanomaterials should be integrated into new methods for predictive toxicology, including the use of upstream biological events as signals of chemical exposure.

11. Develop and maintain relationships with other governments and researchers to share relevant data and information on nanotechnology and nanomaterials' use, applications, and toxicity.

Efforts should be made to leverage relevant exposure- and health-related research from government, academia, and industry. For example, other governments, such as Canada and the EU, already have some nano-specific provisions in their policies, which will result in their developing and obtaining information that could be relevant to policy efforts in California. In addition, academic research is a major source of data on nanomaterials, and California has several such academic centers, including the California NanoSystems Institute at UCLA. Developing and maintaining lines of communication for data and information sharing would leverage existing resources, avoid repetition, and reduce the burden on the government to generate data for decision-making.

4.5.4 Communicating among Relevant Government Agencies, NGOs, and the Public

12. Improve coordination and monitor communication among federal and state agencies, other countries' governments, businesses, and NGOs.

Communicating and coordinating with governmental and nongovernmental entities locally, federally, and internationally will help inform California-specific efforts to develop appropriate policy approaches to nanotechnology.

13. Continue to include opportunities for public input and comment during decision-making processes related to nanomaterials.

Public involvement in decision-making is important for ensuring that the public's concerns are addressed. There are existing provisions in both the California and federal decision-making processes for public comment and input [158, 159] that could be used. Further, holding public meetings regarding nanomaterials would enable continued transparency and stakeholder

participation. Finally, data and information sharing are important for the education and development of an informed consumer base.

TABLE 12. Recommendations for addressing potential health risks from nanomaterials that can be implemented under current California regulatory structure.

Recommendations to address potential nanomaterial health risks that can be implemented under current California regulatory structure
1. Develop a definition of nanomaterials that can be used to identify them.
2. Identify and define priority properties of nanomaterials for risk characterization and collect information about them for each nanomaterial.
3. Develop characteristics by which to define, describe, and group nanomaterials according to conventional or unique properties for risk management decisions.
4. Establish a publicly accessible clearinghouse and inventory of nanomaterial sources and products.
5. Identify and/or develop methods for monitoring nanomaterials in environmental media and through human biomonitoring.
6. Collect information on the fate and transport of nanomaterials, including through monitoring in environmental and biological media.
7. As for other chemicals, focus on identifying and addressing nanomaterials that are persistent, bioaccumulative, and toxic (PBT).
8. Use existing hazard traits from other chemicals and toxicological and environmental-health-related endpoints to assess potential adverse health outcomes from nanomaterial exposure.
9. Evaluate existing risk-assessment guidelines to determine whether they sufficiently cover nanomaterials, adjusting or incorporating nano-specific approaches as needed.
10. Integrate nanomaterials into current efforts to modernize toxicity testing.
11. Develop and maintain relationships with other governments and researchers to share relevant data and information on nanotechnology and nanomaterials' use, applications, and toxicity.
12. Improve coordination and monitor communication among federal and state agencies, other countries' governments, businesses, and NGOs.
13. Continue to include opportunities for public input and comment during decision-making processes related to nanomaterials.

4.6 Relevant California Environmental Health Programs

This section outlines some of the existing programs and departments in California that are relevant to nanomaterials and nanotechnology health-risk and hazard assessments or management.

4.6.1 Office of Environmental Health Hazard Assessment

OEHHA is a department of the California Environmental Protection Agency (Cal/EPA). OEHHA's overall mission is to protect and enhance public health and the environment by scientifically evaluating the risks posed by hazardous substances. As the lead risk and hazard assessor for California, OEHHA has been active in innovating the methodology and process of decision-making by creating new risk models. OEHHA administers many different programs, and this report identifies several that can adopt nano-specific recommendations. Candidates include the Toxic Air Contaminant Program (TAC), Hot Spots, Ambient Air Quality Standards, Children's Health Initiative (including art hazards and child-specific reference doses), the Indoor Air Program, Public Health Goals for drinking water, Pesticides, Fish Consumption Advisories, Fuel Additives, Proposition 65 (Prop 65), Green Chemistry, and biomonitoring programs.

OEHHA also currently has a Cumulative Impacts/Precautionary Approach work group[3] that is designed to provide advice on California's efforts to develop a framework to assess cumulative impacts and implement precautionary approaches. While the work group was formed to support Cal/EPA's Environmental Justice Action Plan, its framework could also be applied to new policy approaches to nanomaterials.

[3] For more information, see http://oehha.ca.gov/ej/.

