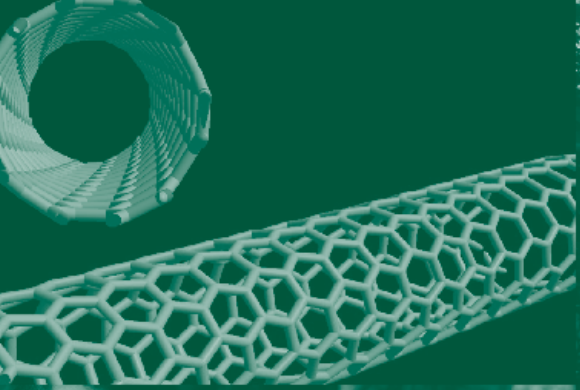
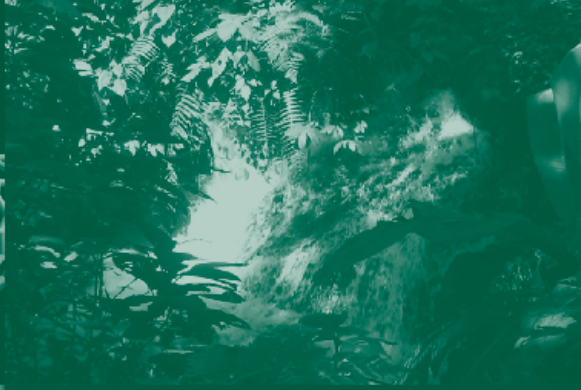

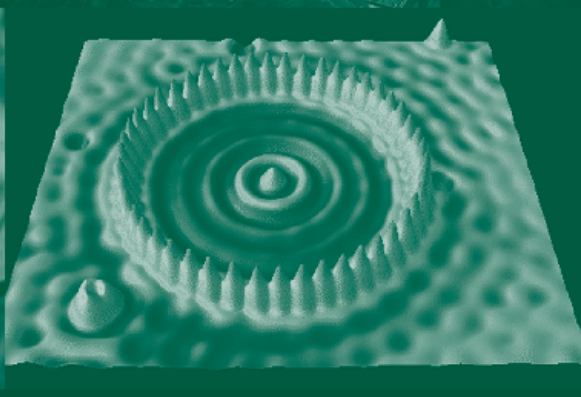

Small is Different: A Science Perspective on the Regulatory Challenges of the Nanoscale

The Expert Panel on Nanotechnology

Council of Canadian Academies
Conseil des académies canadiennes

Science Advice in the Public Interest

SMALL IS DIFFERENT: A SCIENCE PERSPECTIVE ON THE REGULATORY CHALLENGES OF THE NANOSCALE

Report of the Expert Panel on Nanotechnology

THE COUNCIL OF CANADIAN ACADEMIES

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Council of Canadian Academies
Conseil des académies canadiennes

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During the course of its deliberations, the panel sought assistance from many people and organizations that provided valuable advice and information for consideration. Special thanks are due to Mihail Roco for his insightful views on the panel's work. Dr. Roco is the Senior Advisor for Nanotechnology at the National Science Foundation, Chair of the U.S. National Science and Technology Council (NSTC)'s Subcommittee on Nanoscale Science, Engineering and Technology (NSET) and Member of the Scientific and Technical Council (S&TC) at the International Risk Governance Council (IRGC).

The panel thanks the sponsors of the study and the staff of the relevant agencies for the assistance and time they have given the panel throughout its deliberations. It also thanks the staff of the Council of Canadian Academies, without whom the panel would not have been able to complete this work.

Pekka K. Sinervo

Pekka Sinervo, Chair
Expert Panel on Nanotechnology

Report Review

This report was reviewed in draft form by the individuals listed below — a group of reviewers selected by the Council of Canadian Academies for their diverse perspectives, areas of expertise and broad representation of academic, industrial, policy and non-governmental organizations.

The reviewers assessed the objectivity and quality of the report. Their submissions — which will remain confidential — were considered fully by the panel, and most of their suggestions were incorporated into the report. They were not asked to endorse the conclusions nor did they see the final draft of the report before its release. Responsibility for the final content of this report rests entirely with the authoring panel and the Council.

The Council wishes to thank the following individuals for their review of this report:

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Jeffrey Steevens, Research Toxicologist, U.S. Army Engineer Research and Development Center (Vicksburg, MS)

The report review procedure was monitored on behalf of the Council's Board and Scientific Advisory Committee (SAC) by the **Honourable Donald J. Johnston**. Mr. Johnston is the Chairman of the Board at the International Risk Governance Council (IRGC). The role of the report review monitor is to ensure that the panel gives full and fair consideration to the submissions of the report reviewers. The Board of the Council authorizes public release of an expert panel report only after the report review monitor confirms that the Council's report review requirements have been satisfied. The Council thanks Mr. Johnston for his diligent contribution as review monitor.

Peter J. Nicholson, President
Council of Canadian Academies

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Summary

ABSTRACT

Nanomaterials and nanoproducts present exciting new opportunities for improving the quality of life of Canadians. At the same time, the scientific knowledge on which one can quantitatively assess the risks associated with these materials is limited, especially given the diversity of nanomaterials and their potential applications. Many of the uncertainties associated with risk assessment and risk management are not unique to nanomaterials, but have been present in the introduction of other new technologies, such as biotechnology and nuclear technology. These uncertainties have been managed in Canadian regulatory frameworks by taking a precautionary approach — giving priority to ensuring the safety of health and the environment.

This report summarizes the work of the Expert Panel on Nanotechnology (the panel) established by the Council of Canadian Academies (the Council), to assess "…the state of knowledge with respect to existing nanomaterial properties and their health and environmental risks, which could underpin regulatory perspectives on needs for research, risk assessment and surveillance."

Given the current limited state of scientific knowledge regarding many nanomaterials, the panel identifies the need to give priority to the development and resourcing of a strategic research agenda to improve our understanding of the risks associated with each specific class of nanomaterials. Research into metrology, into properties of nanomaterials that are linked to biological responses, and into effective monitoring and surveillance strategies should be given high priority.

Although the panel believes that it is not necessary to create new regulatory mechanisms to address the unique challenges presented by nanomaterials, existing regulatory mechanisms could and should be strengthened. First, an interim classification of nanomaterials should be developed. Second, the current regulatory "triggers" — i.e., the criteria used to identify when a new material or product should be reviewed for health and environmental effects — should be reviewed, as existing mechanisms will not identify all nanomaterials and nanoproducts. Third, standardized approaches for the proper handling of nanomaterials should be developed to ensure proper worker safety. Finally, the current metrological capacity for nanomaterials should be strengthened to ensure effective surveillance of their effects on consumers, workers and the environment.

The panel also focused on specific management-centred regulatory challenges. It identified an adaptive, life-cycle approach to the risk assessment and risk management of nanomaterials as most appropriate. The large number of classes of nanomaterials and the need to make case-by-case assessments of health and environmental risk mandate a coordinated approach across agencies within government, among levels of government and with international partners in order to avoid duplication of effort and the creation of inconsistent or conflicting regulatory regimes. A critical aspect of the management of risks in a regulatory context is the involvement of the public, which includes not only self-identified stakeholders but the broader public who act as citizens and consumers. Providing meaningful avenues for public participation in the formulation of regulatory policies governing nanomaterials is essential for the establishment and maintenance of public confidence in this technology.

The existing Canadian regulatory approaches and risk management strategies are appropriate for the challenges presented by nanomaterials, provided that a greater investment is made in strategic research associated with the risk assessment of these materials, that attention is paid to addressing issues of classification, regulatory triggers and regulatory capacity, and that regulatory agencies coordinate their activities with each other, between federal and provincial levels of government and with the regulatory agencies of other countries.

INTRODUCTION

As our fundamental understanding of the physical world has evolved over the course of the last several centuries, so too has our ability to manipulate matter. We can create an extraordinary variety of materials and finished products, many of which have improved our quality of life. The ability to manipulate matter at the most minute scale — the nanoscale roughly defined as between one and one hundred billionth of a metre — has brought with it the ability to create new classes of materials. These materials, known generically as nanomaterials, have unusual, unexpected properties that are potentially very useful, with applications ranging from new pharmaceuticals to environmental remediation to sports equipment. At the same time, they present concerns arising from potential hazards to human health and the environment that are not well understood.

It is in this context that the Council of Canadian Academies (the Council) was charged by Health Canada as a lead agency, along with several other

departments and agencies of the Government of Canada, to undertake a study focusing on the following question:

> *What is the state of knowledge with respect to existing nanomaterial properties and their health and environmental risks, which could underpin regulatory perspectives on needs for research, risk assessment and surveillance?*

To perform this task, the Council assembled the Expert Panel on Nanotechnology (the panel) comprised of leading scientists involved in research into the fundamental properties of nanomaterials, scientists who are engaged in the study of the hazards and routes of exposure of nanomaterials to humans and the environment, social scientists who are experts on the roles of government and society in the introduction of new technologies, and experts in the public and private sector with a broad range of experience in the development and regulation of new products. This report summarizes the findings of the panel.

As anyone familiar with the history of innovation is aware, new technologies have the potential to harm human health and the environment. For that reason, governments have established clear mechanisms, usually implemented through regulatory procedures based on scientific knowledge, to ensure that any risks are appropriately managed. Mechanisms for regulating beneficial new technologies have been quite successful, if measured by the very significant overall improvement over the last century in the health of Canadians during a time of enormous technological innovation. At the same time, some substances originally characterized as safe have been subsequently found to present serious risks to health and the environment. Examples include polychlorinated biphenyls (PCBs), used as an insulator and later found to be a toxic organic pollutant that bioaccumulates; the herbicide Agent Orange, shown subsequently to release dioxins that are now known to have serious health effects; and the most recent example of bisphenol A, found in some plastics used in food and beverage containers and now suspected of having significant biological effects. These examples illustrate that regulatory mechanisms cannot guarantee that all risks can be eliminated.

The panel study is the first, comprehensive, Canadian effort to address the current state of scientific knowledge regarding the risks presented by engineered nanomaterials, and how that knowledge should guide the approach taken to steward the process through which nanomaterials are responsibly introduced into Canadian trade and commerce.

In the view of the panel, an assessment of what is known and not known about the health and environmental risks of engineered nanomaterials is urgently needed in both the Canadian and international context, given that hundreds of nanoproducts — consumer products employing nanomaterials — are already being marketed internationally. Countries such as the United States and the United Kingdom are actively pursuing assessments that would assist regulatory capacity. In Canada, there are numerous channels through which domestic nanotechnology capacity is being created. This creates, consequently, a need for attention to risk and public trust issues to complement and balance those activities. Indeed, there is a nanotechnology "buzz," both internationally and in Canada, among governments and within academia, industry and non-governmental organizations. This is animated in part by a concern about the risks of nanotechnology and the regulatory implications of those risks.

This summary distills into a few pages the findings arising from eight months of work by the panel. Besides the scientific knowledge of the panel members, these findings were informed by a web-based public consultation on the question of nanomaterial regulations and by informal dialogue with numerous stakeholders. In the end, the panel's findings and conclusions create a picture that hopefully will provide guidance to all the stakeholders involved in the development of this exciting new technology.

