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Nanotechnology: A Review of Exposure, Health Risks and Recent Regulatory Developments

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Summary

- Nanotechnology is the creation of materials, devices, and systems by controlling matter at the nanometer scale (1-100 billionths of a meter).
- Potential exposures to engineered nanoparticles (ENPs) through contact with consumer products or air, water, and food sources are an emerging potential threat to human health.
- ENPs have unique properties and characteristics in addition to size, such as a high surface area-to-volume ratio and surface properties, which may increase their toxicity relative to bulk materials.
- Due to the high-volume production of consumer products containing ENPs, such as silver (Ag NP), carbon nanotubes (CNTs), titanium dioxide (TiO_2 NP), and zinc oxide (ZnO NP), and the use of cerium oxide (CeO_2 NP) in fuel, environmental exposure to these compounds is likely.
- Realistic exposure assessment is hampered by the paucity of knowledge regarding the source and fate of ENPs in the environment, and the lack of analytical methods capable of quantifying ENPs in environmental matrices; however, existing data regarding particulates and ultrafine particles, mineral fibres, and metal fumes may provide insights into potential risks of ENPs.
- There is no conclusive evidence linking exposure to ENPs from air, water, or food sources or from the use and disposal of consumer products to negative impacts on human health.
- Toxicology studies on animal models and animal and human cell lines are available and toxic effects have been identified; however, the relevance and implications of these findings for human populations are still not clear.
- Epidemiologic studies, with realistic exposures to ENPs, are lacking.
- Recent regulatory initiatives in Canada and elsewhere include developing: working definitions for nanomaterials, including their behaviour (e.g., aggregation/agglomeration); labelling requirements for products containing ENPs; collecting existing data and product information for current ENP manufacturers and users, as well as other testing; and addressing data gaps in the field of toxicology and exposure assessment.
- Research initiatives are underway in Canada and the United States to address knowledge gaps in the human exposure and health effects of ENPs.

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- The scientific community is faced with the challenge of developing new risk assessment methodologies capable of identifying exposure characteristics and adverse health effects of ENPs.

Introduction

Scientists, governmental and non-governmental organizations, as well as consumers have expressed concern about potential risks to human health and the environment posed by rapidly emerging nanotechnology applications. The goal of this report is to provide an overview of what is known by addressing the following research question.

Research Question

The primary research question to be addressed is, "What potential human health effects are associated with nanotechnology"? Therefore, in addition to providing a general overview of nanotechnology, the specific objectives of this review will be to:

- identify possible sources of consumer and environmental releases and exposure to ENPs;
- determine what is currently known about the potential human adverse health effects of exposure to ENPs;
- identify recent approaches that regulatory authorities worldwide have taken to address the risks associated with nanotechnology;
- summarize research initiatives in Canada and the United States, aimed at addressing the knowledge gaps in human exposure and health effects of nanotechnology.

Due to the high-volume production of consumer products containing Ag NPs, TiO_2 NPs, ZnO NPs, and CNTs, along with increased use of CeO_2 NPs as a fuel additive, environmental exposure to these compounds is possible.[1-3] This report focuses on these ENPs.

Background

Nanomaterials are matter containing particles at the nanometer scale (1-100 billionths of a meter) and can occur naturally (as a result of volcanic eruptions, forest fires, ocean spray, hydrothermal vent systems, dust volatilization), be created incidentally (as by-products of industrial processes and combustion engines) or be engineered for a specific application.[4,5] Nanotechnology refers to the third category and is the creation of materials, devices, and systems in the nanometer scale. Nanoparticles (NPs) exhibit different optical, electrical, magnetic, chemical, and mechanical properties compared to their bulk counterparts.[6] Nanomaterials containing engineered nanoparticles (ENPs) use these novel properties in a wide range of applications (Table 1) and the number of consumer products containing ENPs is increasing rapidly. In February 2009, Environment Canada, in cooperation with Industry Canada, reported to a committee of the Organisation for Economic Co-operation and Development that over 1600 nano product lines (including stronger, lighter, and more durable sporting equipment; stain, wrinkle free, and antimicrobial clothing; cosmetics, sunscreens, and drugs) were available on the Canadian market, with 68% being imported from 11 countries.[7]

Exposure to nanomaterials in the environment may result from commercial products. The most common ENP listed on a prominent U.S. online consumer product database is silver (Ag NP).[8]

Other common ENPs in consumer products include carbon-based materials (e.g., carbon nanotubes [CNTs] and fullerenes), titanium dioxide (TiO_2 NP), zinc oxide (ZnO NP), and gold. The use of cerium oxide (CeO_2) as an additive in diesel fuels is also increasing.[9]

Table 1: Applications of ENPs[1,4,10-13]

ENP Class	Applications
Carbonaceous compounds	
CNTs and their derivatives	Electronics, computers, plastics, catalysts, batteries, conductive coatings, supercapacitors, water purification systems, orthopedic implants, aircraft, sporting goods, car parts, concrete, ceramics, solar cells, textiles
Fullerenes	Removal of organometallic compounds, cancer treatment, cosmetics, magnetic resonance imaging, X-ray contrasting agent, anti-viral therapy
Metal Oxides	
TiO_2	Sunscreen lotions, cosmetics, skin care products, solar cells, food colorant, clothing, sporting goods, paints, cement, windows, electronic coatings, bioremediation
ZnO	Skin care products, bottle coatings, gas purification, contaminant sensors
CeO_2	Combustion catalyst in diesel fuels, solar cells, oxygen pumps, coatings, electronics, glass/ceramics, ophthalmic lenses
Semi-conductor Devices	
Quantum dots	Medical imaging, targeted therapeutics, solar cells, photovoltaic cells, security links, telecommunications
Zero-valence Metals	
Zero-valent iron	Remediation of water, sediments and soils to remove nitrates, detoxification of organochlorine pesticides and polychlorinated biphenyls
Nanoparticulate silver	Textiles (e.g., socks, shirts, pants), disinfectant sprays, deodorants, laundry soaps, wound dressings, air filters, toothpaste, baby products (milk bottles, teethers), cosmetics, medical instruments, hardware (computer, mobile phones), food storage containers, cooking utensils, food additive/supplements, appliances (hair dryers, vacuum cleaners, washing machines, refrigerators), coatings/paints
Colloidal elemental gold	Tumor therapy, flexible conducting inks or films, catalyst, cosmetics, pregnancy tests, anti-microbial coatings
Polymers	
Dendrimers	Drug delivery, tumor treatment, manufacture of macrocapsules, nanolatex, coloured glasses, chemical sensors, modified electrodes

Although the use of ENPs is predicted to lead to the development of new products in many sectors, concerns have been raised regarding potential risks that may result from exposure during the product life-cycle (i.e., manufacture, use or misuse, and disposal).[14,15] The current proliferating and diverse use of ENPs in consumer products and fuel additives, for example, is expected to increase emissions of NPs to the environment.[2] Actual ENP emissions versus NP emissions from natural and incidental sources are not known.