4.6.2 Department of Toxic Substances Control

The Department of Toxic Substances Control (DTSC) is another division of Cal/EPA that works with OEHHA on some common programs. DTSC recently collected information on carbon nanotubes from California manufacturers, which supplied the information voluntarily, with respect to analytical test methods, fate and transport in the environment, and related information. DTSC plans to expand its information request to manufacturers of other types of nanomaterials in the near future.

The deadline for submitting carbon-nanotube information was in January 2010. Out of 26 entities, 23 responded. Responses ran from 2–3 pages to more than 100. Some responses were very general with few specifics, while some were more lengthy with slightly more detailed information. Larger entities such as the University of California, which maintains many research labs, provided sizable responses. All the responses can be found on the DTSC website.[4] Briefly, they contained very little specific toxicity information or insight into physical characteristics. Requiring submission of specific information would ensure that California could obtain data for determining nanomaterial production and safety in the state.

4.6.3 Division of Occupational Safety and Health

Aside from Cal/EPA, there are other California departments and program offices that focus on health and safety in various environments and settings that could also incorporate nanomaterial-toxicity considerations in their policies or regulatory structure. While it is beyond the scope of this report to suggest recommendations for them, one

[4] http://dtsc.ca.gov/TechnologyDevelopment/Nanotechnology/nanocallin.cfm.

example is the Division of Occupational Safety and Health, otherwise known as Cal/OSHA, within the Department of Industrial Relations. Cal/OSHA's mission is to protect workers and the public from chemical or workplace hazards, and the agency provides consultative assistance to employers. Since workers currently have the highest risk of exposure, efforts by Cal/OSHA to address nanomaterials would provide an important complement to related policy efforts.

4.6.4 Concurrent Environmental-Health Policy Movements in California

Much of environmental-health policy was developed more than 20 years ago. Consequently, it often does not sufficiently incorporate newer scientific understanding of the relationship between environmental chemical exposures and subsequent health risks. As new science continues to emerge, it reveals and illustrates gaps in public-policy approaches to minimizing harmful chemical exposures.

Several new initiatives have emerged to integrate our advancing scientific understanding with improved public policies, including: modernizing regulatory authority addressing manufactured chemicals, including updating testing approaches and regulating chemicals through green chemistry initiatives; enhancing efforts to monitor exposures and health outcomes through environmental-health tracking; and updating approaches to risk assessment. Policy recommendations addressing potential health risks of nanotechnology should consider and leverage these initiatives to more efficiently address the challenges ahead. The following subsections describe three of these initiatives in California and how they could intersect with approaches to nanotechnology policy.

4.6.4.1 Green Chemistry Initiative

The Green Chemistry Initiative in California is a program to promote the availability of safer products in the marketplace while reducing pollution. Two related bills set the framework for the initiative: Assembly Bill 1879 (AB 1879) [160], passed in 2008 and Senate Bill 509 (SB 509) [161], passed in 2009. SB 509 requires the DTSC to establish a Toxics Information Clearinghouse for the collection, maintenance, and distribution of toxicity data. It also requires OEHHA, by January 1, 2011, to evaluate and specify the relevant data to be included in the clearinghouse, including hazard traits and environmental and toxicological endpoints. AB 1879 requires DTSC to adopt regulations by January 1, 2011, to establish processes to identify chemicals of concern and reduce the hazards posed by such chemicals. It also includes provisions to establish a process for investigating alternatives to replace these chemicals of concern. Finally, it allows DTSC to require information regarding such chemicals and to promulgate labeling requirements, limit exposures, and restrict or prohibit use. This authority to require information could be useful to the State in terms of obtaining toxicity information on nanomaterials.

4.6.4.2 California's Environmental Health Tracking and Environmental Contaminant Biomonitoring Programs

In 2001, California put into law its intent to establish an environmental-health surveillance system [162]. The California Environmental Health Tracking Program aims to track disease trends and distribution, environmental threats, and their often complex interrelationship [163]. It is part of a larger national effort coordinated through the Centers for Disease Control and Prevention to establish environmental-public-health tracking systems at the national and state levels and includes cooperation

with national and state biomonitoring efforts to track the levels of chemicals in people's bodies.

A complementary effort is the California Environmental Contaminant Biomonitoring Program, which was established via legislation in 2006 [164]. The program's goals are to determine baseline levels of environmental contaminants in a representative sample of Californians, establish time trends in chemical levels, and assess the effectiveness of current regulatory programs. The biomonitoring program is a collaborative effort of CDPH, OEHHA, and DTSC. CDPH is the lead department for the program.