There have been many studies and reviews of nanotechnology performed over the last decade, with some of the most influential being the studies by the Royal Society and Royal Academy of Engineering of the United Kingdom (UK-RS/RAE, 2004); by the world's largest reinsurer Swiss Re (Swiss Re, 2004); the International Risk Governance Council (IRGC, 2007) and by the Woodrow Wilson International Center for Scholars (Maynard, 2006a, Maynard 2006b). The unique contribution of this report is its clear focus on assessing the state of scientific knowledge concerning engineered nanomaterials from the perspective of risk assessment and regulation. In this regard, it is designed to assist the Government of Canada in developing a robust regulatory approach to these materials, a task that is urgent and time-sensitive. This report therefore provides an overview of what we know generally about nanomaterials, their properties, and how they differ from more conventional materials. It then discusses the current state of the science with regard to the risks associated with exposure to these materials, and identifies specific findings with regard to the nature of the regulatory approach that would most effectively address the issues presented by nanomaterials and products that make use of them.

The sponsors of this assessment requested that the focus of the report be on the scientific knowledge that would inform regulatory perspectives on those engineered nanomaterials that are already in the marketplace in one form or another, or whose entry into trade and commerce could occur over the next several years. In order to maintain that focus, the panel has not discussed several other important issues that might have been included in its mandate, such as the current state of knowledge of the health and environmental effects of incidentally introduced nanomaterials (e.g., ultrafine particle exposure in the workplace), the implications of next-generation nanomaterials that are currently still in very early research and development (R&D), or specific proposals for regulation of nanomaterials *per se*. Rather, the panel hopes that its findings and recommendations will provide a science-based assessment that will assist the sponsors in taking appropriate next steps as quickly as possible in meeting what is an international challenge: the effective regulation of engineered nanomaterials entering trade and commerce.

A PRIMER ON "NANO"

Nanomaterials are defined broadly as those classes of materials that have one or more physical dimensions in the nanoscale — ranging from 1 to 100 nanometres (nm) — or materials with larger dimensions that have structures embedded on their surface that have nanoscale features. A nanometre is one billionth of a metre (10^{-9} m), an incredibly small size that can only be understood by comparison to objects that we already consider quite small — the diameter of a human hair is approximately 100,000 nm, that of a red blood cell is approximately 8,000 nm, and a typical virus measures between 80 and 120 nm in diameter.

Nanomaterials can come in a variety of shapes, with nanoparticles being objects that are less than approximately 100 nm in every dimension. Scientists have been able to create objects from sheets of material formed into tubes with diameters in the nanoscale and lengths of several hundreds or thousands of nanometres. They have also been able to fabricate objects consisting of larger macroscopic devices with nanoscale features. The term nanotechnology has been introduced to encompass the technologies used to manipulate and characterize nanomaterials and nanostructures, as well as the resulting materials and products.

Although we define nanomaterials based simply on their size, what makes them of interest are the very novel properties exhibited by some of these classes of materials. In some cases, the manufacture of a commonly occurring substance in nanoparticle form — where particles of the substance are created

with sizes less than 100 nm — results in a material whose physical and/or biological properties differ substantially from those of the substance in its bulk form. A good example of this is the element gold. Within the macroscopic realm, the factors that govern gold's physical properties are independent of size. However, in 5 nm nanoparticle form, the optical and catalytic properties of gold are vastly different from those of gold in 50 nm nanoparticle form. A second example, also in commercial use, is titanium dioxide (TiO_2), which in nanoparticle form is used as an active ingredient in sunscreen formulae. Its properties in nanoparticle and bulk form are quite different.

Nanomaterials include classes of objects having quite complex physical structure on the nanoscale, exemplified by those materials known collectively as carbon nanotubes (CNTs). Made primarily of carbon rolled up into tubes with diameters of a few or tens of nanometres and lengths of up to several thousand nanometres, CNTs have been shown to conduct electricity and heat exceptionally well and to exhibit extraordinary structural strength. These are all properties not seen in the various forms of bulk carbon.

The novel physical and chemical properties of nanomaterials arise from their extraordinarily small size-scales, and are difficult to predict from the known properties of the same materials in bulk form, or even from theoretical extrapolations based on atomic or molecular properties. At the same time, the knowledge of their properties, while currently limited, is increasing very rapidly given active international efforts; and the ability to more reliably extrapolate and predict the physical properties of nanomaterials is also increasing at a comparable rate. However, the understanding of the biological effects arising from human or environmental exposure to these nanomaterials remains quite limited. Current literature suggests that the unique biological properties of nanomaterials stem from the relationship of their physical and chemical properties with (1) biological transport and environmental fate, (2) portals of entry into organisms, organs and cells, and (3) cellular response.

Public awareness of nanomaterials, and nanotechnology more broadly, appears to be quite modest, as determined by various surveys and studies assessing the public's knowledge of these materials. This has not deterred advocates and critics of nanotechnology from advancing various highly speculative or non-scientific views that from the panel's perspective tend to polarize public discourse. The low level of public awareness creates both the need and the opportunity for various stakeholders and the public to engage in informed discussion on the safe and beneficial introduction of nanomaterials into Canadian trade and commerce.

A SCIENCE PERSPECTIVE ON NANOMATERIAL RISK

As with many new technologies, one of the challenges for regulators confronting nanotechnology arises from the need to ensure public safety when new products and materials are introduced. To achieve this, it has become best practice to perform a risk assessment of new products, to identify potential areas of concern for human health and environmental integrity, and to institute appropriate risk management strategies. Frameworks of scientific risk assessment and risk management are well developed in Canada and abroad. Though there are differences of detail in implementation in each jurisdiction, this risk analysis framework is based on the following steps:

- Identification of the hazards associated with a material;
- Assessment of human and environmental exposure; and
- Identification of appropriate risk management strategies.

These steps provide an approach that can be applied to the evaluation of the potential risks of nanomaterials to human health and the environment. Much greater scientific understanding of the complex behaviours of these materials is, however, required before science-based regulation of the technology can be fully implemented.

Consequently, there are significant challenges in the application of this framework to nanomaterials, arising largely from a lack of scientific knowledge in a number of key areas. The hazard identification process for nanomaterials is difficult because of the limited knowledge of how the diverse physical and chemical properties of nanomaterials affect the biological/toxicological properties of most nanomaterials under development. Although there is a significant body of data on the biological and environmental effects of nanomaterials — one recent review identified over 400 different peer-reviewed studies — there remains significant scientific uncertainty on the degree of exposure to nanomaterials and the resultant biological effects of such exposure.

The principal challenges can be identified as (1) introduction or establishment of a systematic and standardized metrology (i.e., the science and technology of measurement) for physically characterizing nanomaterials, (2) uncertainty in the nature of the dose-response relationship between exposure of nanomaterials and biological effects (hazard characterization), and (3) the difficulties associated with measuring exposure to nanomaterials and surveillance once they are introduced into the environment. Most of these challenges arise from the sheer magnitude of the number of different nanomaterials, and the lack of a

comprehensive predictive model that would allow researchers to effectively classify them into manageable hazards classes.

Metrology – The challenges associated with metrology are substantial, given that the current scientific literature is equivocal on fundamental issues such as what physical properties are of most relevance to the biological interactions of a nanomaterial. Perhaps the only clear consensus at the current time is that the traditional measures of dose — either in terms of mass or volume of a substance — are unlikely to be appropriate when working with nanomaterials. This arises directly from the one physical property shared by all nanomaterials: that they have unusually high ratios of active surface area to volume compared with materials in bulk form. Hence, studies are forced to look at multiple metrics in order to yield reproducible and systematic results. The panel identified at least 10 physical and chemical properties that should be considered in the characterization of a nanomaterial: size, mass, composition, surface area, shape/morphology, crystallinity, surface charge, surface chemistry, solubility, and aggregation and agglomeration. In most cases, standard classification and measurement tools are lacking and limit scientific progress.

Dose-Response – The enormous diversity of nanomaterials and their relevant properties makes it a daunting challenge to conduct *in vitro* and *in vivo*[1] evaluation of their biological effects. Preliminary results show that *in vitro* testing may not always accurately predict hazards. At the same time, reviews of the large number of *in vivo* studies have concluded that most have been limited and difficult to reproduce.

Exposure – The uncertainty regarding the appropriate metrology for nanomaterials has presented very significant difficulties in monitoring nanomaterial exposure in the workplace and the environment. Furthermore, the biological and environmental pathways unique to nanomaterials are still largely unexplored in detail. Issues such as the potential for bioaccumulation and possible long-term persistence in the environment have been studied only for a very small number of nanomaterials.

New ways of measuring exposure, dose and response in relation to nanomaterials require development. This strongly suggests that any regulatory approach adopt a life-cycle strategy for nanomaterials. Although not a new regulatory concept, past experience with chemical substances has shown that

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[1] *In vivo* studies involve tests performed on a living organism, such as a controlled clinical study involving human test subjects while *in vitro* are those carried out on cells or tissues that have been cultured in petri dishes and occur outside of the body.

simply looking at manufactured nanoproducts and their immediate uses is not sufficient to predict long-term health and environmental outcomes.

Overall, the lack of a robust body of comprehensive scientific data on nanomaterial hazards and dose-response relationships, nanomaterial exposure in biological systems and the environment, and long-term consequences to health and the environment provide for only a qualitative risk assessment of a few nanomaterials. These "gaps" in our scientific knowledge should inform priorities for targeted and coordinated research into nanomaterial metrologies, toxicology, exposure routes and long-term health and environmental effects.

UNDERPINNING REGULATORY PERSPECTIVES ON NANOMATERIALS

The Canadian regulatory system is based upon the principle that where there are significant levels of uncertainty in the scientific assessment of risks, it is appropriate to exercise caution in favour of protecting human health and the environment. This presumption in favour of safety, usually denoted the "precautionary principle," would be appropriate in the context of any specific regulatory approach to nanomaterials and nanoproducts, given the uncertainties identified earlier. However, it is important to understand how the precautionary principle is applied as an overall "approach" in Canada. Quoting directly from the Privy Council Office report of 2003 (PCO, 2003): "Sound scientific information and its evaluation must be the basis for applying precaution; the scientific information base and responsibility for producing it may shift as knowledge evolves" and "mechanisms should exist for re-evaluating the basis for decisions and for providing a transparent process for further consideration." This suggests that an adaptive, life-cycle approach should be an element of any regulatory framework for nanomaterials and nanoproducts.

Given the current state of knowledge, the panel identifies the need to give priority to the development and resourcing of a strategic research agenda to improve our understanding of the risks associated with each specific class of nanomaterials. Research into metrology is of highest priority, specifically focused on the development of validated measurement methods and standards, along with nano-capable instrumentation, so that researchers are provided with consistent methodologies and criteria for evaluating nanomaterial properties and their behaviours. Research is needed to identify those properties of nanomaterials that induce biological responses. Research is also needed into the most effective means of monitoring and surveillance of nanomaterials and nanoproducts over their entire life-cycle.

Currently, there are no nanomaterial-specific regulations in effect in Canada, although Health Canada and Environment Canada have both taken first steps in recognizing the potentially unique aspects of nanomaterials. The regulatory agencies are relying on existing legislative authority delegated to them through instruments such as the *Canadian Environmental Protection Act* (EC, 2006). Although the panel is of the view that it is not necessary to create new regulatory mechanisms to address the unique challenges presented by nanomaterials, it does note that the existing regulatory mechanisms could and should be strengthened in a variety of ways.

First, an interim classification of nanomaterials should be developed. Although internationally coordinated efforts in this area are underway under the auspices of the Organisation for Economic Cooperation and Development (OECD) and Canada is playing an appropriate role, adoption of an interim classification mechanism would facilitate the identification and regulation of nanomaterials entering Canadian trade and commerce. In particular, any reporting mechanisms — whether voluntary or mandatory — will be ineffective without standardized terminology.

Second, the current regulatory "triggers" — that is, the criteria used to identify when a new material or product should be reviewed by regulatory bodies for health and environmental effects before introduction into commerce — should be reviewed, as it is not clear that the current triggers would identify all nanomaterials and nanoproducts.