Nanomaterials have unique properties and characteristics in addition to size, such as a high surface area-to-volume ratio and other surface properties, that may increase their toxicity relative to bulk materials.[16] Hence, the evaluation of potential human health risks as a result of consumer and environmental exposure to ENPs is required.

Methods

Given the large number of types of ENPs addressed in the literature, the volume and diversity of primary studies, the recognized limitations of those studies (i.e., the reliance on animal and cell studies), and the need to position the evidence in a rapidly evolving research and policy context, it was determined that the most effective way to address the research question was to undertake a pragmatic review of published reviews.

Literature search:

The literature search for this review used the following bibliographic databases: PubMed (i.e., MEDLINE and non-MEDLINE references), The Cochrane Library, the Centre for Reviews and Dissemination (DARE, NHS EED and HTA databases), EMBASE, Biosis Previews, Scopus, and Web of Science. The search included publications from 2008 to February 2011. Search terms included thesaurus terms where applicable (such as the Medical Subject Headings [MeSH] terms in MEDLINE and EMTREE terms in EMBASE for nanotechnology, nanoparticles, nanomedicine, etc.), as well as additional keywords to capture adverse effects, toxicity, risks, and environmental and health issues.

The search for *grey literature* included web sites, such as the British Columbia Environmental and Occupational Health Research Network (BCEOHRN) grey literature database, the Canadian Centre for Occupational Health and Safety (CCOHS), the U.S. National Institute for Occupational Safety and Health (NIOSH) nanotechnology publications, and the U.S. Environmental Protection Agency (US EPA) and Centers for Disease Control and Prevention (CDC) nanotechnology guidance and publications. Details of the full searches are shown in Appendix 1. Searches were limited to English language documents published in the last three years.

Literature selection and synthesis:

Of the 630 identified documents, 350 were reviewed. Of these, 114 were selected for more detailed review, based on the relevancy of information provided in the title and abstract. The primary criteria for inclusion of the review articles was that 1) primary studies on human exposure or health effects were comprehensively synthesized, and 2) it provided a substantive contribution in terms of the coverage or analysis of research. Greater weight was given to systematic reviews over narrative reviews and well-referenced peer reviews over grey literature overviews. Thirty-one reviews of CNTs, Ag NPs, TiO_2 NPs, ZnO NPs, and CeO_2 NPs were identified. In addition, 13 primary studies assessing ENP exposure were identified from reviews and directly reported. Papers providing information on research gaps, regulatory initiatives or policy relevant background material were selected to fulfill policy interests. It was not possible within the scope of this report to review in detail all relevant nanotechnology research or regulatory initiatives by governmental and academic collaborations. Peer reviewers of this report contributed additional relevant literature which was relevant to the Canadian context.

Exposure to Nanomaterials

Analytical methods to detect and quantify concentrations of ENPs in the environment are still under development.[16] Consequently, little is known about the actual concentrations of ENPs in air, soils or water, or their transport and fate in environmental matrices.[16,17] Current obstacles to the development of reliable analytical methods are detection limits that are not sufficiently low to detect environmentally relevant concentrations of ENPs and a high background of NPs derived from natural and incidental sources.[18] There is also lack of clarity regarding relevant exposure metrics (such as shape, surface area, or agglomeration state).[19] It is unlikely that exposure assessments, based solely on the concentration or mass of a material in a particular environmental medium, will always adequately characterize the relevant attributes of ENPs.[19]

The release of ENPs into the environment, that might result in human exposure, may occur from a variety of sources, including: discharges from sewage treatment plants, waste incineration plants, and landfills; factory releases of air, wastewater, and solid wastes; leaks or spills during transportation; and during the use, degradation, or destruction of consumer products.[15] Once in the environment, ENPs may undergo diverse physical, chemical, and biological transformations (e.g., deposition, adsorption, agglomeration, aggregation, and oxidation/reduction reactions), potentially altering biological impact and fate.[20] Certain local environmental factors (e.g., pH, salinity, microbes, and natural organic matter) may affect the reactivity, mobility, and toxicity of ENPs.[12] The environmental release of ENPs may potentially result in the contamination of drinking water and uptake into the human food chain.[20] In addition, bio-persistence in the environment must be considered.[21]

Thirteen *proof of principle* studies describing releases of ENPs into the environment that could lead to human exposures were identified from the reference lists of research review papers.[1,2,9,22-31] Kaegi et al. show that TiO_2 NPs can enter water via the natural weathering of paints.[22] Two studies indicate that Ag NPs may be released into water from laundering textiles.[23,24] Limbach et al. demonstrate that CeO_2 NPs may escape clearing systems in wastewater treatment plants.[25] Two studies report the release of TiO_2 NPs and Ag NPs into the air during the use of commercially available spray products.[26,27] Data reported by Lioy et al. shows that airborne particles ranging in size from tens of nanometers to tens of micrometers are produced with the application of cosmetic powders.[28] These studies do not provide realistic assessments of actual exposure, though several used modeling approaches to estimate environmental exposure to ENPs.[2,9,29-31] In addition, one study described a categorization framework that could be used for the assessment of consumer exposure.[1]

Possible routes of human exposure to ENPs include inhalation (e.g., use of cosmetic powders, sprays and cleaning products; waste combustion; demolition activities), ingestion (e.g., contamination of food products and drinking water; use of sun-protective lip balms; use of food additives/supplements), and dermal uptake (e.g., use of various consumer products including cosmetics, sunscreen, and sprays).[2,12,19,28,32-38] Also, a potential exposure route is injection of ENPs for medical purposes, but will not be discussed in this report.