Using these two programs, with the combined efforts of CDPH, OEHHA, and DTSC, to address the issue of nanomaterial exposure would be a major step forward. The ability to measure and track nanomaterials in different environmental media and through biomonitoring would be useful in addressing potential health risks from nanotechnology. In addition, the data obtained from biomonitoring and health tracking for nanomaterials could be integrated into public policies to address nanomaterial health risks.

4.7 Specific Recommendations for California OEHHA

OEHHA oversees many different programs. Its main role is to provide hazard and risk-assessment information to risk managers in other departments of Cal/EPA. Given OEHHA's current responsibilities, there are multiple opportunities to integrate nanomaterials into existing regulatory structures, making it possible to take some action on nanomaterials without the need for statutory change.

As a first step, OEHHA should evaluate its programs and ensure that nanomaterials are integrated into activities in parallel with conventional chemicals.

Table 13 sets forth recommendations for additional steps OEHHA could take with regard to concerns about nanomaterials and identifies the OEHHA programs through which these recommendations could be implemented.

While the recommendations set forth in Table 13 apply to multiple programs within OEHHA, OEHHA could also evaluate specific programmatic areas and assess the coverage of nanomaterials within that area. For example, there are multiple opportunities to address nanomaterials in the air through existing air-quality programs, such as the Toxic Air Contaminant program, the Ambient Air Quality Standards, and the Indoor Air Program. More specifically, OEHHA could determine whether and to what extent nanomaterials fall within regulatory programs for particulate matter (PM). OEHHA could also assess whether certain airborne nanomaterials should be designated Toxic Air Contaminants.

Another example is in water quality. OEHHA could identify whether nanomaterials exist in aquatic environments and address potential health risks through public information, such as Fish Advisories, or through regulatory means, such as developing Drinking Water Public Health Goals.

In the areas of public education and advisories, OEHHA maintains the Proposition 65 (Prop 65) list of carcinogens and reproductive toxicants, issues Fish Advisories, and makes other advisory recommendations. Some nanomaterials contain chemicals that have already been identified as reproductive toxins or carcinogens under Prop 65, including cadmium, lead, selenium sulfide,

TABLE 13: Recommendations for the Office of Environmental Health Hazard Assessment (OEHHA) to integrate nanomaterials into existing programs.

Recommendations for OEHHA	Relevant programs or regulatory areas
• Assess whether nanomaterials are covered under existing policy structures; if so, integrate them into current protocols.	• Ambient Air Quality Standards • AB 289 (the ability to require information from manufacturers regarding chemicals of concern)
• Identify whether nano-sized materials or particles are more toxic than the corresponding bulk material. • Review and modify risk-assessment guidance to account for possible increased risk from particular nanomaterial exposures, using an adjustment factor if necessary and accounting for susceptible populations.	• Hot Spots • Toxic Air Contaminant • Children's Health Initiative • Drinking Water Public Health Goal • Fish intake recommendations • Pesticides • Biomonitoring
• Determine the extent of nanomaterial use in products.	• Indoor Air Program • Art Hazard • Fuel additives
• Identify exposure or release profiles of nanomaterials and develop regulatory goals if appropriate.	• Indoor Air Program • Drinking Water Public Health Goal • Pesticides • Fish Advisories
• Identify nanomaterials that contain known carcinogens or are known to cause reproductive harm and develop safe harbor levels for them.	• Proposition 65

respirable carbon particles, and airborne ceramic particles. OEHHA should review the Prop 65 list to determine whether any other listed chemicals are currently used in nanomaterials, which may require warnings. In addition, OEHHA should determine whether fish are bioaccumulating nanomaterials and whether an advisory is warranted.

4.8 Recommendations to Support Successful Approaches to Addressing Health Risks from Nanomaterials

While there is much that OEHHA can do now to address potential health risks from nanomaterials, the efforts will be limited by the current constraints in legal structures many of them related to obtaining the necessary information for making informed health policy decisions. In order to achieve the responsible, health-protective policy traits identified in section 4.2, additional changes will be needed. These recommendations are outside the scope of OEHHA and in many cases would require legislative changes.

4.8.1 Identifying and Testing Products for to Assess Potential Health Risks

1. Require disclosure of where and what nanomaterials are manufactured, in what quantities, and for what new or existing products

To ensure availability of data for a comprehensive inventory of nanomaterial sources and products as recommended in item 4 under Section 4.5, reporting of information for the inventory should to be required. Furthermore, standardized reporting of properties using a systematic approach should be required. Voluntary systems for gathering information have been shown in other environmental chemical contexts to be insufficient for gathering all the required data [165].