Third, the current lack of monitoring tools and standards specific to nanomaterials means that workers and employers cannot effectively monitor worker exposure. Standardized approaches to the proper handling of nanomaterials are required to ensure proper worker safety.

Finally, the current metrological capacity — having the standards and methods for measuring properties and effects of nanomaterials — is insufficient to allow the surveillance of their effects on consumers, workers and the environment.

The panel focused on specific management-centred regulatory challenges. Given the expected evolution in the scientific knowledge surrounding nanomaterial risk assessment and management, a regulatory perspective that takes a life-cycle approach should also be adaptive as it accumulates experience and scientific knowledge evolves. The large number of nanomaterial classes and

the need to make case-by-case assessments of health and environmental risk mandate a coordinated approach to research into risk assessment and management across agencies within government, among levels of government and with international partners in order to avoid duplication of effort and the creation of inconsistent or conflicting regulatory regimes. A successful regulatory environment will depend on the production and distribution of a significant amount of knowledge.

A critical aspect of the management of risks in a regulatory context is the involvement of the public, which includes not only self-identified stakeholders but the broader public who act as citizens and consumers. The level of acceptance of nanomaterials into Canadian trade and commerce will depend on how effectively communication surrounding the benefits and risks of this new technology is performed. While it may be important to producers to communicate the benefits of any new nanomaterials and nanoproducts, government regulatory bodies should focus their efforts on fostering an open and informed public debate. Several examples of how this can be done already exist, such as the "Nanodialogues" approach undertaken in Britain. The establishment of meaningful avenues for public participation in the formulation of regulatory policies governing nanomaterials is essential to the establishment and maintenance of public confidence in this technology. The widest spectrum of stakeholders should be involved in the determination of the approach to regulating the introduction of new nanomaterials and products to the market, especially with respect to the desired level of precaution appropriate to ensure safety to human health and the environment.

SUMMARY OF SPECIFIC FINDINGS

The following represents the key findings of this report (identified by chapter number).

Regarding the definition of nanomaterials and current public awareness of the issues surrounding them:

2.1 Nanotechnology encompasses the technologies used to manipulate and characterize nanostructures as well as the resulting materials and products. Nanomaterials and nanotechnology are not the same thing.

2.2 The physical, chemical and biological properties of many nanomaterials differ from those of their constituent atoms and molecules, and from those of the bulk material.

2.3 The properties of nanomaterials are very diverse due to the many possible permutations of structure, chemical composition and shape.

2.4 Nanomaterials have novel but potentially controllable properties. These allow them to be used as precursors in the development of new products and devices.

2.5 The physical and chemical properties of nanomaterials may lead to unanticipated behaviours in environmental and biological systems.

2.6 Public awareness of nanotechnology in Canada is relatively low and public attitudes are therefore vulnerable to exaggerated claims by both proponents and critics.

Regarding the state of the science informing nanomaterial risk assessment and risk management:

3.1 Nanomaterials can pose particular challenges to risk assessment, and hence to regulation, because they exhibit properties based on their physical structure and their chemistry.

3.2 The diversity of possible nanomaterials is vast and the tolerances of a biological system to changes in the physicochemical properties of nanomaterials that determine their behaviour are poorly understood.

3.3 To date, there are no unique biological effects associated with exposure to nanomaterials, but there is still a poor understanding of how specific nanomaterials lead to specific endpoints.

3.4 Prevailing human and ecological risk assessment frameworks are robust, but their application to nanomaterials requires new ways of measuring exposure, dose and response.

3.5 Changes in the potential for nanomaterials to cause harm at different stages in their life-cycle imply a need for a life-cycle approach to risk assessment.

3.6 There are inadequate data to inform quantitative risk assessments on current and emerging nanomaterials. At most, only qualitative risk assessments are feasible, given the current state of knowledge.

3.7 Systematically targeted research is needed to fill the knowledge gaps and reduce uncertainty.

Regarding regulatory perspectives on nanomaterials:

4.1 Uncertainty in science and regulation can inhibit technology development, and undermine public confidence in the ability to adequately protect human health and environmental quality. Uncertainty in science can be offset by clarity and certainty in the terms and conditions under which such materials may enter trade and commerce.

4.2 Evidence from other industries suggests that the private sector prefers to have regulatory certainty even if the level of precaution invoked is relatively high.

4.3 At present, it is not possible to implement a robust and reliable "science-based" regulatory approach to nanoproducts. In this situation it is important to ensure that the appropriate precautionary measures guide the scientific assessment of risk and the selection of standards of safety.

4.4 A transparent and robust precautionary approach normally includes prior approval before allowing entry into commerce of any material over which there is the type of uncertainty displayed by nanomaterials and nano-enabled products.

4.5 The establishment of meaningful avenues for public participation in the formulation of regulatory policies governing nanotechnology is essential to the establishment of public confidence in the governance of the technology.

4.6 Until such time as a robust, science-based risk management regime is feasible, it is critical to involve the widest spectrum of stakeholders in the determination of the approach to regulating the introduction of new nanomaterials and products to the market, especially with respect to the desired level of precaution as it concerns potential human health and environmental risks.

4.7 Interim terminology and classification are needed to help regulators effectively oversee this emerging group of materials and products.

4.8 Current regulatory triggers are not sufficient to identify all nanomaterials entering the market that may require regulatory oversight.

4.9 In the absence of standardized terminology, information being acquired from monitoring systems is likely to be inconsistent and limited in its usefulness. In the context of occupational settings, standardized information regarding the proper handling of nanomaterials is required to ensure worker safety. New tools are needed to accurately monitor worker exposure.

4.10 The current metrological capacity for identifying and monitoring nanomaterials is insufficient to ensure the surveillance of their effects on consumers, workers and the environment. This is further limited by the inability to ensure adequate identification of existing and future nanomaterials and products containing them.

4.11 An adaptive, life-cycle approach explicitly allows for regulatory adaptation to scientific and technological uncertainties by revising earlier decisions as new information arises.

4.12 The diversity in both material type and usage of nanomaterials, the magnitude of scientific research that is needed and the increasing presence of nanomaterials in both Canadian and international products will require governments to work collaboratively. High levels of intra- and inter-governmental coordination will be needed.

4.13 The safe introduction of nanomaterials into trade and commerce will require a targeted research approach to both risk assessment and risk management. Additional human and monetary investments will be required to respond to the increasing knowledge and management demands being posed by nanotechnology.

4.14 As scientific research fills in the knowledge gaps, the decisions respecting the precautionary measures applied to nanoproducts can be revised.

4.15 Validated measurement methods and standards, along with nano-capable instrumentation, are needed in order to provide researchers with consistent methodologies and criteria for evaluating nanomaterial properties and behaviours.

4.16 Research is needed to identify those properties of a nanomaterial that enable it to elicit an adverse biological response. Further research is needed to identify appropriate regulatory responses regarding nanomaterial exposure.

4.17 Research, monitoring and surveillance (over the entire life-cycle of the material) will all need to be carried out in order to assess where and how these exposures are most likely to occur.

IN CONCLUSION

Nanomaterials and nanoproducts present exciting new opportunities for improving the quality of life of Canadians. At the same time, the scientific knowledge on which one can quantitatively assess the risks associated with these materials is limited, especially given the diversity of nanomaterials and their potential applications. Many of the uncertainties associated with risk assessment and risk management are not unique to nanomaterials, but have been present in the introduction of other new technologies, such as biotechnology and nuclear technology. These uncertainties have been managed in Canadian regulatory frameworks by taking a precautionary approach, giving priority to ensuring the safety of health and the environment.

The panel believes this is an appropriate approach to the introduction of this new technology. The existing Canadian regulatory approaches and risk management strategies are appropriate to this new challenge, provided that a greater investment is made in strategic research associated with the risk assessment of these materials, that attention is paid to addressing issues of classification, regulatory triggers and regulatory capacity, and that regulatory agencies coordinate their activities with each other, between federal and provincial levels of government and with the regulatory efforts in other countries.

Chapter 1 – Introduction

An assessment of what is known and not known about the health and environmental risks of nanotechnology is urgently needed in both the Canadian and international context. The safe and effective development of nanotechnology will depend on science-based regulation, which in turn will require a clear assessment of what is currently known about the risks of emerging nanotechnologies, and a plan of action for filling critical knowledge gaps. In the Canadian context, this means identifying what is needed to underpin good decision making, and how progress can be made through both domestic programs and international collaboration. In Canada, there are numerous channels through which domestic nanotechnology capacity is being created and, consequently, there is a need for attention to risk and public trust issues to complement and balance those activities. Indeed, there is a nanotechnology "buzz," both internationally and in Canada, among governments, and within academia, industry and non-governmental organizations. This is animated in part by a concern for the risks of nanotechnology and the regulatory implications of those risks.

Nevertheless, despite the growing interest in nanotechnology and concern regarding health and environmental risks, both within government and the public in general there is limited understanding of what exactly nanotechnology is — e.g., its characteristics and uses — and what risks it might pose. A broader understanding of nanotechnology is required if governments and the public are to respond appropriately and effectively.

CHARGE TO THE PANEL

To that end, the Council of Canadian Academies (the Council) has been asked by the Government of Canada to conduct an assessment on the health and environmental risks of nanomaterial properties with a view to providing government departments with a sound knowledge base from which to develop appropriate approaches to the regulation of nanotechnology.

The lead sponsoring department, Health Canada, along with other interested departments and agencies — including Environment Canada, the Canadian Food Inspection Agency, Fisheries and Oceans Canada and the National

Research Council of Canada — charged the following question to the Council of Canadian Academies:

> *What is the state of knowledge with respect to existing nanomaterial properties and their health and environmental risks, which could underpin regulatory perspectives on needs for research, risk assessment and surveillance?*

In particular, there is need to know why, and how, nanotechnology challenges Canada's existing regulatory system. Are there unique regulatory challenges presented by nanotechnology? What health and environmental risks are posed by nanotechnology and how significant are those risks? In short, is "small" really different?

The introduction of a new technology into society carries with it the potential to harm human health and the environment. For that reason, governments have established clear mechanisms, usually implemented through regulatory procedures based on the most up-to-date scientific knowledge, to ensure that any risks are appropriately managed so that the benefits that arise from these new technologies are not compromised. These mechanisms have been quite successful, if measured by the very significant overall improvement over the last century in the health of Canadians during a period of enormous technological innovation. At the same time, some substances originally characterized as safe have been subsequently found to present serious risks to health and the environment. Examples include polychlorinated biphenyls (PCBs), used as an insulator and later found to be a toxic organic pollutant that bioaccumulates; the herbicide Agent Orange, shown subsequently to release dioxins that are now known to have serious health effects; and the most recent example of bisphenol A, found in some plastics used in food and beverage containers and now suspected of having significant biological effects. These examples illustrate that regulatory mechanisms cannot guarantee that all risks can be eliminated.

This study by the Expert Panel on Nanotechnology (the panel) represents a comprehensive effort to address the current state of scientific knowledge regarding nanomaterials, and how that should guide the approach taken to steward the process through which nanomaterials are responsibly introduced into Canadian trade and commerce. As will become clear in the body of the report, nanomaterials present unique challenges to regulation.