Due to high-volume production of consumer products containing Ag NPs, TiO_2 NPs, ZnO NPs, and CNTs, plus the increasing use of CeO_2 NP in fuel, environmental release of these compounds into the environment is possible.[1-3] Speculations have been made as to the potential routes of release and exposure to these ENPs. A potential source of Ag NPs in water may be from water discharged from washing machines after cleaning fabrics that have been impregnated with silver as an antimicrobial agent[16]; Ag NPs may be released into the air by spraying (e.g., liquid cleaning products or personal care sprays), dry powder dispersion (e.g., vacuum cleaners and hair dryers), and during disposal (e.g., incineration and treatment of liquid waste).[11] Sources of TiO_2 NPs in water include: cosmetics and coatings; disposed paints and sprays; abrasion of metals and plastics.[16] TiO_2 NPs may also be released into the air through use of commercial sprays.[26] Use of sunscreens could lead to release of TiO_2 and ZnO NPs into water.[38] Wear and tear of products containing CNTs (such as sporting equipment, plastics, and textiles) could generate release of fine particulate matter into the atmosphere.[13] Other potential sources of CNTs in the atmosphere include release during incineration of industrial and medical solid waste, as well as treatment of liquid waste.[13] CNTs are believed to bio-persistent in the environment and may bio-accumulate along the food chain.[21] The most likely source of CeO_2 NPs in the environment would be from use as a diesel fuel additive.[3,17]

Health Risks/Impacts of Nanomaterials

NPs from Natural or Incidental Sources

Although this report focuses on emerging ENPs research, there is sizable literature on the toxicology of nanomaterials from natural or incidental sources, preceding the current nanoengineering era.[39] The established body of evidence on known effects provides important background knowledge on the toxic potential of uncontained free nanomaterials on cellular function and system specific effects on the respiratory, nervous, lymphatic, gastrointestinal and dermal systems, and on the liver, spleen, and kidney.[39] Of particular concern are findings from epidemiologic studies that provide strong evidence that inhaling ultrafine dust particles leads to oxidative stress in the lungs and, through ambient exposure, can lead to pulmonary diseases in occupational settings and excess mortality and morbidity in susceptible populations.[39]

Epidemiologic studies, demonstrating the association between diesel particulate exposures and negative human health effects, were considered sufficiently strong to warrant the regulatory control of diesel emissions.[3] Subsequent, clinical research, conducted on volunteer populations using short-term exposures to diesel exhaust, has demonstrated lung and systemic inflammation, thrombogenesis, impaired vascular function, and abnormalities in brain electrical activity.[40] Diesel NPs are known to dominate diesel particulate concentrations.[40] Although several sources of human exposure to inhaled particles exist (e.g., metal fumes, welding), the evidence on diesel exhaust is the most reproducible because ambient particle exposure is dependent on atmospheric conditions and local environment, including prevailing weather patterns.[41] Studies of particulate matter (PM_{10}, $PM_{2.5}$) are also of interest, particularly with regard to evaluation of susceptible populations, such as children, asthmatics, and others. Although the available research on fine and ultrafine particles is both more extensive and robust for drawing conclusions, it has also been more extensively reviewed, whereas the emerging evidence on ENP has not.

Carbon nanotubes (CNTs)

Twenty-two reviews identified findings from primary studies that assess the potential impact of CNTs on human health.[13,21,34,39,42-59] Most were not systematic. The lone systematic review and critical appraisal concluded that it is "*somewhat possible* for the CNFs[b] to penetrate the human cells in the targeted organs and to cause cellular damage."[57] The usefulness of CNTs is that they can be *functionalized*; that is, different molecules or atoms can be bound to the carbon atoms of single-walled carbon nanotubes (SWNTs) to provide desired characteristics. There are over 50,000 functionalized CNTs[50]; several have been identified as exhibiting similar toxicity but at different potencies.[13] The diversity of functionalized CNT precludes the generalization of findings from existing animal model studies, as well as human and animal cell research.[50] In vitro findings of toxicological differences in functionalized CNTs have not been consistently confirmed by in vivo studies,[33] though functionalized CNTs appear to be more toxic than non-functionalized (purified) CNTs,[39] possibly because non-functionalized CNTs are not effectively recognized by macrophages.[28]

Current evidence indicates that oxidative stress and inflammation are the main mechanisms of toxicity, raising concerns about the genotoxic and carcinogenic potential of CNTs.[13] Although studies assessing genotoxicity show conflicting results, the ability of SWNTs to penetrate the cellular nucleus highlights the need for further evaluation.[56] A dose-dependent increase in DNA

[b] CNTs are perfectly symmetrical tubes of carbon nanofibers (CNFs). CNFs can also be configured as cups, plates or cones

damage induced by CNTs has been documented.[56] Studies have reported *asbestos-like* toxicity resulting from intraperitoneal injection of CNTs into rats and mice.[60] Some CNTs behave like fibers and have other similarities to asbestos, leading some researchers to hypothesize that their adverse event profile may be similar.[47,52] However, this hypothesis has not yet been confirmed and there is a paucity of well-designed inhalation studies testing this theory. CNTs have also been linked to accelerated protein fibrillation, which has been connected to neurodegenerative disorders.[42] Interactions between human dermal cells and CNTs have been observed, although dermal penetration has not.[34] It is considered unlikely that inert CNTs can be effectively metabolized by enzymes in the body.[37]

Silver nanoparticles (Ag NPs)

Four reviews were identified that examined evidence for the toxic effects of Ag NPs.[11,61-63] Prior to availability in ENP formulations, the beneficial antiseptic properties of silver ions were exploited in medical applications with known toxic effects at high levels of exposure. A case study of an overdose to Ag NP, contained in a wound dressing product used to treat extensive leg wounds, has been documented[63]; after six days of treatment, the patient developed grey discolouration and reported symptoms of tiredness and lack of appetite with elevated silver levels in the urine and blood.[63] This case underscores the potential for adverse health events at high levels of exposure in therapeutic interventions but does not inform debates on environmental exposure.

In vitro and in vivo toxicity studies in mammalian species show that Ag NPs have the capability to enter cells and cause cellular damage to the skin, liver, lung, brain, vascular system, and reproductive organs.[63] This observed cytotoxicity is attributed to oxidative stress from both silver ion generation and the Ag NP itself.[63] Some studies indicate that Ag NPs may be unsafe even at non-cytotoxic doses, due to the ability to induce gene expression and toxicity in stem cells.[61] Inhaled Ag NPs of 15 nm diameter have been shown to have the highest toxicity in rat alveolar macrophages when compared to larger Ag NPs, possibly as a result of the comparable size to protein in biological cells.[62]

