

Health and safety implications of occupational exposure to engineered nanomaterials

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The rapid growth and commercialization of nanotechnology are currently outpacing health and safety recommendations for engineered nanomaterials. As the production and use of nanomaterials increase, so does the possibility that there will be exposure of workers and the public to these materials. This review provides a summary of current research and regulatory efforts related to occupational exposure and medical surveillance for the nanotechnology workforce, focusing on the most prevalent industrial nanomaterials currently moving through the research, development, and manufacturing pipelines. Their applications and usage precedes a discussion of occupational health and safety efforts, including exposure assessment, occupational health surveillance, and regulatory considerations for these nanomaterials. © 2011 Wiley Periodicals, Inc.

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INTRODUCTION

Nanotechnology represents a collection of capabilities, processes, and techniques aimed at the manipulation and engineering of matter at the nanoscale. Domestic and international investments in nanotechnology research and development (R&D), particularly as the global economy is increasingly driven by innovation, are steadily rising. In 2000, the United States launched the National Nanotechnology Initiative (NNI), and since that time Congress has appropriated approximately \$14.2 billion for nanotechnology R&D, including approximately \$1.8 billion in FY2011. More than 60 nations have established similar programs. In 2006 alone, total global public R&D investments reached an estimated \$6.4 billion, complemented by an estimated private sector investment of \$6.0 billion.¹ Lux

Research estimates that by 2014 \$2.6 trillion in manufactured goods will contain at least one engineered nanomaterial.²

While moving forward to develop and incorporate engineered nanomaterials into product pipelines, one common challenge shared by all stakeholders is how to address any emerging health and safety implications. Engineered nanomaterials produced and handled in industrial and academic settings present potentially new challenges to understanding, predicting, and managing potential health risks to workers, consumers, and the environment. The rapid growth and projected acceleration of nanotechnology makes understanding, predicting, and managing the health risks associated with occupational, environmental, and consumer exposures to nanomaterials an essential research focus area.

The overall risk equation, Risk = Hazard × Exposure, has two important components. The first being hazard and the second is exposure. Hazard refers to the inherent properties of a substance with the potential to cause adverse, or harmful, effects. Exposure is a quantitative measurement of the extent to which a given hazard is present. Risk is the probability that an adverse effect will occur to someone if exposed to the hazard. As the production and use of

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engineered nanomaterials increase, so does the possibility that there will be exposure of workers and/or the public to these materials.³ Many recent reviews emphasize the importance of exposure and risk evaluation of nanomaterials.^{4–7} Potential routes of exposure depend on the processes, materials, protective equipment, and controls used during research, development, manufacturing, and disposal (Figure 1).⁸ Currently, the synthesis of nanomaterials is the most well-documented step with respect to potential exposure to nanoparticles during production. Still, the potential for human exposure during nanoparticle processing is not adequately addressed; moreover, most manufacturers are not eager to disclose proprietary information about nanomaterials in their products. Based on recent occupational exposure studies and nanotoxicology data, inhalation is suspected to be the most prevalent and potentially harmful route of human exposure to nanoparticles^{3,9}; however, dermal absorption and ingestion are also potential routes of exposure. These routes are also under investigation, but to a lesser extent than inhalation exposure.^{10,11}

Nanomaterial toxicity is being studied extensively *in vitro* and in animal models. *In vitro* tests

tend to be more versatile and less expensive for investigating mechanisms of nanoparticle–biological system interactions, such as detection of reactive oxygen species and rapid toxicity screening. Dose-dependent toxicity data for certain nanomaterials including titanium dioxide, carbonaceous nanomaterials (e.g., carbon black and carbon nanotubes), and alumina are being assembled and analyzed.¹² Toxicity of metal-containing nanomaterials (e.g., copper, silver, zinc oxide, cerium oxide, gold) are also under investigation both *in vitro* and *in vivo* because of the increasing prevalence of these materials in consumer products and medical applications.^{13–20}

An assessment of the potential risks and hazards associated with human exposure to engineered nanomaterials has gained increasing attention in the literature,^{7,21,22} including field studies evaluating workers' exposure and elucidating what measurement techniques should be used to monitor occupational exposures.^{23–26} Recent review articles provide an overview of occupational health and safety research in workplaces where nanomaterials are present.^{27–29} Next steps include the development