OBJECTIVES AND SCOPE OF THE REPORT

This report focuses on the *scientific* and *technological* considerations (interpreted broadly) that in part define and can help to meet the challenge of developing

an appropriate regulatory regime for engineered nanomaterials. A substantial part of the report is therefore devoted to assessing what is known, and not known, about the health and environmental risks of nanomaterials. Moreover, the report will offer an account of the unique regulatory challenges presented by nanotechnologies in light of findings about the nature and behaviour of nanoscale materials more generally. The report includes discussion of some of the reasons why there are gaps in our knowledge — e.g., the lack of fully developed measurement tools, test methods and material characterizations — and thus indicates where to give priority in order to develop a more comprehensive account of the potential health and environmental risks of nanomaterials. Finally, given that regulatory approaches to nanomaterials will be needed in the short- to medium-term, the report assesses a number of other factors — including science and technology priorities, public awareness and engagement, and regulatory management — which could provide a firmer basis on which government and the public could generate policies and approaches to the regulation of nanomaterials.

The panel addressed a very specific charge from its sponsors, and has worked to ensure that this report addresses, to the extent possible, its various aspects. The panel recognizes that by the very nature of the charge, it has not addressed a host of issues that reasonably could be included in a broader agenda. It has not made specific recommendations regarding which regulatory tools would best manage the risks presented by nanomaterials. It has not provided a detailed, prioritized research agenda that would be most appropriate to develop Canadian capacity to innovate and regulate in this arena. It has not made specific recommendations regarding next steps for the sponsoring agencies, as it believes that the presentation of its conclusions in the form of findings most readily provides the sponsors with the necessary flexibility to take next steps following appropriate consultation and coordination. It has not considered the implications of the development of speculative "next-generation" nanomaterials and nanoproducts, especially those involving the convergence of multiple technologies. Finally, it has not abstracted its findings, specific to engineered nanomaterials, or to other new, potentially biologically and environmentally disruptive technologies.

PROCESS

The panel was convened in June 2007, and met with the lead sponsors of the study in July 2007 to clarify the mandate and confirm that the original charge to the panel was appropriate. The panel then held five face-to-face meetings, starting in August 2007 and ending in May 2008, and numerous meetings of

groups of panel members to summarize findings and prepare drafts of sections of the report.

The panel composition brought together leaders in the science of nanomaterials, nanomaterial risk assessment, social scientists involved in the ethics of risk management and regulation of substances, and private sector members involved in the development and commercialization of these novel materials. As part of its work, the panel initiated a call for evidence in fall 2007 through which stakeholder groups (see Appendix A) were solicited for comment on a set of key questions. The panel reviewed the results of this consultation, and incorporated that information into its deliberations and formulating its findings.

The panel began to identify the key findings in early 2008 over the course of its face-to-face meetings and developed a full draft report by April 2008. Following external report review, and subsequent revisions to address specific issues identified by the reviewers, the panel finalized its report and presented it to the sponsors in June 2008.

Chapter II – A Primer on "Nano"

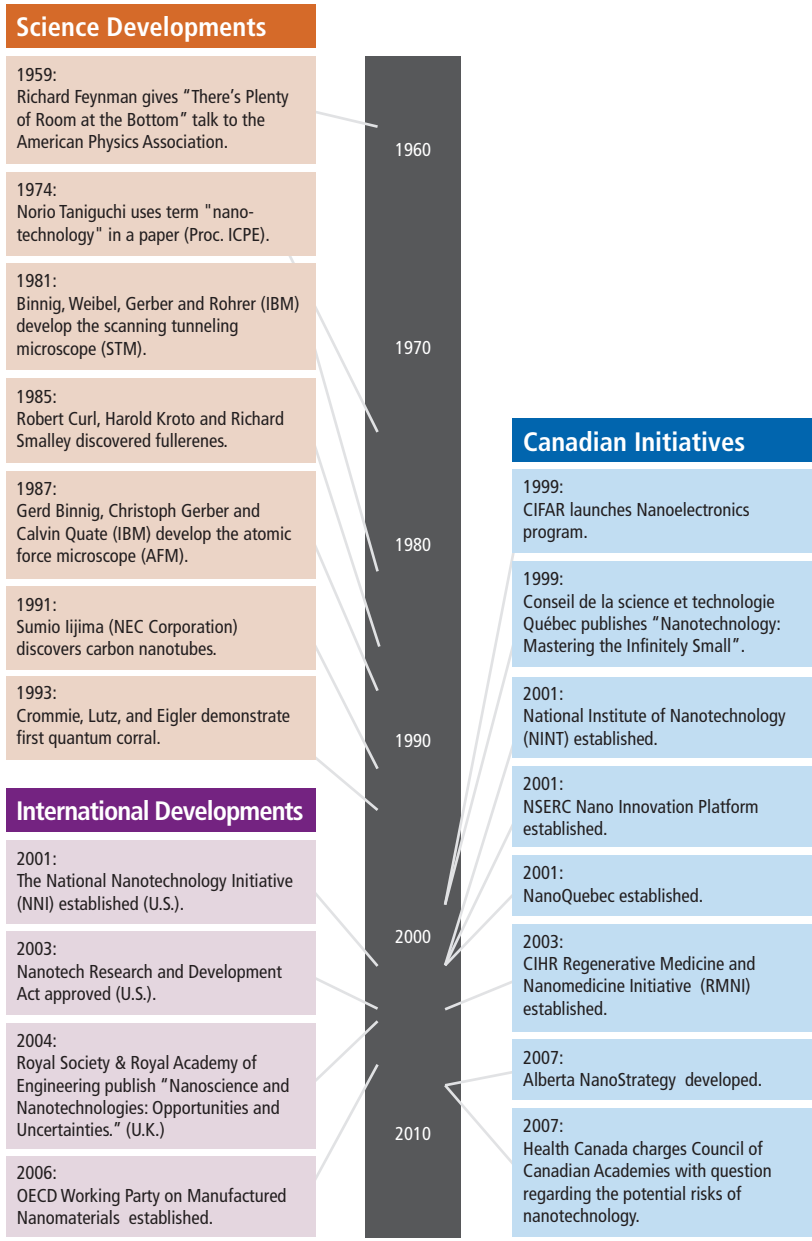
The definitions provided by the National Nanotechnoloy Initiative (NNI) in the United States provide an excellent starting point for a discussion on nano:

> *Nanoscience involves research to discover new behaviors and properties of materials with dimensions at the nanoscale which ranges roughly from 1 to 100 nanometers (nm). Nanotechnology is the way discoveries made at the nanoscale are put to work. Nanotechnology is more than throwing together a batch of nanoscale materials – it requires the ability to manipulate and control those materials in a useful way.*
>
> *(NNI, 2008)*

Scientists have been attempting to exploit nanoscale features for decades in the creation of polymers, for example, as well as in computer chips (UK-RS/RAE, 2004). In 1959, Richard Feynman gave a famous talk "There's Plenty of Room at the Bottom" where he invited scientists to enter a new field of physics, one that tackles the problem of manipulating and controlling things on an ultra-small scale (Feynman, 1960). Yet it was not until the mid-to late 1970s that scientists really coined the term "nanotechnology." By the mid 1980s, scientists had developed advanced microscopic techniques that would eventually enable the manipulation of individual atoms on a surface (Figure 2.1). The discovery of fullerenes in 1985, followed by carbon nanotubes in 1991, sparked a rise in commercial interest surrounding nanomaterials. Since the early 1990s, nanomaterials have been incorporated into numerous types of consumer products — e.g., sunscreens and cosmetics, stain and water repellent clothing, paints, anti-reflective and anti-fogging glass, and sports equipment. The recent development of new classes of nanomaterials, their "potential" exposure (via commercial products) to the general population and the environment, and some preliminary data on biological effects have yielded concerns about their safety.

In contrast to these engineered nanomaterials, it is worth noting that exposure to nanoparticles is hardly a new occurrence. Entities that exist on the nanoscale — in one form or another — have been with us for millennia. There are, for example, *naturally occurring* nanoparticles in salt spray from the ocean and forest-fire combustion. *Incidental* nanoparticles are also found in welding fumes, cooking and diesel exhaust (UNESCO, 2006). A Swiss Re report (2004) notes that "Nanotechnology was used years ago in some manufacturing techniques, yet industrialists were not really aware of it as such. When the first tires were made with carbon black in the 1920s to reduce abrasion by the road surface, no one realized that the improved tire quality was due to the enclosed ultra-small particles." Nanoparticles may have even played a role in cosmetics as early as

2000 B.C. by the ancient Egyptians. A technique used by the Egyptians when developing hair dyes has some shared elements with modern nanotechnology



(Council of Canadian Academies)

Figure 2.1
A Selective History of Nanotechnology

(Walter *et al.*, 2006). That is not to say that the Egyptians consciously and intentionally manipulated nanoscale materials, but it does mean that nanomaterials are not new in the environment. There is a history of using nanoparticles in various applications, however the impact of nanomaterials on health and the environment has been an untold story.

In formulating the charge to the panel, the sponsors requested that the focus of the report be on the scientific knowledge that would inform regulatory perspectives on those engineered nanomaterials that are already in the marketplace in one form or another, or whose entry into trade and commerce could occur over the next several years. In order to maintain that focus, this report does not discuss several other issues that might have been included in its mandate, such as the current state of knowledge of the health and environmental effects of *incidentally* introduced nanomaterials (e.g., ultrafine particle exposure in the workplace). That said, there is likely much to be learned about nanomaterials by studying incidental and naturally occurring nanoparticles. And conversely, the development of measurement tools to study engineered nanomaterials will likely result in an increased understanding of the behaviour and effects of incidental nanoparticles.

SOME BASIC TERMS AND CONCEPTS

It seems as though everywhere one looks these days, the term "nano" can be found. Electronics (Apple's iPod Nano MP3 player), cars (Tata Motors' Nano car) and cosmetics (L'Oreal's nanosomes) have adopted the term to advertise their unprecedented sizes. Nutritional substitutes boast the use of *nanotechnology* in their fabrication processes to create "new and improved" formulations. Companies promote the use of *nanomaterials* in everyday items such as sports equipment or clothing. Household items offer promises of reduced daily maintenance requirements due to the incorporation of *nanoparticles* into various components. But along with the novelty and promises of "nano" have come warnings of unexpected consequences should this new technology be allowed to progress unchecked. These concerns have been voiced not only by the general public but also by scientists (Scheufele *et al.*, 2007). As a result, governments around the world are being called upon to develop regulatory frameworks that respond to these polarized views of nanotechnology.

Glossary of Key Terms Used in this Report

Nanoscale: A size range going from approximately 1 nm (10^{-9} m) at the lower end to 100 nm at the upper end.

Nanoparticle: A particle that is approximately between 1 nm and 100 nm in all three dimensions. The lower limit in this definition (approximately 1 nm) has limited physical significance but is introduced to avoid single and small groups of atoms and molecules from being designated as nanoparticles. The upper limit (approximately 100 nm) does not imply that particles with larger dimensions might not be of significance from a health or environmental point of view. Although the term "nanoparticle" is often used to include particles that are only nanoscale in one or two dimensions, in this report such particles are defined as "nanoplates" and "nanotubes" or "nanowires," respectively.

Nano-structured: A material that has a structure comprising contiguous elements with one or more dimensions in the nanoscale (excluding any primary structure associated with component atoms or molecules).

Nanomaterial: A material having one or more external dimensions in the nanoscale or a material that is nano-structured.

Nanotechnology: The intentional manipulation of matter at the nanoscale, to create materials and products with nanostructure-dependent properties. The term nanotechnology encompasses the technologies used to manipulate and characterize nanostructures, as well as the resulting materials and products.

Nanoproduct: Any product that incorporates nanotechnology. Nanoproducts include products using nanoscale features, like semiconductor chips; products coated with nanometre-thick films, such as some stain resistant textiles; and products containing engineered nanoparticles, like some sunscreens.