Zinc oxide (ZnO) and titanium dioxide (TiO_2) nanoparticles

ZnO and TiO_2 NPs are often reviewed together as they appear in the same sunscreen, diaper rash ointment, and other cosmetic products. Reviews have come to different summary conclusions on the available body of evidence. A review by Schilling et al, with authors from the cosmetics industry (including Unilever, Johnson & Johnson, L'Oreal, Procter & Gamble), concluded: "For 'nano' TiO_2 and ZnO, there is an abundance of data, largely favorable, using standardized toxicological methods, i.e., OECD, ICH[c], etc., and a 20+ year history of human use without clinical anecdotes/case reports or documented adverse events, all of which support the safety of these metal oxides."[64]

A review, by an Australian government research organization and industry sponsored research endeavor[d], presents evidence of inflammation from animal models following acute and chronic exposure to ZnO NPs.[38] The review notes that inter-species differences make it difficult to extrapolate this data to humans. It is also reported that there is scant information relevant to potential workplace hazards from inhalation, dermal exposure to dust, or oral ingestion posed by ZnO NPs manufactured for sunscreens. The review reports that it did not identify any studies investigating the possible translocation of ZnO NPs from lungs or the gastrointestinal tract into systemic circulation, concluding that while it is possible that the inhalation of ZnO aerosols containing nanoparticles could lead to adverse health effects in humans, specific research into the potential translocation and secondary health effects of ZnO NPs is lacking.[38] TiO_2 NPs are also widely used in construction materials.[12] TiO_2 irradiated with UV light or sunlight produce

[c] OECD = Organisation for Economic Co-operation and Development, ICH = the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
[d] Future Manufacturing Flagship program of the Commonwealth Scientific and Industrial Research Organisation (CSIRO)

reactive oxygen species (ROS)[e], which is known to cause inflammation, cytotoxicity and DNA damage in mammalian cells.[12]

Cerium oxide (CeO_2) nanoparticles

Three reviews examined research relevant to evaluating the possible health effects of CeO_2 NP exposure.[3,65,66] In vivo studies, using exposures to actual environmental concentrations of CeO_2 NPs produced from using fuel additives, were not found.[3,65] A genotoxicology review identified a study on human cells that did not find that CeO_2 produced DNA damage.[59] Due to the increasing reports of use of CeO_2 as a fuel additive, additional studies are needed.

Effect of ENPs on Special Populations

Evaluating the risk of adverse events in susceptible individuals (e.g., children and the elderly) and subpopulations with comorbidities (e.g., respiratory and cardiac conditions) is a priority for risk management.[67,68] Although there are no epidemiologic studies specific to ENPs exposure in special populations, there is evidence from studies of air pollution that NPs are deposited in the lungs to a greater extent in individuals with existing lung conditions such as asthma, and may exacerbate existing disease.[39,69,70] It is also recognized that NPs of different sizes can have different effects on different parts of the lung with smaller particles depositing closer to epithelial structures. This data may have implications for children with developing lungs as well as patients with asthma and chronic obstructive pulmonary disease.[71] Furthermore, in vivo studies in mice with allergic asthma have demonstrated that inhaled SWNTs increases susceptibility to pulmonary fibrosis.[72] CNTs have been associated with immunosuppressive effects, which may increase the susceptibility of certain populations (such as asthmatics) to microbial infections.[51]

Occupational Health Effects

In 2009, a case series was published that is purported to be the first confirmed report of adverse effects to humans as a result of an occupational exposure to NPs.[73] Eight women (aged 19 to 47), exposed to airborne polyacrylic ester NP for 5 to 13 months at the same workplace in China, were hospitalized with shortness of breath and two subsequently died. Consistent findings of pleural effusion, fibrosis, and granuloma were documented. NPs identified in the cytoplasm and karyoplasms of cases matched NPs recovered from the workplace. Although this case series provides credible evidence of a causal link in the particular circumstance[74] and highlights the risk potential of ENPs more generally, the unknown level of exposure, previous exposures and health status, and egregious failure to implement safe work practices make the applicability of these findings to other contexts problematic. However, the short time period to the development of significant morbidity and mortality is a cause of concern.

A review of the literature searched to 2008, on occupational exposures to ENPs, found a dearth of research from which to draw definitive conclusions but instead provided comprehensive recommendations to fill existing gaps.[75]

There are 12 published International Organization for Standardization (ISO) standards for nanotechnology, including one on health and safety practices in occupational settings, though this latter has not yet been formally adopted in Canada. There are over 21 nanotechnology standards under development. Canada participates in development of standards pertaining to nanotechnologies through the committees of ISO Canadian Standards Association (CSA Standards) and Standards Council of Canada (SCC).[76]

[e] Reactive molecules that contain the oxygen atom

Recent Developments in Nanotechnology Regulation

Canada

The regulatory framework for nanomaterials in Canada includes the Canadian Environmental Protection Act, the Pest Control Products Act, the Fertilizers Act, the Feeds Act, and the Food and Drugs Act.[77] In 2010, Health Canada released an interim policy statement outlining a working definition for nanomaterials to be used in gathering safety information and to support the administration of legislative and regulatory frameworks.[78] The definition states that any manufactured product is considered to be a nanomaterial if it is at or within the nanoscale (1-100 billionths of a meter) in at least one spatial dimension or exhibits one or more nanoscale phenomena (properties which are attributable to size and distinguishable from the bulk material). The scope of the working definition is intended to be broad so that all government legislative and regulatory programs are captured. The statement was prepared following consultation with international stakeholders, industry trade groups, standards associations, and other Canadian federal departments.

In June 2008, the Canadian Government announced that Environment Canada and Health Canada would be pursuing a mandatory information gathering survey under the authority of the Canadian Environmental Protection Act.[7] Canadian officials originally hoped to issue this requirement in the spring of 2009 but have since stated that they cannot predict when it will be implemented.[14] Companies and institutions that have manufactured or imported more than one kilogram of nanomaterials would be required to submit information on these products, including their physical and chemical properties, toxicological data, volume produced, manufacturing processes, and uses. Health and Environment Canada hopes to use this one-time request to gather information to be used in the development of a regulatory framework and to inform risk assessments.