2. Require reporting of properties that can identify nanomaterials that are persistent, bioaccumulative, and toxic (PBT). Phase out uses consistent with approaches for other PBTs.

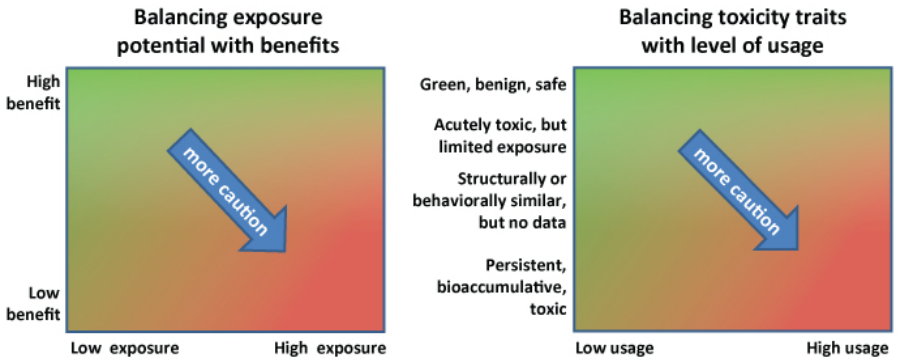
As identified in Chapter 2, past chemical-policy experience highlights the need to identify the potential for persistence and bioaccumulation of nanomaterials, as build-up of exogenous chemicals has often been found to be detrimental well after extensive release into the environment and subsequent build-up in biological and human tissues. Reporting should be required for nanomaterial properties that are consistent with those of other chemical properties used by REACH and US EPA to define PBT compounds. Further, given the serious consequences of post-market management of PBTs, identification and phase out prior to entry on the market, consistent with approaches in REACH is recommended.

3. Develop a framework for making policy and regulatory decisions that balances the uses and benefits of nanomaterials with their toxicity and exposure potential.

A framework and process for making decisions balancing use and benefits with toxicity and exposure potential are needed. This is of critical importance given that we often have little or no information about toxicity potential, and tools are needed to address known, population-wide exposures in a timely fashion. This is particularly salient for exposures to products and exposures to sensitive populations that may not have a significant public-health or societal benefit.

Figure 15 provides a schematic diagram of two prioritizing and balancing approaches: one addresses the benefit of using nanomaterials in a product given the potential risks from large-scale public exposure, and the other addresses the level of use of a nanomaterial given its relative toxicity profile. Nanomaterials promise to benefit society in many ways, from electronics to green technologies to better medical devices, but they also carry risks. Accordingly, we need to develop policy tools that allow the development of nanomaterials with economic, public-health, or social benefits while minimizing exposure to those with unknown or harmful health and environmental consequences.

FIGURE 15: Relationships between exposure potential and benefit from product use (15A) and known toxicity and level of use (15B).



4. Require testing of release and exposure potential for nanomaterials in consumer products for both existing and new products.

As identified in Section 4.5.1, current policy and regulatory structures do not require information to identify and manage potential health risks from exposures to new or existing nanomaterials. This has resulted in large data gaps for materials on the marketplace and will likely continue as new materials enter the marketplace. Ideally, information on where, what, and how much nanomaterials are going to be manufactured should be required prior to entering the marketplace. However, for those nanomaterials already in the marketplace, this information should be required to remain on the market. This recommendation focuses on consumer products because their use can result in widespread exposure, and the applications are not always of critical public-health benefit. Given the dearth in current knowledge of exposure potential for nanomaterials, a first step would be to prioritize consumer products for assessment. This could include identifying nonessential products with a high exposure profile and no critical public-health benefit and limiting their use in commerce until proven reasonably safe.

Take, for example, nanosilver-coated baby bottles, a product designed for use with infants. Given that bottles can be disinfected using methods such as soap and boiling water, and given the potential for high exposure coupled with our limited knowledge of the long-term effects of exposure to silver at vulnerable periods of development, the use of nanosilver in baby bottles potentially exposes a vulnerable population without providing a critical public-health benefit. Such products should have to be submitted to toxicity testing to ensure their safety in order to be on the market.