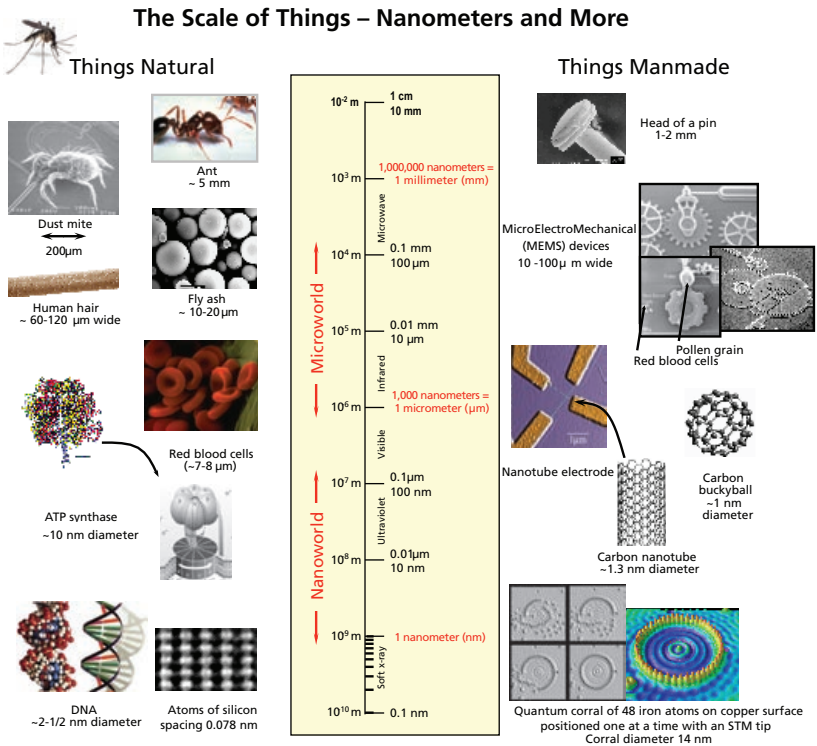
Engineered nanoparticle: A nanoparticle that has been intentionally produced in a manufacturing process. This definition includes naturally occurring nanoparticles that have been processed in some way prior to being supplied or used as a commercial product (e.g., nanoclays, which exist in nature, but are processed to extract and use their constituent nanoparticles).

Ultrafine particle: A nanoparticle that occurs naturally, or the unintended by-product of a process.

Aggregate: A collection of particles that are strongly bonded or fused together, where the resulting external surface area may be significantly smaller than the calculated surface area of the individual component particles.

Agglomerate: A collection of loosely bound particles or aggregates, or mixtures of the two, where the resulting external surface area is similar to the sum of the surface areas of the individual components.

There exists an inherent conundrum when it comes to defining and regulating "nano." In order for policy development to occur, regulators need to know what exactly "nano" is, so they can tell its users/producers how to safely and productively work with the new materials and products that will emerge. This requires an awareness of the types of research and products being developed. Scientists in turn (both from an academic and an industrial standpoint) may not know how or when to report such activities or products since there is no rigorously established set of definitions for what constitutes nanotechnology, nanoproducts, nanomaterials, etc. Although a number of organizations have developed terminologies associated with nanotechnology, there is considerable debate and there is no overall consensus on terms and definitions. The terms and definitions provided in the Glossary of Key Terms on page 24 draw on recent guidance documents and publicly available specifications issued by the British Standards Institute (BSI) in the United Kingdom (BSI, 2007).



(DOE, 2006)

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Figure 2.2

Graphical depiction of the macro to nano-scale

A nanometre is one billionth of a metre (10^{-9} metre). To get some perspective, consider that the width of a human hair is somewhere between 60,000 nm and 120,000 nm, a red blood cell is about 7,000 nm across, a mycoplasma bacterium is in the range of 200 nm, a typical flu virus falls between 80 nm and 120 nm, large proteins are 5 nm to 10 nm, DNA is approximately 2.5 nm in diameter and an atom of gold measures about 0.14 nm (Figure 2.2). Various things exist that are measurable on the nanoscale; that is to say they fall within a size range of approximately 1 to 100 nm in size. Some of these objects are naturally occurring — cellular components, protein assemblies and DNA — while others have been intentionally engineered — e.g., nanotube electrodes and quantum corrals. Then there are those materials that have always existed in nature, yet only recently have scientists developed the ability to manufacture them under controlled conditions — e.g., carbon nanotubes (Box 2.1) and Buckminsterfullerenes.

Nanotechnology has been defined as the intentional manipulation of matter at the nanoscale to create materials and products with nanostructure-dependent properties. The term nanotechnology encompasses the technologies used to manipulate and characterize nanostructures, as well as the resulting materials and products. Consequently, many diverse technologies come under the nanotechnology umbrella — spanning electron microscopes to composite materials fabrication to cosmetics manufacturing. Nanotechnology has refined traditional synthetic processes in order to make materials with a known size range in lieu of materials comprised of an unknown distribution of particle sizes. In this way, the technology being used is not "new" but the materials that are being produced may be.

Nanomaterials have been described as those materials having one or more external dimensions in the nanoscale or a material that is nanostructured.[2] Nanomaterials can exhibit properties that differ from those of the same material with larger dimensions and can be categorized by how many of their external dimensions fall within the nanoscale. For example, *nanoparticles* have three dimensions in the nanoscale, nanowires have two dimensions and nanofilms have one. Thus all nanoparticles are nanomaterials but not all nanomaterials are nanoparticles — e.g., an ultrathin film is a nanomaterial but not a nanoparticle.

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[2] See "Glossary of Key Terms" for definition.

Box 2.1 — Carbon Nanotubes (CNTs)

Carbon blacks (amorphous carbon nanoparticles) have been used for decades in paint pigments and for reinforcement in rubber (tires) and plastics. But recently, a new class of carbon-based nanomaterials — carbon nanotubes — has emerged as one of the most promising engineered nanomaterials discovered in the late 20th century.

What they are:

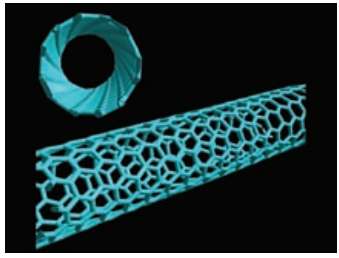
Carbon nanotubes are tubes formed from carbon atoms, which may be as small as a nanometre in diameter and hundreds or thousands of nanometres long. A single-walled carbon nanotube is a one-atom thick sheet of graphite (called graphene) rolled up into a seamless cylinder with a diameter on the order of one nanometre. Where multiple sheets of graphene are arranged into concentric cylinders, the result is a multi-walled carbon nanotube. By varying the number of walls, the way the carbon atoms are arranged and the chemicals attached to the nanotubes, a vast array of different nanotube types may be produced — all having different properties.

What they do:

Carbon nanotubes exhibit extraordinary strength for their weight, can be either extremely efficient conductors of electricity or semiconductors depending on their form — and conduct heat exceedingly efficiently.

Where they are used:

The automotive, aerospace, household appliances, telecommunications equipment, sporting goods and medical industries have been investigating the use of carbon nanotubes in their products.



For more information see: (Baughman *et al*., 2002) and (Sinnott and Andrews, 2001).

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Nanoproducts are those items that incorporate nanotechnology. This could be via the integration of nanomaterials — e.g., titanium dioxide (Box 2.2) — into sunscreens, the use of a nanometre-thick film to render textiles stain resistant or the integration of carbon nanotube transistors into electronic devices. While nanoproducts incorporate the use of nanotechnology, not all of these objects will necessarily contain nanoparticles. Thus, a subcategory of nanoproducts would be those products containing engineered nanoparticles.

Engineered nanoparticles are those that have been intentionally produced during a manufacturing process. This definition includes naturally occurring nanoparticles that have been processed in some way prior to being supplied or used as a commercial product — e.g., nanoclays (Box 2.3), which exist in nature, but are extracted and subsequently processed in order to use their constituent nanoparticles. The Woodrow Wilson International Center for Scholars' Project on Emerging Nanotechnologies (PEN) maintains an inventory of nanotechnology-based consumer products currently on the market (PEN, 2007a). Most products in the inventory satisfy the following criteria:

- They can be readily purchased by consumers;
- They are identified as nano-based by the manufacturer OR by another source; and
- The nano-based claims for the product seem reasonable.

(David Hawxhurst, Woodrow Wilson International Center for Scholars)
Reproduced with permission from David Hawxhurst.

Figure 2.3
A Sample of Existing Nanoproducts

As of April 2008, the nanotechnology consumer products inventory contained over 600 products or product lines (Figure 2.3). These products are produced by 305 companies located in 20 countries.

Box 2.2 — Nano Titanium Dioxide (TiO_2)

Titanium is the ninth most common element in the earth's crust and is present in a variety of naturally occurring minerals. Researchers are looking at nanoparticle titanium dioxide (TiO_2) to create more efficient solar cells, better implants, self-cleaning and antibacterial products, and numerous other applications.

What it is:

Nano TiO_2 particles may consist of one of two crystal structures — anatase or rutile TiO_2 — or may be a mixture of the two. In large quantities nano TiO_2 forms a low density white powder.

What it does:

TiO_2 nanoparticles are transparent to visible light, but opaque to ultraviolet (UV) light, making them ideal for use in sunscreens and stain/wear resistant textiles. Depending on their structure, they generate free radicals under UV light, making them an attractive antimicrobial agent.

Where it is used:

TiO_2 nanoparticles can be found in household appliances (refrigerators, hairdryers and curling irons), sports equipment (golf clubs), kitchenware (cookware and storage containers) cosmetics, and over the counter drugs such as sunscreens. It is used on surfaces and in water as a germicide/purifying agent, and is the active component of some self-cleaning glass products.

For more information see: (Chen and Peng, 2007)

Reproduced with permission from Alex Parlini, Project on Emerging Nanotechnologies (PEN).

WHAT IS FUNDAMENTALLY DIFFERENT ABOUT "NANO?"

To understand how nanomaterials will behave in biological and environmental systems, it is necessary to identify and understand the characteristics of these materials that make them unique. By definition, the distinguishing characteristic of a nanomaterial is size. At a more fundamental level, however, it is not necessarily the size of the material that is of interest but rather its properties. Carbon provides a good example of how the property of a material changes as a function of its size. In bulk,[3] carbon exists in various forms — e.g., graphite (well known in pencil lead) and diamond. The vastly different bulk physical and chemical properties are related to small differences in the positions of carbon atoms and thus the nature of the chemical bonds between the carbon atoms. Rolling up a sheet consisting of a single layer of carbon atoms (graphene) leads to the formation of carbon nanotubes. These one-dimensional objects surpass all known materials in strength-to-mass properties. Graphene has extraordinary electronic properties as well. Reducing the scale even further leads to soccer ball-shaped structures of carbon about one nanometre in diameter (Fullerene C_{60} or Buckminster Fullerence), again with very different properties — e.g., the electronic energy levels resulting from the formation of this nanomaterial allow for very efficient oxidation reactions. These different forms of carbon have vastly different properties as a result of the dimension of the material and the nature of the chemical bonds. All can be found naturally (e.g., in soot in your chimney) and/or produced artificially in large quantities.

The properties of nanomaterials can be very diverse due to the many possible permutations of structure, chemical composition and shape. For example, nanoparticles composed of the same atoms — such as carbon — can be arranged into different sizes, shapes and chiralities.[4] They can be further modified with different surface chemistries. The family of carbon-based nanoparticles could have more than 100 different physical and molecular structures and properties. In contrast to macroscopic objects (bulk materials), small changes in the structure of nanomaterials can lead to large changes in their properties.