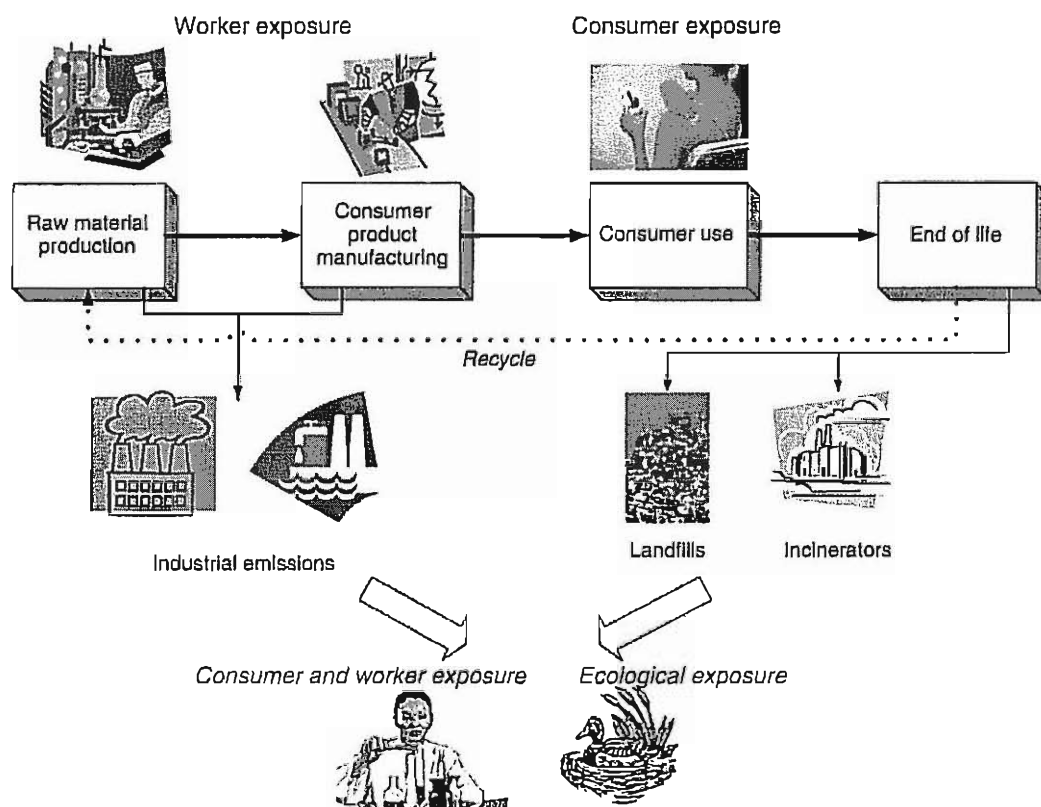


FIGURE 1 | Life cycle risk assessment for human and environmental exposure to nanomaterials.

of exposure assessment protocols involving nanoparticle classification, identification of biologically relevant characteristics and relevant physical exposure metrics.³ Clearly, validated exposure assessment and hazard surveillance methodologies are needed for the workplace and environment, in addition to *in vivo* and *in vitro* studies, to fully assess the human health implications of exposure to engineered nanomaterials.

This review focuses on some of the most prevalent engineered nanomaterials used by industry today—carbon black, silica (SiO₂), silver (Ag), titanium dioxide (TiO₂), zinc oxide (ZnO), and cerium oxide (CeO₂)—including their production, usage, and relevant occupational health and safety considerations as well as regulatory considerations.

ENGINEERED NANOMATERIAL PRODUCTION AND USAGE

The rapid growth of nanotechnology applications in industries such as pharmaceuticals, electronics, cosmetics, health care, energy, agriculture, and many more is accelerating. The Project on Emerging Nanotechnologies (PEN) has been tracking the number of consumer products containing engineered nanomaterials since March 2006. The number increased 397% from 212 to 1014 in just 4 years.³⁰ As the expansion of nanotechnology-enabled products continues, nanotechnology is anticipated to impact the worldwide economy by \$2.4 trillion by 2015.^{2,31} Additionally, the National Science Foundation projects that by 2020, the field of nanotechnology will employ some 6 million workers, 2 million of whom are expected to be in the United States.^{32,33} Therefore, occupational and public exposure to engineered nanomaterials will have a dramatic increase in the near future because of the ubiquity of nanomaterials in many consumer products and medical applications.³⁴