United States

In June 2011, a set of principles "to guide development and implementation of policies for the oversight of nanotechnology applications and nanomaterials" were jointly released by the U.S. National Economic Council (NEC), the Office of Management and Budget (OMB), the Office of Science and Technology Policy (OSTP), and the Office of the U.S. Trade Representative (USTR). The purpose of this document was described as follows:

> To summarize generally applicable principles relevant to promoting a balanced, science-based approach to regulating nanomaterials and other applications of nanotechnology in a manner that protects human health, safety, and the environment without prejudging new technologies or creating unnecessary barriers to trade or hampering innovation. These principles build on the foundation provided by current regulatory statutes and do not supersede existing legal authorities or hinder Federal agencies from enforcing or applying their existing statutory and regulatory authority as mandated by law.[79]

In coordination with this effort, the U.S. Food & Drug Agency released *Guidance for Industry* entitled *Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology*.[80]

The impact of these documents on decision-making within the existing U.S. regulatory frameworks is yet to be determined. Recent attempts to enact legislation to regulate nanomaterials (Nanotechnology Safety Act of 2010 and the Safety Cosmetics Act of 2011) were unsuccessful. In January 2008, the United States (U.S.) Environmental Protection Agency (EPA) launched a Nanoscale Materials Stewardship Program; a voluntary information submission program.[81] An interim report released a year later highlighted limited industry participation and the program was discontinued in December 2009.[81,82]
The EPA is currently working on a mandatory data collection and data development regulation.[83] The EPA is also developing *Significant New Use Rules* to regulate the use, manufacture, and

distribution of nanoscale versions of conventionally scaled chemicals that are already on the Toxic Substances Control Act inventory.[84] If a company wants to use a chemical in a way that has been designated as a significant new use, it must submit to the EPA a *Significant New Use Notice* containing information such as chemical identification, material characterization, physical/chemical properties, commercial uses, production volume, exposure and fate data, and toxicity data. Upon receipt of a notice, the EPA has 90 days to evaluate the intended use and, if warranted, to prohibit or limit activities that may present an unreasonable risk to human health and the environment.

Australia

In 2008, Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS) issued a voluntary call to industry and researchers for information on intended use, life-cycle, environmental fate, and toxicological data of nanomaterials.[85] The data will be used to prepare a public report on the use and development of nanomaterials in industrial, cosmetic, and personal care products in Australia. In January 2011, NICNAS launched new requirements for the notification of nano-forms of chemicals not listed on the Australian Inventory of Chemical Substances.[86] Adjustments to NICNAS's New Chemicals Program processes mean that all industrial nanomaterials will undergo a pre-market assessment by NICNAS. Nano-forms of chemicals already listed on the Australian Inventory of Chemical Substances are considered to be existing chemicals and, at present, can be legally introduced and used in Australia without notification to NICNAS.[87] A mandatory notification and assessment program for nano-forms of existing chemicals is under development.

Europe

The European Union has developed a European Cosmetics Regulation that requires all nanomaterial ingredients to be clearly indicated in the list of ingredients and all nanomaterial-containing cosmetics to undergo pre-market assessment for safety six months before the product is placed on the European market.[88] The regulation also calls for the European Commission to compile a publicly available catalogue of all nanomaterials used in cosmetic products placed on the market, including those used as colorants, UV filters, and preservatives. Although this regulation was released in November 2009, its provisions are not scheduled to go into effect until July 2013.[14] In 2010, the European Commission accepted amendments to the Novel Foods Regulation supporting systematic mandatory labeling and pre-market authorization of all foods containing engineered nanomaterials.[89] The European Commission is also expected to launch a regulatory definition of the term *nanomaterials* in 2011.[90,91] In 2010, France finalized its compulsory scheme for nanomaterials requiring those who manufacture, import, or market nanomaterials to periodically report the identity, quantity, and uses of the substances.[83] France has joined discussions with Italy, The Netherlands, Germany, and Belgium in the development of national mandatory reporting schemes.[83]

Interventions

Where there is uncertainty about the risk to human or environmental health, as there is with nanomaterials, the *Precautionary Principle* is frequently evoked.[92] The *Precautionary Principle* states that, in cases of serious or irreversible threats to the health of humans or ecosystems, acknowledged scientific uncertainty should not be used as a reason to postpone preventive measures.[92] The *Precautionary Principle* has guided public policy development across many environmental and public health areas and is written into legislation in Canada and elsewhere. In accordance, the Quebec Institut de Recherché Robert-Sauvé en Santé et en Sécurité du Travail outlines preventive measures that can be applied to protect workers from occupational exposures,[39] as does the U.S. National Institute of Occupational Safety and Health (NIOSH), and the Occupational Safety and Health Administration (OSHA) in the U.S.[70]

A criticism of the use of precautionary measures, where adverse health effects are not well understood or quantified, is it may detract from the development and use of scientific evidence suitable for risk management, because decisions are being made without such evidence.[92] In the case of nanotechnology, there does not appear to be a warrant for the application of the *Precautionary Principle* in the absence of evidence of a causal link to adverse health effects. On the other hand, the lack of safety data suitable for risk assessment would appear to be the strongest warrant.[93] A 2008 Council of Canadian Academies report advises that "At present, it is not possible to implement a robust and reliable 'science-based' regulatory approach to nanoproducts. In this situation it is even more important to ensure that the appropriate precautionary measures guide the scientific assessment of risk and the selection of standards of safety."[92]

Research Gaps

Exposure Assessment

Reliable sampling and analysis methods to detect and quantify concentrations of ENPs in the environment are not yet available.[16] The impact of physical, chemical, and biological transformations on environmental fate and toxicity of ENPs is largely unexplored.[16,17] Further research is required to discern the effects of local environmental factors (such as pH, salinity, microbes, and natural organic matter) on the reactivity, mobility, bioavailability, and toxicity of ENPs.[12] There is a lack of clarity regarding relevant exposure metrics (such as shape, surface area, or agglomeration state), as it is unlikely that exposure assessments, based solely on the concentration or mass of a material, will always adequately characterize the relevant attributes of ENPs in a particular environmental medium.[19]

Health Risk Assessment

The scientific community has only recently been organized and funded to investigate potential adverse health events of ENPs, whereas nano-engineering is decades ahead in designing and bringing new nanomaterials to market at a regular pace.[26] The scope of the evaluative endeavor is therefore sizable. A number of Canadian funding agencies and academics are contributing to the global effort.[94] The U.S. NanoHealth and Safety Enterprise Initiative program aims to decipher interactions of ENPs with biological systems, to uncover fundamental principles and thereby expedite safe design.[95] In addition, the U.S. NIOSH is undertaking several research studies aimed at elucidating mechanisms of toxic action and variables that may be of importance in evaluating risk of NPs, working collectively with industry and academic and research institutions.[96] Whereas toxicity is known to be variable by particle, it is also a well-established tenant of toxicology that chemical substances have nontoxic dose ranges beyond which all become toxic to human health.[47] A criticism of existing research on animal and cell lines is that where effects are found, they are related to exposures that are unrealistically high, compared to likely real world scenarios, or were administered through mechanisms that are not biologically relevant to humans.[36] On the other hand, without a clear dose, metric as well as unknown effects of interactions of multiple exposures, nontoxic dose ranges cannot be clearly defined.[95,97]