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[3] Bulk material is a substance that is in large enough form so that it does not possess properties that one can directly relate to size and shape of nanoscale features.

[4] Chirality is a symmetry feature of certain molecules referring to forms that bear a relationship to one another analogous to a left and right hand. Chirality affects several optical and biological properties of molecules.

Box 2.3 — Nanoclay Composites

Nanoclays are being used as additives to polymers in order to take advantage of their improved heat resistance, reduced permeability and flame retardance.

What they are:

Nanoclay composites are nanometre-thick clay plates derived from naturally occurring clays. They are typically modified, layered silicates (minerals, such as mica, that are composed of silicon and oxygen) and are incorporated in small amounts in polymers.

What they do:

Nanoclay composites modify the properties of polymers when used as an additive, including reducing the rate at which oxygen and other gases will pass through a given thickness of plastic. They can also act as a flame retardant.

Where they are used:

Nanoclay composites are currently used in the car manufacturing industry (Toyota timing belt covers, Mitsubishi engine covers, GMC step assistant components, GMC and Chevrolet doors, and Honda seat backs). Mitsubishi Gas Chemical and Nanocor have also developed nanoclay composites for plastic bottle applications.

For more information see: (Gao, 2004)

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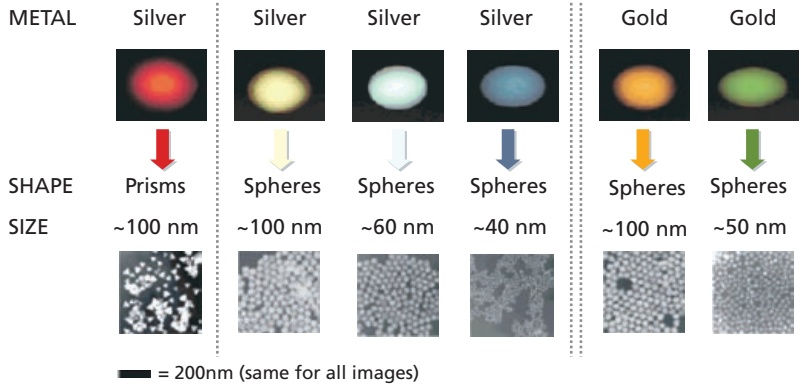
Nanomaterials sit at the juncture of what traditionally has been considered as two distinct domains — "molecular" structures and "physical" structures.[5] While this will be elaborated upon in Chapter III, it is important to recognize that there is, in fact, a continuum from molecular to physical structures. What distinguishes nanomaterials is that they possess properties of both. This is especially important when trying to think about possible hazards. Given the convergence of molecular with physical characteristics, the effects of

[5] The term "physical structure" is used in this report to encompass properties such as dimension, aspect ratio, size and crystal structure.

nanomaterials may be related to their molecular attributes, their physical attributes or both. The current lack of understanding regarding the hazards of nanomaterials arises in part due to the two-sided nature of this phenomenon.

This convergence of the molecular and the physical, while it is a fundamental distinguishing feature of nanomaterials, is not a new concept. Biology has presented many examples of nanoparticles with defined molecular structures — e.g., proteins, DNA and biological membranes. These are all, at one level, physical structures that also possess defined molecular structures. In these cases, it is well-known that small changes in the molecular structures can have profound effects on physical characteristics. This can in turn lead to significant differences in biological behaviour — e.g., DNA mutations and their impact on gene expression and cell signaling, amino acid changes and their effect on protein misfolding. These biological occurrences may provide insights for scientists into important characteristics or features of manufactured nanomaterials.



(Rosi and Mirkin, 2005)

Figure 2.4

Dependence of Optical Properties (e.g., colour) on Material, Size and Shape

The Physical Aspects

Nanomaterials possess interesting and unique size- and shape-dependent physical properties. Due to this relationship, academic and industrial researchers have access to a large number of precursors for synthesizing them. As compared to traditional methods of creating precursors, one can now simply change the geometry of the nanomaterials to produce something with a desired property. This relationship can be understood as arising from the following physical effects.

Breakdown of scaling laws and "quantum effects": The properties of matter arise from the behaviour of the atomic components of a system. For example, gold (at the same temperature and pressure) remains in its solid form and has the same general properties whether it exists as a large statue, a small coin or a tiny filling in a tooth. Within the macroscopic realm, the factors that govern gold's physical properties are independent of size. The properties of nanomaterials, however, can be fundamentally different than those of macroscopic versions of the same materials. As the size of an object approaches the nanoscale, the electronic nature of that substance changes. This change in the internal electronic properties (i.e., the separation of electron energy levels) alters the overall physical and chemical properties. In these cases, it is said that quantum mechanical effects start to dominate.

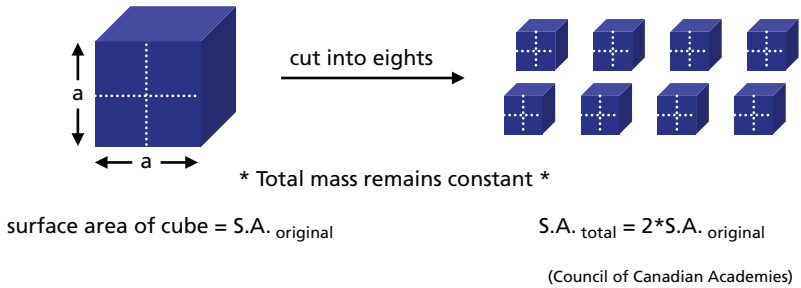


Figure 2.5
Increase in Surface Area and Particle Number for the Same Mass and Volume

This property can be illustrated by the relationship between nanoscale gold or silver (Box 2.4) and their particle size. Gold and silver in bulk form are shiny, yellow or grayish metals. When their dimensions fall in the nanoscale range, quantum mechanical effects lead to a fundamental change of their optical properties — i.e., their colour becomes a sensitive function of size (Figure 2.4). These size-dependent optical properties are the basis for some of the stained glass windows in medieval cathedrals. This feature of nanoscale gold

or silver allows them to be used in biomedical applications, such as sensors and drugs (cancer treatment by gold nanoshells), photovoltaics, display and illumination technologies. These properties would not have been predictable based on an extrapolation from the macroscopic properties of the bulk metals. A further example of the breakdown in scaling due to quantum mechanical effects is electrical resistance. The resistance in a wire scales smoothly in an inverse fashion with the cross-sectional area of the wire. If the cross-sectional area, however, is only a few atoms wide, resistance becomes quantized (step-like), which becomes relevant in applications based on nanoelectronics.

Increase in the surface to volume ratio: Cutting a macroscopic cube of material into smaller cubes results in an increase of the surface to volume ratio of the material. As an example, a cube that is one centimetre (cm) in all dimensions, when cut into smaller cubes, each being a half centimetre in dimension, results in the formation of eight cubes where the total volume and mass of theses cubes remains unchanged. The total surface area represented, however, is double the surface area of the original cube (Figure 2.5). If this same one centimetre cube were divided into "nanocubes" — i.e., cubes where each dimension was approximately one nanometre — the resulting 10^{21} cubes would have a total surface area of approximately 6000 m^2 (approximately four hockey rinks). In this case, the surface to volume ratio goes from 6 to 6 x 10^7 cm^{-1}, an increase of 10 million! Similarly, if a one micrometre (μm) particle is cut into one nanometre-sized particles, the surface to volume ratio increases by a factor of 1,000, the number of particles increases by one billion. Nanoparticles thus have a vastly increased surface to volume and surface to mass ratio when compared to larger particles. Note that the total volume and the total mass have not changed.[6] Since many chemical reactions occur at surfaces, it stands to reason that the chemical reactivity is thus much higher for nanoparticles or nanomaterials than for an equivalent mass of larger particles. In other words, the chemical reactivity per unit mass of nanomaterials is thus dramatically changed. Nanosilver is an example where increased surface area results in enhanced reactivity. Similarly, nanogold also shows an increased surface reactivity due to increased surface area. However, in contrast to silver, nanogold between 2 nm and 50 nm becomes a highly effective, catalytic, carbon monoxide converter, with important applications in car exhaust systems (Cortie, 2003). This enhanced reactivity happens only within a very narrow size distribution due to quantum effects. More generally, the enlarged surface area (silver) and the enhanced surface reactivity (gold) of nanomaterials play an important role in the emergence of new properties (such as their catalytic effects).

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[6] Note that this geometric scaling of the surface to volume ratio is approximately 1/d where d is the dimension of the system.

Box 2.4 — Nanosilver

Silver has been used for the treatment of medical ailments for millenia due to its natural antibacterial and antifungal properties. Nanosilver particles have extremely large relative surface areas, increasing their contact with bacteria or fungi as well as the release of antimicrobial silver ions, and thus vastly improving their bactericidal and fungicidal effectiveness.

What it is:

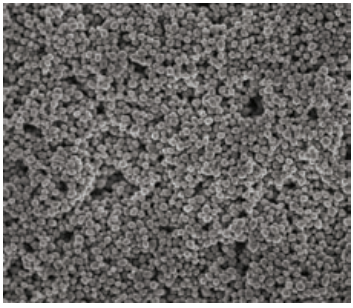
In many commercial products, nanosilver is present as a suspension of nanosilver particles. Recently, manufacturers have also begun incorporating nanosilver particles onto the surfaces of products, and into composite materials.

What it does:

Silver suspensions have long been known to be potent antimicrobial agents that interfere with microbial, but not mammalian, cell membranes. Through a variety of mechanisms, silver kills bacteria and fungi.

Where it is used:

Nanoscale particles are claimed to be found in upwards of 140 consumer products on the market today. Examples include water treatment devices, food storage containers, cosmetic products and disinfectant sprays.



For more information see: (Allsopp *et al*., 2007)
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In addition to changes in reactivity, the increased surface to volume ratio of nanomaterials can lead to changes in the thermodynamic properties of a material (e.g., melting temperature). These new properties arise from changing factors such as the number of adjoining neighbours or the bonding nature of the atoms. For example, tin, in bulk, has a melting point of approximately 230ºC whereas nanotin (approximately 20 nm in diameter) melts at a substantially lower temperature. This allows it to be used to replace bulk lead in soldering applications.

The dynamic nature of nanomaterials: Nanoparticles can exhibit very different surface chemical composition or internal atomic (crystallographic) structure compared to their bulk or alloy composition. This is a result of the very different arrangement of atoms at the surface of the bulk material. Different facets or surface orientations can alter the chemical reactivities, solubility, agglomeration properties, binding kinetics or surface potentials of a nanomaterial. The latter is relevant to how ions behave in solution (e.g., diffusion properties) or how biological molecules interact with the "nano" surface. Because these properties can change as nanomaterials are introduced into different environments throughout their life-cycles, this leads to potential time-dependence in specific properties such as chemical reactivity.

In short, sufficiently reducing the size of a material can result in changes to its optical, electron transport and thermodynamic properties as well as to its chemical reactivity. In contrast to the macroscopic scale, even small changes in the size of a nanomaterial can lead to dramatic property changes. Small structural changes can arise from interactions with the environment (e.g., due to chemical reactions or UV light exposure), resulting in the properties of some nanomaterials being very dynamic and possibly transient. As an example, nanoparticles that lose part of their surface coating can agglomerate or become highly reactive. When controlled, one can envision using this property as a localized anti-cancer drug; on the other hand it could pose a challenge in assessing environmental or biological impact if uncontrolled.