Nanotechnology is rapidly stepping into agriculture and food sciences. Nanomaterials are currently being used in food packaging and sprays for preservation³⁵; and additional applications in the food sector are quickly emerging.³⁶ For example, packaging material with silicate nanoparticles has been developed to slow the oxygen penetration and extend food shelf life, whereas nanocoating sprays are being used to preserve fruits and vegetables.³⁷ Nanoparticles and nano-emulsions are being utilized in foods to optimize quality, for example, to ensure easy pouring, enhance the flavor, or deliver nutrients more efficiently.³⁸

Other agricultural applications aim to identify and remove toxic pollutants from the environment, with the goal of improving food safety.^{39,40} Examples include the development of 'smart' systems for

pathogen detection in livestock, food products, or plants.^{41,42} Another promising area of application is in the development of nanosensors to detect and remediate environmental pollution. For example, certain metal and metal oxide nanoparticles, such as Ag, Fe, ZnO, and Fe₃O₄, can be used to detect heavy metal ions and volatile organic compounds in water and soil.^{39,40}

Other examples of novel nanomaterial applications include rare-earth nanocapsules for use in cryogenic magnetic refrigerators⁴³; nanoscale heterostructures consisting of a metal core and monocrystalline semiconductor shell for uses in microelectronics⁴⁴; and the development of new types of nanocomposites for use in energy conversion. Some of the most widely used nanomaterials include carbon-based nanomaterials (carbon black, fullerenes, carbon nanotubes), Ag, Si, TiO₂, ZnO, and CeO₂ (Table 1).⁴⁵

Carbon-based Nanomaterials

Carbon-based nanomaterials are produced in large quantities (e.g., on a ton scale for carbon nanotubes) for a variety of applications and are the most common nanomaterials found in consumer products.^{45,46} Carbon black consists of graphitic domains linked together to form near round shapes.⁴⁷ Carbon nanotubes are sheets of graphite rolled up to make a tube. They typically have a diameter on the order of 1–4 nm and length on the order of few millimeters. Nanotubes are formed as single or multiple concentric tubes. Owing to their large surface area, unique electrical properties and potentially high molecular adsorption capacity, carbon nanotubes are very attractive for various applications including electrical energy storage devices and hydrogen storage media.^{47,48} Other applications of carbon nanotubes are summarized in Table 1. Composites of carbon nanotubes with polymers provide high electrical conductivity and high strength and stiffness, which may lead to the development of ultrasensitive materials for use as reinforcement fibers.⁴⁹ Another common type of carbon-based nanomaterials are fullerenes, which were first discovered in 1985.⁵⁰ Fullerenes are now well-understood systems, and their applications hinge on their small size.⁴⁴ The future of fullerenes will likely be in biomedical applications, such as drug delivery systems, as well as in the fields of electronics, cosmetics, and superconductors.^{47,51}

Si-based Nanomaterials

Silicon-based nanomaterials are the third most common nanomaterial type contained in consumer products which account for 17% of all nano-enabled

TABLE 1 | Current Nanomaterial Applications in Consumer Products

Nanomaterials	Percentage of Consumer Products ⁴⁵	Applications
Carbon based	34%	Carbon black: car tires, antistatic textiles, for coloring rubber, ink, and leather ⁴⁷ Carbon nanotube: electromagnetic shielding, electron field emitters, super capacitors, batteries, tips in scanning probe microscopes ⁴⁸
Ag	30%	Laundry detergents, water filters, food storage containers, textiles, clothing, shoes ⁵⁵
Si based	17%	SiO ₂ : biosensing and bioimaging, such as cell staining; DNA detection and separation; rapid single bacterium detection; biotechnological application in DNA protection ⁵² Si: potential for use in batteries with extended storage times, microelectronics, solar energy applications ⁵³
TiO ₂	9%	Colored pigments, automotive paint systems, UV protection, cosmetics, plastics, wood-protection systems, catalytic processes, toothpaste, food colorants, nutritional supplements, and hundreds of other personal care products ^{56,57}
ZnO	9%	Sunscreens and fabric treatments for UV shielding ⁵⁸
CeO ₂	1%	Electrolytes for solid oxide fuel cells, oxygen sensors, automobile exhaust catalysts, broad-spectrum sunscreens ⁵⁹

consumer products.⁴⁵ These include both pure silicon (Si), which is a semiconductor, and silicon dioxide (SiO₂), or silica, an insulator. In particular, silica nanoparticles hold great promise in the biotechnology field because of their remarkable stability in biological fluids and ability to buffer with high ionic strength solutions.⁵² A review by O'Farrell et al. further describes the synthesis and applications of Si nanoparticles.⁵³