ENPs differ in characteristics, properties and effects, compared to their bulk element counterparts.[6] Therefore, original research is required to understand the mechanisms of toxicity for nano-sized particles, rather than relying on safety and health information for larger-sized particles. A standardized taxonomy of NP chemical and structural characteristics, including size, surface area-to-mass ratio, shape, crystal structure, surface chemistry, and surface defects, needs be adopted to facilitate standardized reporting and creation of knowledge.[95] A standardized taxonomy will facilitate the development of understanding how these characteristics relate to properties (electrical, optical, magnetic), as well as toxicity in living systems and will allow comparability across studies.[95]

Epidemiologic studies with realistic exposures to specific ENPs are lacking. Consideration of several issues, including ENP heterogeneity, temporal factors (including determining when there would be adequate exposures and latency to begin conducting epidemiologic studies), exposure characterization, relevant disease endpoints, and the identification of the study population, will provide the foundation of initiating epidemiologic research.[98]

Government Research Initiatives

Several research initiatives are underway to address knowledge gaps in the human exposure and health effects of nanotechnology. In Canada, nanotechnology research activities are spearheaded by the federal government, provincial governments, universities, and national institutes.[99] The flagship research organization at the federal level is the National Research Council (NRC). The major concentration of research activities is found in Alberta, British Columbia, Ontario, and Quebec.[99] The National Institute for Nanotechnology (NINT), Canada's largest and most technologically advanced nanotechnology research facility, has been established in partnership with the NRC, University of Alberta, and Province of Alberta.[100] In June 2010, the Government of Canada provided $23.4 million over two years to support research at NINT.[101] In addition, the Natural Sciences and Engineering Research Council, the Canadian Institutes of Health Research, and the Canadian Foundation for Innovation have granting programs to fund applied research in nanotechnology.[100]

The National Nanotechnology Initiative (NNI) is the U.S. Federal Government's multiagency, multidisciplinary nanotechnology research and development program.[102] The NNI was established in 2001 to enable collaboration among the participating Federal agencies and provides a framework of shared goals, priorities, and strategies.[102] The proposed NNI budget of $1.76 billion for 2011 will bring the cumulative investment since launch to nearly $14 billion.[103] Nanotechnology-related environmental, health, and safety research is an essential component of the NNI's coordinated research framework and investments have increased substantially from $87 million in 2009 to a requested $117 million for 2011.[103]

Conclusion

Nanotechnology is an emerging science with broad applications and potential benefits, but it also carries many unknowns regarding its impact on human health. This review summarizes evidence for the potential toxic effects of CNTs, Ag NPs, ZnO NPs, TiO_2 NPs, and CeO_2 NPs and identifies gaps and weaknesses in the current human exposure and health effects research on ENPs. Little is currently known about the pathways of ENPs in the environment and their resultant toxicity from environmental and consumer exposure. Toxicology studies on animal models and animal and human cell lines are advancing, but are currently insufficient for comprehensive risk assessment and policy development. Given the lack of ENP characterization data, it is difficult to assess whether even the limited toxicology studies are valid or generalizable. ENP-specific epidemiologic studies with realistic exposures are lacking. Therefore, ENPs of particular and immediate concern to public and environmental health have yet to be identified.

Risk assessment of nanomaterials is complicated by limited exposure information, no clear dose metric, and the lack of characterization of ENPs. There is a pressing need to develop monitoring devices capable of measuring those aspects of ENP exposures that may result in toxic responses in humans. Recent regulatory initiatives collectively hold promise for addressing some of the many challenges regulators face when it comes to protecting human health and the environment

from the potential risks of nanomaterials. These elements include: developing working definitions of nanomaterials; labeling products containing ENPs; collecting existing data and product information; addressing the data gaps in the field of toxicology and exposure assessment. Research initiatives are underway to address knowledge gaps in human exposure and health effects of nanotechnology.
Establishing a conclusive link between human health outcomes and ENP exposure requires rigorous epidemiologic and toxicology research. The adaptation of traditional risk assessment instruments and methods is needed. Although science is advancing rapidly, there are many challenges that need to be overcome before nanoscale investigations are sufficient to determine if ENPs pose a risk to human health.

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Appendix 1: Literature search strategy

PubMed (5 Feb., 2011)
http://www.ncbi.nlm.nih.gov/pubmed/advanced - #

#81 Search #79 OR #80 Limits: published in the last 3 years	663
#80 Search #73 Limits: Meta-Analysis, Practice Guideline, Review, Consensus Development Conference, Consensus Development Conference, NIH, Legislation, Scientific Integrity Review, English	1120
#79 Search #76 OR #78	129
#78 Related Citations for PubMed (Select 19568840)	109
#76 Search #74 AND #75	24
#75 Search review[ti] OR overview[ti] OR systematic[ti]	234020
#74 Search #73 AND (in process[sb] OR publisher[sb] OR pubmednotmedline[sb])	830
#73 Search #52 AND #72	13232
#72 Search #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71	6186562
#71 Search technology assessment, biomedical	9321
#70 Search environmental pollution	289698
#69 Search occupational[ti]	36412
#68 Search environment*[ti]	82642
#67 Search exposure[ti]	82681
#66 Search risk[ti]	201059
#65 Search "health effects"[ti]	2507
#64 Search safety[ti]	52839
#63 Search public health	4633061
#62 Search legislation & jurisprudence	191382
#61 Search government regulation	16863
#60 Search risk assessment	208459
#59 Search environmental health	116631
#58 Search toxicology	95501
#57 Search environmental exposure	169584
#56 Search inhalation exposure	16995
#55 Search standards	528291
#54 Search toxicity	420934
#53 Search adverse effects	1515513
#52 Search #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51	76678
#51 Search nanotubes	12104
#50 Search nanofibers	1729
#49 Search nanocompounds	9
#48 Search nanomaterials	46654
#47 Search nanomedicine	2056
#46 Search nanostructures	44910
#45 Search nanoparticles	40140
#44 Search nanotechnology	25823

PubMed – with additional adverse effects filters (7 Feb., 2011)