5. Increase efforts to protect and educate workers, researchers, and downstream users of nanomaterials:

- **Integrate workplace exposure-monitoring-registries and worker health-monitoring programs**
- **Update and improve occupational health-education programs to inform workers of possible risks and safe-handling practices to reduce or mitigate exposure to nanomaterials**
- **Integrate nanomaterial safe-handling practices into standard lab-safety training for students and for academic, industrial, and other laboratory workers**

Workers are currently the population most highly exposed to nanomaterials, making it imperative to focus on efforts to protect their health. Important measures include implementing health-monitoring, exposure-monitoring, and reporting practices for workers who handle or are exposed to nanomaterials. Integrating monitoring and reporting would facilitate heeding early health warnings and putting practices into place to mitigate future risks. Occupational-health experts and employers can base their risk-management strategies on National Institute for Occupational Safety and Health (NIOSH) research and other groups' efforts, such as the NanoRisk Framework promulgated by Dupont and the Environmental Working Group.

In addition, because nanomaterials are an interdisciplinary technology used in a wide range of industries and research settings, it is important to have appropriate safety training and handling techniques for researchers and other workers who might be exposed on the job. Some general guidelines from groups such as NIOSH and government labs already exist [166] and include engineering controls such as proper ventilation, personal protective equipment, and safe-handling and clean-up procedures.

6. Require sufficient toxicological testing of nanomaterials—preferably pre-market and also post-market as necessary—to assess risks to manufacturing and other workers and to downstream users, including consumers and susceptible subpopulations such as infants.

Addressing potential health effects from exposure to nanomaterials requires sufficient toxicity information to conduct either hazard identification or quantitative risk assessment. As discussed in Chapter 3, there has been no systematic approach to toxicity testing. Consistent with calls for modernizing current regulatory approaches for testing toxic chemicals, sufficient toxicity information should be required from manufacturers to determine potential health risks posed by nanomaterials. Ongoing state and national efforts to upgrade testing requirements for manufactured chemicals should include nanomaterials. Ideally, testing of nanomaterials would occur prior to their introduction into the marketplace. However, because nanomaterials are already in use, post-testing to remain on the market should be required and completed within a reasonable, but expeditious, timeframe.

7. Implement a labeling system that requires labeling of products that contain nanomaterials.

Part of being able to make informed decisions is having the appropriate information for chemicals and nanomaterials in an easily obtainable format. Labeling systems for products are an effective way to alert consumers to the presence of nanomaterials so they can make informed choices about the products they buy. Labeling is also important for proper product disposal where take-back systems are used to avoid contamination of the waste stream.

4.8.2 Supporting Research

8. Increase funding and support for targeted, nano-specific research to fill data gaps.

This and other reports identify numerous data gaps that need to be filled to better understand the public-health implications of and make informed decisions about nanomaterial use. While California does not have a specific research program related to nanomaterials, it can support other efforts, such as at the national level, to increase research funding in this area.

9. Conduct targeted research on the biological fate, transport, and distribution of nanomaterials, including sources, exposure routes, and internal distributions. Integrate this research with information gathered on exposure potential.

We need to improve our understanding of the biokinetics of nanomaterials to understand the extent to which nanomaterials enter and distribute in the body and whether particular organs or physiological systems are susceptible or particular targets. Focused studies should be complemented with research on unique properties that may predict biokinetics.

TABLE 14. Recommendations to support successful approaches to address potential health risks from nanomaterials that are currently outside the scope of OEHHA.

Recommendations to support successful approaches to address potential health risks from nanomaterials currently outside the scope of OEHHA
1. Require disclosure of where and what nanomaterials are manufactured, in what quantities, and for what new or existing products
2. Require reporting of properties that can identify nanomaterials that are persistent, bioaccumulative, and toxic (PBT). Phase out uses consistent with approaches for other PBTs.
3. Develop a framework for making policy and regulatory decisions that balances the uses and benefits of nanomaterials with their toxicity and exposure potential.
4. Require testing of release and exposure potential for nanomaterials in consumer products for both existing and new products.
5. Increase efforts to protect and educate workers, researchers, and downstream users of nanomaterials
6. Require sufficient toxicological testing of nanomaterials—preferably pre-market and also post-market as necessary—to assess risks to manufacturing and other workers and to downstream users, including consumers and susceptible subpopulations such as infants.
7. Implement a labeling system that requires labeling of products that contain nanomaterials.
8. Increase funding and support for targeted, nano-specific research to fill data gaps.
9. Conduct targeted research on the biological fate, transport, and distribution of nanomaterials, including sources, exposure routes, and internal distributions. Integrate this research with information gathered on exposure potential.