Metal and Metal Oxide Nanomaterials

Metal and metal oxide nanoparticles are currently either being used or under development for antimicrobial, self-decontaminating, and UV-blocking functions for both military protection gear and civilian health products. Metal and metal oxide nanoparticles can be produced by liquid-phase chemical methods, colloidal synthesis, vapor deposition techniques, and hydrolysis.⁵⁴ Nanoscale particles of Ag, TiO₂, ZnO, and CeO₂ are among the most common materials currently incorporated into market goods.⁴⁵ Although CeO₂ was only contained in 1% of consumer products on the market in 2006,⁴⁵ widespread potential applications of CeO₂ nanoparticles may raise the level of public exposure (Table 1).

OCCUPATIONAL HEALTH AND SAFETY OF NANOMATERIALS

The growing use of engineered nanomaterials in products creates an important need in understanding, predicting, and managing the potential health risks associated with human exposure,³⁴ especially

in workplaces where they are being fabricated and incorporated into products. For workers handling nanomaterials, inhalation of nanoparticles is the route of occupational exposure harboring the most concern, followed by dermal exposure and ingestion.³⁴ The main concern about exposure to engineered nanoparticles is that either due to their size or other novel physiochemical characteristics, they may exert unpredictable biological effects once they enter the human body.⁶⁰ In addition to unpredictable biological effects, nanomaterials pose a higher risk for fire/explosion and catalytic reactions than their larger counterparts.³⁴

Occupational Exposure and Industrial Hygiene

Owing to concerns about occupational exposure to nanomaterials, the National Institute for Occupational Safety and Health (NIOSH) and other public and private entities are encouraging collaborative efforts to develop safe handling recommendations for workers potentially exposed to engineered nanomaterials. One such recommendation is the development of occupational health surveillance programs that are inclusive of engineered nanomaterials.^{60,61} Occupational health surveillance is the systematic collection of exposure and health data for a group of workers with the goal of early detection of disease and ultimate prevention of disease.⁶² Additionally, an occupational health surveillance program can also be used to determine whether the hierarchy of controls for prevention of illness and injury are effective.⁶² The development of such programs requires answers to critical questions about nanoparticle characteristics relevant to toxicity,

where and how exposure is occurring in industrial processes, engineering controls, personal protective equipment, and health effects of exposure.⁶³ Benchmark occupational exposure limits for nanomaterials were suggested by the British Standards Organization (BSO) in January 2008. The document titled 'Guide to safe handling and disposal of manufactured nanomaterials' (BSI PD 6699-2:2007) recommends starting exposure values, called benchmark exposure levels (BELs), for four different classes of nanomaterials. It proposes 0.01 fibers/mL for fibrous nanomaterials, 1.5 mg/m³ for fine TiO₂, and 0.1 mg/m³ for ultrafine TiO₂. These levels are based on assumptions and speculation, rather than hard science. In the U.S., NIOSH recommended exposure limits (RELs) are 2.4 mg/m³, 0.3 mg/m³, and 7 µg/m³ for fine TiO₂, ultrafine TiO₂, and carbon nanotubes, respectively. NIOSH also has a REL for fumed ZnO of 5 mg/m³, which is a material that often exists at the nanoscale. At this time, occupational health surveillance will mostly take the form of qualitative exposure assessment (e.g., job hazard analyses) and comparative quantitative analyses, which typically trigger the need for occupational health surveillance for a particular hazard in quantitative terms.⁶² These qualitative assessments may be coupled with semi-quantitative methods^{5,6} to gain a more complete picture of occupational exposure.