#41	Search #40 NOT #39 Limits: published in the last 3 years	127
#40	Search #13 Limits: Meta-Analysis, Practice Guideline, Review, Consensus Development Conference, Consensus Development Conference, NIH, Scientific Integrity Review, English, published in the last 3 years	556
#13	Search #8 AND #12	7182
#39	Search #37 OR #38	595
#38	Search #34 Limits: Meta-Analysis, Practice Guideline, Review, Consensus Development Conference, Consensus Development Conference, NIH, Legislation, Scientific Integrity Review, English, published in the last 3 years	593
#37	Search #35 AND #36	2
#36	Search review[ti] AND overview[ti] OR systematic[ti]	26989
#35	Search #34 AND (in process[sb] OR publisher[sb] OR pubmednotmedline[sb])	749
#34	Search #8 AND #33	13103
#33	Search #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32	6186562
#32	Search technology assessment, biomedical	9321
#31	Search environmental pollution	289698
#30	Search occupational[ti]	36412
#29	Search environment*[ti]	82642
#28	Search exposure[ti]	82681
#27	Search risk[ti]	201059
#26	Search "health effects"[ti]	2507
#25	Search safety[ti]	52839
#24	Search public health	4633061
#23	Search legislation & jurisprudence	191382
#22	Search government regulation	16863
#21	Search risk assessment	208459
#20	Search environmental health	116631
#19	Search toxicology	95501
#18	Search environmental exposure	169584
#17	Search inhalation exposure	16995
#16	Search standards	528291
#15	Search toxicity	420934
#14	Search adverse effects	1515513
#12	Search #9 OR #10 OR #11	5848310
#11	Search adverse effect*[text word] OR adverse event*[text word] OR adverse incident*[text word] OR complication*[text word] OR harm*[text word] OR injurious effect*[text word] OR injurious event*[text word] OR injurious incident*[text word] OR morbidity[text word] OR mortality[text word] OR risk*[text word] OR side effect*[text word] OR treatment outcome*[text word] OR undesirable effect*[text word] OR undesirable event*[text word] OR undesirable incident*[text word] OR tolerability[ti] OR toxicity[tiab] OR toxic[tiab] OR safety[ti] OR safe[ti] OR safeties[ti]	4537876

#10	Search Ethics[MeSH] OR Harm Reduction[MeSH] OR Intraoperative Complications[MeSH] OR Morbidity[MeSH] OR Mortality[MeSH] OR Postoperative Complications[MeSH] OR Psychology[MeSH] OR Risk[MeSH] OR Safety[MeSH] OR Treatment Outcome[MeSH] OR "Teratogens"[MeSH] OR "Abnormalities, Drug-Induced"[MeSH]	1891570
#9	Search Adverse Effects[MeSH Subheading] OR Complications[MeSH Subheading] OR Ethics[MeSH Subheading] OR Morbidity[MeSH Subheading] OR Mortality[MeSH Subheading] OR Psychology[MeSH Subheading]	4200772
#8	Search #2 OR #3 OR #4 OR #5 OR #6 OR #7	72439
#7	Search nanocompounds	9
#6	Search nanomaterials	46654
#5	Search nanomedicine	2056
#4	Search nanostructures	44910
#3	Search nanoparticles	40140
#2	Search nanotechnology	25823

The Cochrane Library (issue 1, 2011)

Cochrane Reviews [2] | Other Reviews [1] | Clinical Trials [38] | Methods Studies [0] | Technology Assessments [2] | Economic Evaluations [2] | Cochrane Groups [0]

"nanotechnology or nanomedicine or nanoparticles or nanostructures, from 2008 to 2011”

Centre for Reviews and Dissemination (DARE, NHS EED, HTA) databases (11 Feb., 2011)

1	nanotechnology	5
2	nanomedicine	1
3	nanoparticles	2
4	nanostructures	0
5	#1 OR #2 OR #3 OR #4 RESTRICT YR 2008 2011	1

EMBASE (OVID 1980 to 2011 Week 05 – final search 11 Feb., 2011)

1	*NANOTECHNOLOGY/	10134
2	*NANOMEDICINE/	555
3	*nanoparticle/	15739
4	*nanomaterial/	7426
5	*nanofiber/	745
6	*NANOTUBE/	2330
7	1 or 2 or 3 or 4 or 5 or 6	32661
8	adverse drug reaction/	101352
9	(adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.	224173
10	side effect$.ti,ab.	176862
11	(unintended adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.	598

12	(unwanted adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.	4064
13	(unintentional adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.	101
14	(unexpected adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.	3694
15	(undesirable adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.	5531
16	(harm or harms or harmful).ti,ab.	49870
17	exp iatrogenic disease/	378985
18	drug safety/	168085
19	exp drug toxicity/	49509
20	toxicity.ti,ab.	234094
21	complication$.ti.	93567
22	safety.ti.	62131
23	*standard/	2768
24	*law/	26938
25	*exposure/	3182
26	*environmental exposure/	13908
27	*TOXICOLOGY/	7641
28	*environmental health/	8582
29	*risk assessment/	19432
30	*government regulation/	5189
31	*pollution/	9708
32	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	1218026
33	32 and 7	2104
34	meta analysis/	52674
35	exp "systematic review"/	38254
36	review.ti.	216949
37	34 or 35 or 36	274133
38	33 and 37	39
39	7 and 37	137
40	7 and 32	2104
41	limit 40 to (human and english language and (evidence based medicine or concensus development or meta analysis or outcomes research or "systematic review") and yr="2008 -Current" and (report or "review"))	1
42	38 or 39 or 41	138

EMBASE – search including technology assessment, biomedical

1	*NANOTECHNOLOGY/	10134
2	*NANOMEDICINE/	555

3	*nanoparticle/	15739
4	*nanomaterial/	7426
5	*nanofiber/	745
6	*NANOTUBE/	2330
7	1 or 2 or 3 or 4 or 5 or 6	32661
8	adverse drug reaction/	101352
9	(adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.	224173
10	side effect$.ti,ab.	176862
11	(unintended adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.	598
12	(unwanted adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.	4064
13	(unintentional adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.	101
14	(unexpected adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.	3694
15	(undesirable adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.	5531
16	(harm or harms or harmful).ti,ab.	49870
17	exp iatrogenic disease/	378985
18	drug safety/	168085
19	exp drug toxicity/	49509
20	toxicity.ti,ab.	234094
21	complication$.ti.	93567
22	safety.ti.	62131
23	*standard/	2768
24	*law/	26938
25	*exposure/	3182
26	*environmental exposure/	13908
27	*TOXICOLOGY/	7641
28	*environmental health/	8582
29	*risk assessment/	19432
30	*government regulation/	5189
31	*pollution/	9708
32	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	1218026
33	32 and 7	2104
34	meta analysis/	52674
35	exp "systematic review"/	38254
36	review.ti.	216949
37	exp biomedical technology assessment/	10676