4.9 Concluding Remarks

Nanomaterials are still relatively new to the marketplace, so a window of opportunity now exists to develop and implement effective health protections to guide the development of the industry. At the same time, given that nanomaterials are already being used in consumer products, there is a heightened need to increase the pace at which we assess and address them. It is important to remember that risk management does not aim to stop nanotechnology but, rather, to encourage responsible development of nanomaterials given their promise to improve important sectors of commerce such as energy storage and conversion, environmental remediation, and drug delivery and diagnostics.

While some of the recommendations in this report may require legislative action, we can improve current regulatory approaches now to enhance the use of available science for decision-making that protects human health and the environment. For example, we can improve our ability to identify where qualitative data is sufficient for decision-making to reduce harmful exposures and where quantitative data is required.

Furthermore, as much as there is to learn from the history of regulating manufactured chemicals, we cannot rely solely on "past lessons" to address every exposure or health concern that nanomaterials may present. The ability to anticipate potential problems and act quickly without being unduly constrained by current or conventional approaches and frameworks would help enable more flexible policy to react to changing exposure or toxicity scenarios.

Many of the recommendations in this chapter require negotiation; consideration of competing interests; and, in some cases, technological innovation. Learning from past chemical-policy lessons will mean changing our approach to manufactured chemicals, whether they are nano-sized or more traditional. Fundamentally, requiring sufficient data to ascertain whether materials pose a significant risk to the population is imperative, especially when they are used in everyday consumer products. California continues to be the leader in progressive chemicals policy, and the growing field of nanotechnology presents a new opportunity for the State to develop innovative technologies and policies that will enhance both public health and economic growth.

LIST OF ABBREVIATIONS

AB	Assembly Bill (California)
Ag	silver
Al	aluminum
Au	gold
AUS	Australia
C_{60}	buckyball (buckminsterfullerene)
Cal/EPA	California Environmental Protection Agency
Cal/OSHA	California Division of Occupational Safety and Health
CAN	Canada
CDPH	California Department of Public Health
CdS	cadmium sulfide
CdSe	cadmium selenide
CdTe	cadmium telluride
CNS	central nervous system
Cu	copper
DDT	dichlorodiphenyltrichloroethane
DES	diethylstilbestrol
DTSC	Department of Toxic Substances Control
EEA	European Environment Agency
EU	European Union
EWG	Environmental Working Group
FDA	Food and Drug Administration
Fe	iron
Fe_2O_3	iron oxide
Fe_3O_4	iron oxide
FGBC	foreign giant body cell
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FoE	Friends of the Earth
GAO	Government Accountability Office
IARC	International Agency for Research on Cancer
K_{oc}	soil organic carbon-water partition coefficient
K_{ow}	octanol-water partition coefficient
La	lanthanum
µm	micron
mg/kg	milligrams per kilogram
MgO	magnesium oxide
MWCNT	multi-walled carbon nanotube
NAS	National Academy of Sciences
NASA	National Aeronautics and Space Administration
NGO	nongovernmental organization
NIOSH	National Institute for Occupational Safety and Health
nm	nanometer
NNI	National Nanotechnology Initiative
NRC	National Research Council
OECD	Organisation for Economic Co-operation and Development
OEHHA	Office of Environmental Health Hazard Assessment
OH	hydroxide ion

PBDEs	polybrominated diphenyl ethers
PBT	persistent, bioaccumulative, and toxic
PCBs	polychlorinated biphenyls
PEN	Project on Emerging Nanotechnologies
PFOA	perfluorooctanoic acid
PFOS	perfluorooctanesulfonic acid or perfluorooctane sulfonate
PM	particulate matter
PMN	polymorphonuclear leukocyte
PNS	peripheral nervous system
ppm	parts per million
Prop 65	Proposition 65
QD	quantum dot
REACH	Registration, Evaluation, Authorisation, and Restriction of Chemical Substances (EU regulation)
ROS	reactive oxygen species
SB	Senate Bill (California)
SiO_2	silicon dioxide or silica
Sn	tin
SWCNT	single-walled carbon nanotube
TAC	Toxic Air Contaminant (California program administered by OEHHA)
Ti	titanium
TiO_2	titanium dioxide
TSCA	Toxic Substances Control Act
UK	United Kingdom
US	United States
US EPA	United States Environmental Protection Agency
Zn	zinc
ZnO	zinc oxide
ZnS	zinc sulfide

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