Although it is feasible at this time to conduct qualitative hazard surveillance and exposure assessment for nanomaterials, practical knowledge about measuring and controlling nanomaterial-specific hazards remains limited. This is likely because of numerous challenges in describing and characterizing exposure and identification of the health effects of exposure to engineered nanomaterials. First, workers are potentially exposed to nanomaterials throughout the lifecycle of the material, including the sourcing, processing, manufacturing, use, and disposal (Figure 1), yet it is not clear if or how toxicity varies at different lifecycle stages. Additionally, it is expected that exposure will vary greatly across workplaces and may even vary within workspaces by job or task.⁶³ Conducting exposure assessments for engineered nanomaterials utilizing a lifecycle analysis framework contributes to the scientific understanding of exposure to nanomaterials and is a necessary component of developing risk assessment and risk management strategies for nanomaterials. While there are still many hurdles in understanding exposure to nanomaterials—including an uncertainty of their hazard potential, undetermined exposure metrics complicated by a lack of standardized measurement methodologies for nanoscale materials, and an uncertainty of what biological intermediates (i.e., biomarkers) and health outcomes are

associated with exposure to nanomaterials—exposure assessment is an essential first step in designing appropriate and adequate risk management programs.

Challenges in Understanding Occupational Exposure

The uncertainty surrounding the hazard potential of nanomaterials presents challenges to managing potential health risks to workers. Hazard identification is a critical step in exposure assessment that requires careful study of the physical and toxicological principles of a material,⁶⁴ yet for many nanomaterials there is insufficient physical and toxicological information available. Toxicological research suggests that some nanoparticles may elicit a greater immune response than larger particles of the same material and total mass⁶⁵ and that once inhaled, nanoparticles can enter the bloodstream and translocate to other organs.^{66,67} Meanwhile, uncertainty remains regarding which physiochemical characteristics (e.g., size, shape, surface area, charge, surface chemistry, crystal structure, solubility, pH, reactive oxygen species (ROS) production, and state of agglomeration/aggregation) most strongly influence a nanomaterial's interaction with biological systems and ultimate hazard potential. Further complicating the understanding of nanomaterial toxicity is the variability (different chemical composition, synthesis route for the same chemical formula, or batch-to-batch variations in the same manufacturing facility) of nanomaterials that are used in the production of or contained in consumer products.

The selection of an exposure metric (e.g., particle number, surface area, or mass concentration) is not always straightforward if the hazard is new,⁶⁴ as is the case with identifying the appropriate exposure metric(s) for nanomaterials.⁵ Additionally, the selection of exposure metrics is a challenge for any hazard where the health effects of exposure have not been established or the toxicological mechanism of action for the hazard is not known.⁶⁴ Further complicating the selection of exposure metrics for nanomaterials is the lack of standardization of measurement methodologies and sampling strategies. So while employers are encouraged to utilize risk management programs to protect their employees, there is no consensus on standards for measuring nanoparticle exposure in the workplace.⁵ Recent studies have utilized multifaceted sampling approaches typically utilizing both direct-reading handheld instruments (i.e., condensation and optical particle counters) and filter-based air sampling followed by chemical and microscopic analyses.^{5,6,68}

Short- and long-term health outcomes resulting from exposure to engineered nanomaterials have been

hypothesized based on ultrafine particulate research and *in vitro* and *in vivo* nanotoxicology data; however, many questions remain in predicting human health effects due to engineered nanomaterial exposures. Research efforts thus far suggest that cardiovascular, pulmonary, and inflammatory responses may occur because of exposure to engineered nanomaterials. For example, exposure to single-walled carbon nanotubes has been linked to possible adverse cellular responses in mesothelial cells.⁶⁹ However, most of the anticipated disease endpoints are nonspecific, common in the general population, have many confounding risk factors (e.g., obesity, smoking and diet), and long latency periods making epidemiologic research and medical surveillance difficult at this time. Of the few studies investigating short-term human exposure to nanomaterials, none have showed reproducible health outcomes suitable for informing comprehensive occupational medical surveillance programs.⁶⁰ Targeted medical surveillance requires (1) knowledge regarding actual or potential exposure to a health hazard, (2) known or suspected health effects that may result from the exposure, (3) the availability of medical/clinical tests with acceptable sensitivity and specificity to detect such health effects (ideally at an early stage), and (4) an established causal relationship between exposure and effect.⁶⁰ Certain existing medical tests (e.g., heart rate variability, blood clotting parameters, and proinflammatory cytokines) are nonspecific and require specialized, expensive equipment, whereas others (e.g., ECG, chest X-ray, and pulmonary function tests) are well-established diagnostic tools but are more appropriate for use in a symptomatic individual or a high-risk population with anticipated typical findings.⁶⁰ It is recommended that workplaces continue the use of established medical surveillance programs while pilot studies and research-driven nanomaterial-specific medical surveillance or screening programs are conducted.^{34,60} Traditional medical surveillance that is conducted in facilities where nanomaterials are produced or used is strongly encouraged and can potentially be used in future epidemiologic studies or contribute to the establishment of exposure registries.^{29,60} Research that contributes to hazard surveillance and medical surveillance should be done concurrently to develop effective nanomaterial-specific occupational health guidelines. This research draws on toxicology research findings and contributes to the establishment of exposure registries and epidemiologic research (Figure 2).