38	34 or 35 or 36 or 37	284476
39	7 and 32 and 38	56
40	limit 39 to (english language and yr="2008 -Current")	41

Web of Science (with conference proceedings) (ISI Web of Knowledge) (15 Feb., 2011)

Title=(nanotechnology OR nanomedicine OR nanoparticle* OR nanomaterial* OR nanofiber* OR nanotube*) AND Title=(review* OR meta-analysis OR summary OR synthesis OR overview OR assessment) AND Title=(adverse OR effect* OR exposure OR pollution OR environment* OR toxicity OR toxicology OR risk* OR regulation OR regulatory)
Timespan=2008-2011. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH.
Results: 323

Biosis Previews (ISI Web of Knowledge) (15 Feb., 2011)

Databases=PREVIEWS Timespan=2008-2011

Title=(nanotechnology OR nanomedicine OR nanoparticle* OR nanomaterial* OR nanofiber* OR nanotube*) AND Title=(review* OR meta-analysis OR summary OR synthesis OR overview OR assessment) AND Title=(adverse OR effect* OR exposure OR pollution OR environment* OR toxicity OR toxicology OR risk* OR regulation OR regulatory)
Results: 73

Scopus (12 Feb., 2011)

25	((TITLE(nanotechnology OR nanomedicine OR nanoparticle* OR nanomaterial* OR nanofiber* OR nanotube*)) AND (TITLE(adverse OR exposure OR toxicity OR standard* OR environmental OR toxicology OR "health effect*" OR risk* OR pollution OR assessment)) AND (TITLE(adverse OR risk OR environment* OR pollution OR "health effect*" OR toxicity OR toxicology OR exposure OR standard* OR regulation* OR regulatory))) AND (TITLE(review OR systematic OR overview OR synthesis OR meta-analysis OR assessment)) AND (LIMIT-TO(PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008))	120
24	((TITLE(nanotechnology OR nanomedicine OR nanoparticle* OR nanomaterial* OR nanofiber* OR nanotube*)) AND (TITLE(adverse OR exposure OR toxicity OR standard* OR environmental OR toxicology OR "health effect*" OR risk* OR pollution OR assessment)) AND (TITLE(adverse OR risk OR environment* OR pollution OR "health effect*" OR toxicity OR toxicology OR exposure OR standard* OR regulation* OR regulatory))) AND (TITLE(review OR systematic OR overview OR synthesis OR meta-analysis OR assessment))	171
23	TITLE(review OR systematic OR overview OR synthesis OR meta-analysis OR assessment)	1,329,392
22	(TITLE(nanotechnology OR nanomedicine OR nanoparticle* OR nanomaterial* OR nanofiber* OR nanotube*)) AND (TITLE(adverse OR exposure OR toxicity OR standard* OR environmental OR toxicology OR "health effect*" OR risk* OR pollution OR assessment)) AND (TITLE(adverse OR risk OR environment* OR pollution OR "health effect*" OR toxicity OR toxicology OR exposure OR standard* OR regulation* OR regulatory))	1,340
21	TITLE(adverse OR risk OR environment* OR pollution OR "health effect*" OR toxicity OR toxicology OR exposure OR standard* OR regulation* OR regulatory)	1,246,752
20	TITLE(adverse OR exposure OR toxicity OR standard* OR environmental OR	1,071,691

	toxicology OR "health effect*" OR risk* OR pollution OR assessment)	
19	TITLE(nanotechnology OR nanomedicine OR nanoparticle* OR nanomaterial* OR nanofiber* OR nanotube*)	118,812

LILACS (15 Feb., 2011)
nanotechnology [Title words] or nanomedicine [Title words] or nanomaterials [Title words]
Results: 18 (only 2 references in English were relevant, one was pre-2007, one was a duplicate)

Grey literature search(unless otherwise noted search terms were: nanotechnology OR nanotechnologies OR nanomedicine)

- New York Academy of Medicine Grey literature collection http://www.nyam.org/library/online-resources/grey-literature-report/
- NLM Gateway http://gateway.nlm.nih.gov/gw/Cmd?GMResultsSummary%26loc=nccs
(nanotechnology OR nanotechnologies OR nanomedicine) AND (safety OR environment OR health OR adverse OR toxic*) Limits English, 2008-2011
- NHS Evidence http://www.evidence.nhs.uk/default.aspx
- US Centers for Disease Control and Prevention (CDC) Nanotechnology guidance and publications http://www.cdc.gov/niosh/topics/nanotech/pubs.html
- National Institute for Occupational Safety and Health Nanotechnology publications database search – NIOSHTIC-2
'ultrafine*' OR ('nano*' AND 'particle*') OR 'nanotech*' OR 'nanomaterial*' OR 'nanoparticle*' OR 'nanotube*' - published from 01/2008 to 04/2011
- British Columbia Environmental and Occupational Health Research Network (BCEOHRN) Grey literature database http://bceohrn.ca/search/greylit_search
- ProQuest Dissertations and Theses
176 documents found for: ((nanotechnology OR nanotechnologies OR nanomedicine) AND (safety OR environment OR health OR adverse OR toxic*)) AND PDN(>1/1/2008) AND PDN(<12/31/2011) AND LN(EN) 9 selected references
- Toxipedia http://toxipedia.org/display/toxipedia/Toxipedia (mainly older web links here)
- TRIP Database http://www.tripdatabase.com/ (mainly clinical medicine resources)
- Google.ca www.google.ca
((nanotechnology OR nanotechnologies OR nanomedicine) AND (safety OR environment OR health OR adverse OR toxic*)) **scanned first 10 pages only

Additional web sites:
- University of California, Santa Barbara. Center for Nanotechnology in Society http://www.cein.ucsb.edu/research/
- Rice University. Center for Biological and Environmental Nanotechnology http://cben.rice.edu/showhome.aspx
- SafeNANO http://www.safenano.org/
- National Nanotechnology Initiative http://www.nano.gov/
- Project on Emerging Nanotechnologies http://www.nanotechproject.org/
- Enviro-Health links Nanotechnology http://sis.nlm.nih.gov/enviro/nanotechnology.html
- OECD database on research into the safety of manufactured nanomaterials http://www.oecd.org/document/26/0,3746,en_2649_37015404_42464730_1_1_1_1,00.html
- GoodNanoGuide http://www.goodnanoguide.org/tiki-index.php?page=HomePage
- Canadian Centre for Occupational Health and Safety http://www.ccohs.ca/

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