Loss of predictability/theory/modelling: There exist well-established and validated techniques for calculating the properties of molecules or bulk materials (larger than about 100 nm in dimension). These, however, cannot necessarily be extrapolated down to nanomaterials or nanoparticles. In terms of dimensions, nanomaterials are located in the size continuum between molecules and bulk materials. Calculating, modelling and predicting properties of nanomaterials is very challenging. This is due to the fact that commonly used approximations for the macroscale break down when applied to the

nanoscale. Modelling tools in traditional materials science are based on system-scales far too large to be applicable to nanomaterials. On the other hand, quantum modelling — which deals with appropriately-sized systems for the nanoscale — is limited in its ability to predict things such as chemical reaction rates or pathways. As such, it cannot be reliably applied to predict many relevant nanomaterial properties. The fundamental challenge is that modelling the properties/behaviours of nanomaterials is a many body problem. It surpasses current modelling capabilities that work for most modest-size chemicals but are not sufficiently large to use the tools of statistical mechanics that work accurately for purely macroscopic properties.

The Biological Aspects

Biological systems are naturally organized into specific sizes and shapes. Organs are composed of cells aggregated together into a functional unit. Within the cell, are biological molecules, organelles and structures that keep the cell alive and functioning properly; cells have all types of functions and chemistries. Biological systems communicate with one another by restricting and permitting specific molecules to go in and out of a cell via membranes and channels. Molecular sizes and shapes and non-covalent forces dictate interactions of foreign molecules/structures with cells, tissues and organ systems. Within the biological context, the behaviour of nanostructures in biological systems relates to their size, shape and surface chemistry. Current literature suggests that the unique biological properties of nanomaterials stems from the relationship of their physical and chemical properties with (1) biological transport, fate and kinetics, (2) portals of entry, and (3) cellular response (e.g., protein signaling cascade). Compared to the understanding of the optical, electronic, and magnetic properties of nanomaterials, there has been only limited research that focuses on obtaining a clear understanding of the interactions between biological systems and the physical and chemical properties of nanomaterials.

The properties discussed above show the remarkable ability of nanomaterials to exhibit novel characteristics as a result of their reduced size. Having examined some of the fundamental differences in the *physical* aspects of nanomaterials, a second question can be asked: Do these changes in physical properties result in novel *biological* properties or behaviours of nanomaterials? Some recent findings have shown that the transport and interactions of nanoparticles with biological systems are related to their physical dimensions.

In examining the behaviour of nanomaterials in biological systems, consideration is most often given to the characteristics that govern the following properties:

- Absorption — how readily can the particle cross biological barriers (e.g., skin, cell membranes and blood-brain barrier);
- Distribution — how easy is it for the particle to travel to other locations and what organs do the particles tend to target;
- Metabolism — does the material get broken down into further constituents; and
- Excretion — do the particles get excreted or do they accumulate in various tissues.

This ADME framework provides a structure that can be used to address the potential biological effects of nanomaterials.

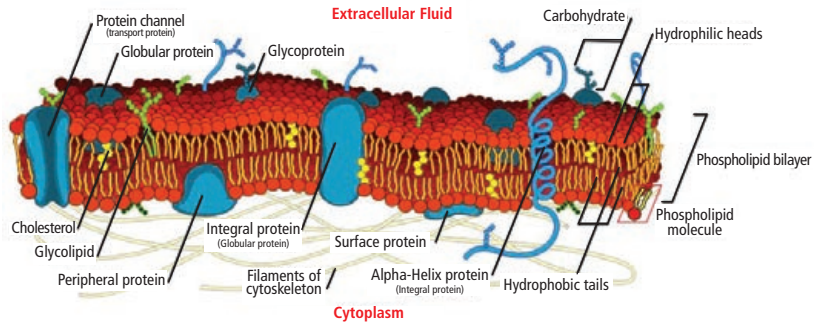

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Figure 2.6
Graphical Depiction of the Cell Membrane

The body contains a variety of protective barriers that prevent substances from being able to access its more vulnerable components. These include everything from the skin to the blood-brain barrier (a membrane that filters non-productive chemicals from productive ones as blood flows to the brain). These barriers are composed of various types of cells, each of which has its own structure and function. Together, they govern every process that occurs within the body. The primary defense mechanism of a cell lies in its membrane structure and function (Figure 2.6). In order to cross from the outside to the inside of a cell, a material must pass through the cell membrane. In mammals,

this is a multi-layered lipid structure which dictates what may, and may not, enter the cell. Controlled permeation of the cell membrane can occur in either an active fashion (where the cell must expend energy) or a passive fashion (such as diffusion).

In all of these cases, the ability of a substance to pass through the membrane relies upon its physicochemical properties. One of the primary concerns regarding exposure to nanomaterials is their potential (due to their reduced size) to usurp traditional biological protective mechanisms. This in turn would provide them access to sensitive cellular processes that could result in enhanced toxicological effects.

Size- and Shape- Dependent Effects in Cells: Evidence suggests that the transport of nanoparticles into and out of the cell is dependent on size (Chithrani *et al.*, 2006). Looking at the uptake of sub-100 nm metal particles, Chithrani *et al.* showed that both size and shape influenced the rate of uptake and resultant cellular concentration (Chithrani *et al.*, 2006, Chithrani and Chan, 2007). In these studies, gold nanoparticles that had diameters in the 40 nm to 60 nm range were taken up at the fastest rate and highest concentration in comparison to other sub-100 nm nanoparticles, while smaller nanoparticles (1 nm to 40 nm) were removed from the cells at a faster rate than those that were larger. This size-dependent process was demonstrated using immortalized cell lines.[7] In another example, Nabiev *et al.* (2007) reported that quantum dots (Box 2.5) were capable of exploiting the cell's transport machinery, resulting in delivery to specific intranuclear destinations. They showed that the smallest quantum dot can enter the nucleus and bind with nuclear structures while larger quantum dots cannot. Additionally, Jiang *et al.* (2008) showed that the coating of gold and silver nanoparticles with cytotoxic antibodies can kill cells in a size-dependent process. Further study will be needed to determine if this process is universal among nanoparticles or if the cytotoxic effect is a result of the chemistry of the nanoparticles.

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[7] Immortalized cell lines are commonly used by researchers to study the effects of a substance on cellular pathways. They are cells harvested from various species, organ types, etc. that are cultivated in a laboratory. Immortalized cells are capable of extended proliferation while maintaining the identical genotype and tissue markers of the parental tissue, thereby allowing for the use of consistent material throughout a research project.

Box 2.5 — Quantum Dots

Quantum dots are nanoparticles where the physical and chemical properties are governed by quantum physics.

What they are:

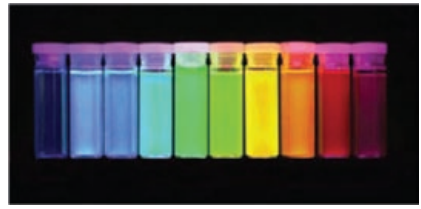
Quantum dots are semi-conductor nanocrystals — often made from cadmium selenide — where all three dimensions are small enough to influence the normal behaviour of electrons within the material. This leads to a range of unusual properties that are dependent on the size of the particles. Quantum dots are typically a few nanometres in diameter.

What they do:

Quantum dots absorb and emit different wavelengths of light very efficiently, depending on their size. Under utraviolet light, they fluoresce extremely brightly, and do not degrade as readily as chemical dyes.

Where you find them:

Quantum dots are currently sold as nanoparticles. In the future, quantum dots may be useful in the development of electronics (as components in electronic circuits), light emitting diodes, solar panels (to improve the transfer of solar energy), and medicines (as probes or contrast agents for imaging and diagnostic applications).



For more information see: (Alivisatos, 1996) and (Michalet *et al*., 2005)
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Size- and Shape- Dependent Effects in Organisms: While studies such as those described above are useful tools in understanding cellular responses, they are limited in their capacity to elucidate what happens upon the introduction of nanomaterials at the systems level. Thus, effective management of nanomaterials (or any substance) requires an understanding of what will happen at the organismal level of the plant or animal.

Researchers have therefore begun examining the effect of nanomaterials in living mammals. Recent studies by Balogh *et al.* (2007) looked at how gold nanocomposites[8] distribute in mouse tumour models. Their results showed that nanocomposites of different size and/or surface charge had high levels of uptake (selective targeting) to certain organs even without specific targeting entities placed on their surfaces. Geng *et al.* (2007) recently examined the effect of shape by comparing the transport and trafficking of flexible, filament-shaped nanoparticles with nanospheres of similar chemistry in rodents. The results showed that longer fibres have a longer persistence and slower cellular uptake than both shorter filaments and spherical particles of the same chemistry (Geng, *et al.* 2007).

One of the primary areas of research for quantum dots is the diagnosis and treatment of human disease. However, if the quantum dots, once delivered to the body, are not capable of being excreted or biodegraded to harmless by-products, their toxicity could potentially increase. Choi and co-workers have recently looked at the renal clearance of quantum dots in rodents. Results showed that quantum dot nanoparticles that were smaller than 5.5 nm resulted in "rapid and efficient urinary excretion and elimination of the quantum dots from the body" (Choi *et al.*, 2007).

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[8] Nanocomposites are combinations of materials that form a solid composite material, where one or more components are nanomaterials. For instance, a suspension of nanoparticles in a polymer to give a high performance material would be a nanocomposite.

Box 2.6 — Nanocerium oxide (ceria)

Cerium is the most abundant of the rare-earth elements and has high electrical conductivity, reactivity, and softness. Many commercial applications of nanoscale cerium oxide (ceria) are under investigation.

What it is:

Nanoceria consists of cerium oxide particles typically 5 to 40 nm in diameter.

What it does:

Nanoceria is an efficient catalyst, and is expected to show a range of interesting electrical, magnetic, optical and biological properties. Recent research has also suggested that nanoceria may have promise as the basis for treating diabetes, Alzheimer's disease, strokes and various eye-disorders.

Where it is used:

Nanocerium oxide particles are added to diesel fuel to increase combustion efficiency.

For more information see: (HEI, 2001)
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All of these studies suggest that size and shape can dictate the bio-distribution, clearance, and behaviour of the nanoparticles in a living organism. Thus, similar to the *in vitro*[9] experiments, it appears that the behaviour of nanoparticles in more complex *in vivo* systems can be dependent on size, charge and shape. Many researchers are trying to establish a trend relationship between the nanoparticle geometry and *in vivo* behaviour, making this a particularly active area of research. Although more investigation is required, preliminary studies suggest that the transport, accumulation, kinetics, and subsequent molecular effects of nanoparticles are both size- and shape- dependent.

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[9] *In vivo* studies involve tests performed on a living organism, such as a controlled clinical study involving human test subjects while *in vitro* are those carried out on cells or tissues that have been cultured in petri dishes and occur outside of the body.

The Ecological and Environmental Aspects

Nanomaterials are being introduced into a breadth of products, increasing the likelihood that they will find their way into the environment at some point of their life-cycle (e.g., during manufacturing, consumer usage, disposal, or recycling). Nanomaterials may be released (either incidentally or intentionally) into the air, water, or land, depending on the type of nanomaterial and its use. Similar to chemical substances, nanomaterials may move in the environment through biological pathways (e.g., ecological food webs)[10] and abiotic paths.[11] The circumstances under which nanomaterials may be released from products are not currently well-understood. However, based on past experiences with chemical substances, it can reasonably be anticipated that some nanomaterials that enter the environment may be transported by environmental pathways and during this transport, may be transformed, accumulated in specific media and enter ecological food webs. These environmental pathways may allow nanomaterials to adversely affect environmental receptors such as ecosystems, and may also allow for indirect human exposure pathways — in drinking water, for example.