REGULATION OF ENGINEERED NANOMATERIALS

The regulation of nanotechnology is challenging because it is a platform technology encompassing many different fields and applications. An additional complication is a lack of consensus regarding terminology, the unknowns surrounding potential toxicity, and the lack of validated quantitative risk assessment methodologies. Nanotechnology is generally defined by its scale, but the exact definition of what constitutes a nanoparticle or nanomaterial varies by country and even among entities within countries. In order to facilitate a common language for the development of regulations and recommendations, national [e.g., Environmental Protection Agency (EPA)] and international [e.g., International Standards Organization (ISO) and the Organization for Economic Cooperation and Development (OECD)] groups are currently working to overcome these barriers and arrive at shared definitions. Nearly every country with a substantial investment in nanotechnology has allocated government funds to groups that are responsible for developing research agendas as well as frameworks for the responsible advancement of nanotechnology. Thus far in the United States, these efforts have stopped short of any formal regulations. An additional complication is the number of agencies potentially involved in the regulation of nanotechnology. The primary U.S. agencies expressing concerns are the Food and Drug Administration (FDA), the EPA, the Occupational Safety and Health Administration (OSHA), the Consumer Product Safety Commission (CPSC), and the Department of Agriculture (USDA). Striking a balance between innovation and risk management is essential as nanotechnology moves forward; however, governments are typically more interested in R&D than new regulatory frameworks for risk reduction.⁷⁰ While agencies within governments are charged with protection of workers and the public, they also do not want to stifle scientific and economic progress.⁷⁰ High quality, interdisciplinary research is essential in informing policy and regulation that will strike an appropriate balance between promoting innovation and minimizing human health and environmental risks.

In the USA, there are several federal agencies that have deployed work groups and task forces to address these emerging issues. Meanwhile, states like California have taken next steps in a more proactive approach. The entity leading nanotechnology regulation in California is the Department of Toxic Substances Control (DTSC). The DTSC views nanotechnology as the new 'plastic'

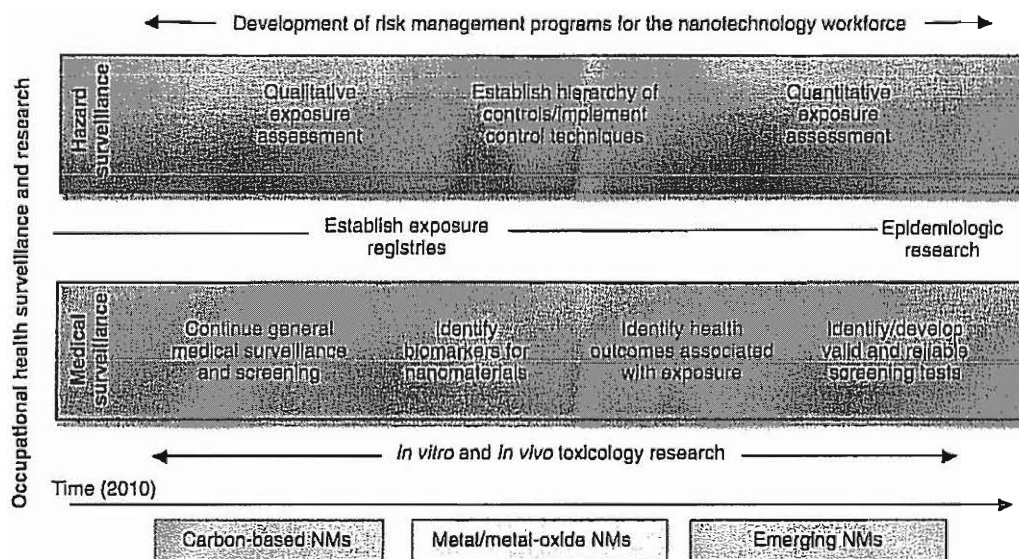


FIGURE 2 | Concurrent progression of occupational health surveillance and research.

because of its prevalence in many applications and consumer products.⁷¹ At this time, the DTSC is focusing on systematically gathering information and monitoring the movement of other regulatory agencies.⁷¹ In January 2009, the DTSC requested information on analytical testing methods, fate and transport in the environment, and other relevant information from the manufacturers or importers of carbon nanotubes in California. This was a mandatory request sanctioned under the *Health and Safety Code*, Chapter 669, sections 57018-57020.⁷² They have also issued a similar voluntary request for metal and metal oxide nanomaterials, including aluminum oxide, silicon dioxide, titanium dioxide, zinc oxide, silver, zerovalent iron, and cerium oxide.⁷²

The FDA is the agency responsible for the regulation of nanotechnology applications in food, cosmetics, drugs and medical devices in the U.S. In response to the emerging regulatory challenges posed by nanotechnologies, the FDA established a task force in August 2006 to determine the regulatory approaches that would allow the continued development of innovative, safe, and effective nanotechnology applications.⁷³ At that time, the FDA determined that their current procedures were adequate for dealing with products containing nanomaterials.⁷⁴ Currently, the FDA treats nano-enabled drugs like any other new drug.

The EPA is both supporting research in nanotechnology and evaluating its regulatory responsibilities to protect human health and the environment.⁷⁵ The agency initiated a voluntary Nanoscale Materials Stewardship Program (NMSP), which ended in

December 2009. Only 31 companies responded to this voluntary request for information, and although much important information was gathered, significant knowledge gaps remain. Therefore, the EPA has moved forward with taking regulatory action under the auspices of the Toxic Substances Control Act (TSCA). The agency proposed a Significant New Use Rule (SNUR) for carbon-based nanomaterials in September 2010.⁷⁵ The information gathering rule proposes that entities who manufacture certain nanoscale materials notify the EPA of information including production volume, methods of manufacture and processing, exposure and release information, and available health and safety data. The test rule proposes to require testing for these nanoscale materials that are already in commerce. Currently, the EPA is actively regulating nanomaterials considered to be 'new'; however, the rules being developed would allow the EPA greater latitude in regulating both new and existing nanomaterials.⁷⁶ Enacting these rules under TSCA would also turn the NMSP into a mandatory data collection effort.⁷⁶ In May 2011, EPA promulgated a final SNUR under Section 5(a)(2) of the TSCA for the chemical substance identified generically as multiwalled carbon nanotubes (MWCNT). Under the final SNUR, persons intending to manufacture, import, or process MWCNT for a use that is designated as a significant new use by the final rule must notify EPA at least 90 days before commencing that activity. The EPA states that it believes the final rule is necessary 'because the chemical substance may be hazardous to human health,' and the required notification would provide EPA with the opportunity

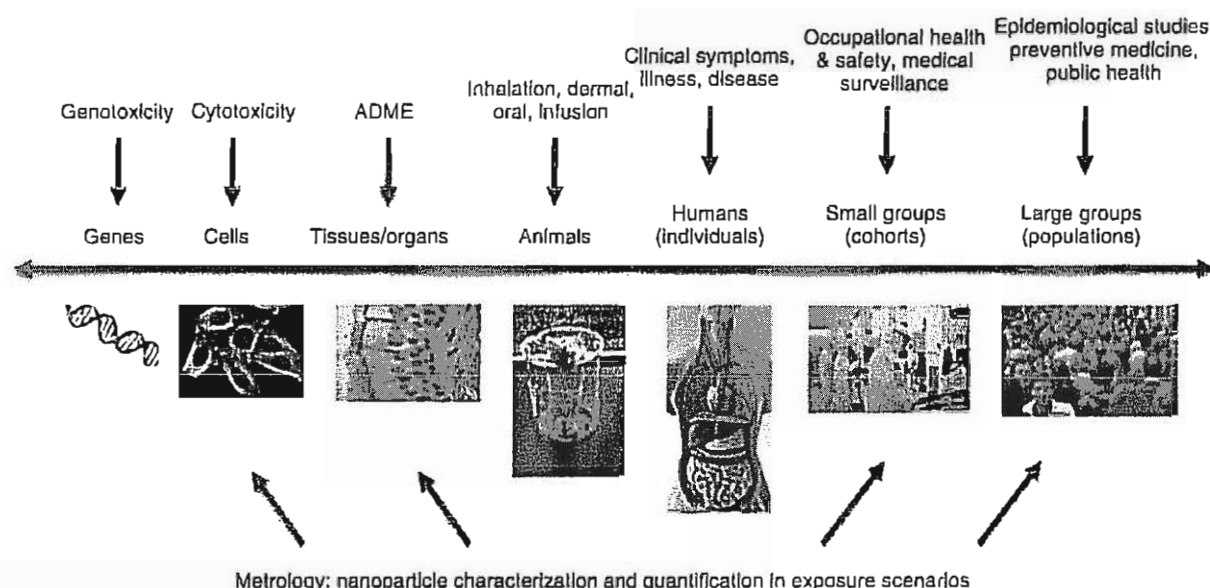


FIGURE 3 | Nanohealth and safety research continuum.

to evaluate the intended use and, if necessary, to prohibit or limit that activity before it occurs. The final rule became effective in June 2011.

OSHA, a division of the Department of Labor, is responsible for ensuring the health and safety of workers. OSHA adopts regulations (standards) that describe the methods by which employers must protect their workers.⁷⁷ While OSHA has not issued any standards specific to engineered nanomaterials, many existing standards are relevant to employees who are working with nanomaterials.⁷⁸ Most of these standards fall under the General Industry Standards and include personal protective equipment, respiratory protection, hand protection, and certain substance-specific standards.⁷⁸ OSHA, in concert with its research arm, NIOSH, is continuing to investigate health effects and safety concerns germane to the growing nanotechnology workforce.

Internationally, the REACH Regulation in the European Union (EU) represents the most comprehensive chemical legislation in the world.⁷⁹ REACH is the Registration, Evaluation, Authorization, and Restriction of Chemicals and was initiated in June 2007 replacing about 40 pieces of existing chemical legislation. It is substance-based legislation and clearly places the onus on industry to identify, report, and manage any risks that chemicals may pose to health and environment (the precautionary principle).^{80,81} In addition to chemical legislation, REACH created the European Chemicals Agency (ECHA), which is tasked with coordination and implementation of the overall process.

Companies that manufacture or use more than 1 ton of a substance per year are required to submit

a registration dossier for the chemical, if more than 10 tons are produced or used a chemical safety report must be produced as well.⁸¹ The first phase of REACH registration ended on November 30, 2010, with the other registration phases slated to end in 2013 and 2018.⁸²

There are no provisions in REACH referring specifically to nanomaterials; however, nanomaterials are considered a 'substance' as defined by REACH.⁸¹ Therefore, when a nanomaterial is introduced to the market the registration dossier must be updated with information on the form of the nanomaterial substance (including different classification, labeling, and risk management measures), even if the bulk substance is already on the market.⁸¹ It is possible that additional testing/information will be required for the nanoform, but at this time there are no specific guidelines for testing nanomaterials.⁸¹ Furthermore, the European Chemical Agency may request any information on the substance it deems necessary for its evaluation.⁸¹

FUTURE DIRECTIONS

As engineered nanomaterials become industrially ubiquitous, the need for health and safety research becomes increasingly important, and, ideally, this research will be conducted proactively and in collaboration with partners from government, academia, and industry from multiple countries. Research along the entire health and safety continuum—from genotoxicology to epidemiology—should proceed simultaneously and collaboratively to provide the most accurate and comprehensive picture (Figure 3).

Investigating the potential for human exposure in occupational settings should include research conducted at R&D facilities as well as manufacturing and industrial sites. While exposure and risk assessment protocols are being developed, precautionary measures and general occupational health surveillance guidelines are recommended for workers and worksites. Continued evaluation of the potential health risks associated with exposure to nanomaterials is essential to ensure their safe handling and application.⁶⁰ Ongoing scientific evaluation and

research will inform an evidence-based regulatory framework.

Pilot programs and research initiatives to establish epidemiologic cohorts, exposure registries, biomonitoring, and medical surveillance could illuminate points of concern and predict future challenges. Together, scientists, engineers, business leaders, regulators, and consumers must align efforts to address emerging health and safety issues unique to engineered nanomaterials to maximize the positive impacts of nanotechnology while minimizing and mitigating any and all associated risks.

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