Convergent Technologies

In the current state of research, scientists are essentially studying and elucidating how biological molecules and systems organize themselves into a specific molecular hierarchical structure and how these hierarchical structures dictate the function. For example, a number of viruses are essentially composed of a few proteins organized into a sub-200 nm system that contains genetic materials to allow them to multiply. The proteins on the virus affect how they interact with a specific cell. As nanomaterials become more sophisticated (where multiple functions are built into a system at the nanoscale by assembling different nanoparticles into one unit), scientists are starting to use information obtained from biological systems to help in their design. A convergence

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[10] Ecological food webs describe the relationships among species within a given environment that feed on each other. An example of an ecological food web is found in an ocean system. Phytoplankton are at the base of the food web, creating energy from sunlight and acting as food for the next level of the food chain, which becomes a food source for another and so on. This ecosystem focuses on how substances might move from their initial release into all components of it, through biological transfer.

[11] Abiotic paths include the transport and fate of substances in the environment that do not involve biological organisms. An example is the release of particles into the air that are transformed by sunlight, or the migration of a substance from groundwater to surface water.

between nanotechnology and biology is emerging to build multi-functional nanomaterials that could act as both a diagnostic and therapeutic system. This will be an important growth area in nanomaterial research in the next several decades. To enable these developments, engineers have already built machines that can synthesize biomolecules, such as peptides, that are used as building blocks for creating multi-functional nanomaterials. A question that arises from this convergence is how to evaluate a multi-functional nanomaterial when it can (1) behave like the individual nanoparticles, (2) behave differently based on the interactions of the nanoparticles with each other, and (3) behave differently based on the effect of biological molecules with the nanoparticles, or a combination effect from each component.

THE IMPORTANCE OF NANOMATERIALS

Throughout history, humans have defined specific "ages" by the dominating material of its time (e.g., the Stone Age, the Iron Age and the Silicon Age). In his 1986 Nobel Lecture, Heinrich Rohrer took this notion a step further and suggested that it was not merely the existence of the material, but rather the ability to manufacture and utilize these materials that was the major accomplishment (Rohrer and Binnig, 1986). The ability to manipulate materials on the millimetre scale resulted in the development of the steam engine and ushered in the industrial revolution. Once scientists discovered how to work with materials on the micrometre scale, society saw the introduction of products based on miniaturized transistors, such as computers, calculators, and cell phones, thus initiating the "silicon" revolution. Therefore, Rohrer argued that as researchers develop and refine their ability to produce materials at the nanoscale, society is being introduced to a range of new products, and today can be said to be experiencing the beginning of the nanotechnology revolution.

Box 2.7 — Commercial Activity in Canada

Commercial activity in nanotechnology has been limited in Canada but there are signs that nanotechnology revenues, research and development (R&D) expenditures, and venture capital investment are on the rise. According to the most recent statistics available, 88 Canadian firms (of 11,800 surveyed in a mandatory survey) reported involvement in nanotechnology. Thirty of those 88 firms (34 per cent) were based in Ontario; 25 firms (28 per cent) were in Quebec; 19 firms (21 per cent) were in British Columbia; and 12 firms (14 per cent) were in Alberta. All but eight of those firms indicated that they were active in R&D, and more than a quarter of them indicated that they were in the production and/or marketing stage. Nanomaterials (43 per cent) and nanobiotechnology (42 per cent) were identified by the firms as their areas of greatest involvement, with nanomedicine, nanophotonics and nanoeletronics also making a mark in the survey (McNiven, 2007).

With respect to revenues and resources, those firms involved in nanotechnology activities reported $28 million in "nanotechnology revenues" in 2005, which represents an increase of 19 per cent over 2004. Moreover, the survey respondents forecasted that their 2007 nanotechnology revenues would reach $56 million. R&D expenditures on nanotechnology by the surveyed firms were over $40 million in 2005 — a 12 per cent increase over 2004 — and the expectation was that nearly $60 million would be spent in 2007. While 22 firms reported attempts to raise capital for nanotechnology activities in 2005, only eight were successful and they managed to raise just over $16 million (McNiven, 2007).

While the extent of Canadian firms' nanotechnology activities and revenues is modest on a world scale, there is nevertheless a trend towards increased involvement and expectations of increased revenues. If the market continues increasingly to reward those firms involved in nanotechnology, then we should expect both new firms to enter the Canadian nanotechnology market and increased efforts by existing firms.

There do not exist accurate and comprehensive data on the penetration of nanotechnology-related products into the Canadian market from companies based in other countries. Nevertheless, some observations can be made. An analysis of databases on nanoproducts entering Canada from the United States, commissioned by Industry Canada, reveals that at least 132 U.S.-based companies export a minimum of 517 nanotechnology products to Canada (Senik and Associates, 2007).

Potential Benefits

Nanotechnology has allowed the development of a new class of materials with new properties that are precursors for the development of new devices and products with improved functionality. The wide-ranging implications of these products (e.g., improved medical diagnostics and treatment or increased security capability) have resulted in significant investments by both government and industry. Science and technology (S&T) strategies in various countries have been revised in order to focus more resources towards the nanotechnology that they think will lead to the next major breakthroughs in science (NNI, 2007; NanoNet, 2005).

While the developments in the S&T of the nanoscale will likely have intrinsic rewards for researchers, what interests health professionals, manufacturers, consumers and others is the potential for practical applications of nanomaterials that have medical, environmental and commercial benefits or appeal. Indeed, the "buzz" about nano is driven as much, or more, by the emergence (or expectation) of nanoproducts and their applications than it is by developments in the science itself.

Estimates from Lux Research (2006) suggest that by 2014 about 15 per cent of manufactured output globally will be based on nanotechnology. While this and other estimates of the future impact of nanotechnologies are speculative (IRGC, 2007), it seems clear that the increasingly sophisticated ability to engineer materials at a nanoscale will have a profound impact on the manufacturing sector and industrial production over the coming decades.

As a platform or enabling technology, nanotechnology has the potential to be used in an incredibly diverse range of applications. Early generation nanotechnologies are being used to enhance a wide range of consumer products, from the latest computers to stain resistant clothing to cosmetics. In fact, the modern digital device industry would not be where it is today without the processor speeds and storage capacities that nanotechnology has enabled. As noted earlier, the Project on Emerging Nanotechnologies (PEN) on-line inventory of manufacturer-identified nanotechnology consumer products currently lists over 600 such products. But it is likely that these are only a foretaste of the broader commercial potential of emerging nanotechnologies.

Many nanotechnology research and development programs focus on how these emerging technologies can address social issues and increase quality of life (NNI, 2007). Nanotechnologies currently under development in laboratories

have the potential to enhance existing products and even lead to completely new technologies, in the search for solutions to some of the most pressing challenges facing society. For instance, nanotechnologies are being developed to provide new approaches to developing renewable energy sources (NREL, 2008), to significantly improve battery storage and performance (Chan *et al.*, 2008), and to sequester carbon dioxide (Banerjee *et al.*, 2008). Precise engineering of structures at the nanoscale and the use of nanocomposites is leading to materials that are simultaneously lighter and stronger than what can currently be achieved. Materials that are literally as light as plastic and as strong as steel are now under development — their successful commercialization will revolutionize the transport industry and quite possibly the construction industry.

Box 2.8 — Medical Nanoproducts in Canada

According to a recent report by the Health Portfolio Nanotechnology Working Group (HPNWG, 2007), there are currently three "nanomedicines" that have been approved for use in Canada.

Rapamune: Used to relieve organ rejection in patients receiving allogeneic renal transplants, rapamune was previously available as an oral solution in bottles or sachets. The oral solution requires refrigeration storage, and must be mixed with water or orange juice prior to administration. A new Rapamune tablet developed with nanocrystals has provided patients with more convenient administration and storage. Approved January 5, 2005.

Acticoat: An antimicrobial barrier dressing which uses nanocrystalline silver technology (silver nanoparticles measuring 1 nm to 100 nm in diameter) received a medical device license as of January 16, 2006. Used in the prevention of bacterial infection in serious burns, chronic wounds, serious traumatic or surgical wounds.

Abraxane: Aluminum-bound nanoparticles of paclitaxel was approved on June 7, 2006, under a Notice of Compliance for the treatment of metastatic breast cancer. Paclitaxel stops cancer cells from growing and dividing by interfering with cell structures.

Advanced nanomaterials and nano-enabled materials are also attractive for use in medical devices, and open the window to a new generation of high-performance implants and prosthetics (Roco and Bainbridge, 2002). The use of nanotechnology in the pharmaceutical industry could lead to some of the most exciting developments in the next few years by improving drug formulation and efficiency in delivery. This could lead to improvements in the treatment of disease with lower drug dose requirements and fewer side effects. Nanotechnology is also giving researchers the tools to construct medical treatments that blur the distinction between drugs and devices; attacking diseases through targeted and multi-stage actions. For instance, researchers at Rice University have developed nanoparticles coated with a gold shell carefully tuned to a particular wavelength of infrared light (Hirsch *et al.*, 2003). The plan is that when these "nanoshells" are injected into the bloodstream, they will pass through the leaky blood vessels around tumours and accumulate there. Once enough have collected in the tumour, irradiation with the correct wavelength of light causes the nanoshells to heat up and kill the cancerous cells, leaving healthy tissue intact. More sophisticated "smart" nanoparticles, under development at the University of Michigan, are engineered to contain a number of components that enable them to target and destroy diseased cells (Majoros and Baker Jr., 2008). These nanoparticles can be engineered with coatings that enable them to stick to cancer cells with contrast agents that allow physicians to track their progress in the body. Furthermore, they have sensitizers that allow them to receive a signal and act on it — usually an instruction to kill the cancer cell to which they are attached.

The Project on Emerging Nanotechnologies identified 133 applications of nanotechnology relating to drugs, delivery systems, medical diagnostics and devices that are currently under development, and acknowledges that this is most likely just a fraction of the total number of products in the pipeline. In the future, we are likely to see an increasing convergence between artificially constructed nanosystems and our bodies, as researchers learn how to manipulate biology at the nanoscale to treat diseases and even enhance human capabilities (PEN, 2008).

PUBLIC KNOWLEDGE AND CONCERNS

Among the challenges related to the future of nanotechnology is the proliferation of misleading claims, both in terms of its potential benefits and potential risks. These "nano-mythologies," as they might be called, are of two kinds. On the one hand, there is "nano-hype" — exaggerated claims about the potential benefits of nanotechnologies. On the other hand, there is "nano-phobia" –

excessive fear of the potential risks of nanotechnologies. In both cases, the claims outpace or even ignore the existing science.

"Nanobots" serve as an interesting case study for both the nano-hype and the nano-phobia that have surfaced. In one case, these hypothetical molecular-sized robots would purportedly be introduced into the body in a controlled fashion. Once there, they would be able to work with individual cells and perhaps even manipulate genetic material. The outcomes, some authors have extolled, could be the eradication of disease or even "perpetual life." But nanobots have also been associated with a nightmarish "grey goo scenario." In his book *Engines of Creation* (which develops the idea of nanoscale machines that can build new materials, molecule by molecule), Eric Drexler raised concerns about self-replicators engineered to gather resources from natural environments. These could (if constructed but not controlled) convert biomass on a massive scale into a "grey goo of identical self-replicators"[12] (Drexler, 1986).

Nanobots remain in the realm of science fiction, yet excitement and concern over what they could or might do has appeared in the popular press. This is not an isolated case of science taking a back seat when it comes to nanotechnology. Unfounded nano-phobia and nano-hype could well derail science-based discussion about the potential benefits and risks of nanotechnologies. Consequently, there is a need to assess much of the material that is reported about nanotechnologies through a critical eye, and for those involved in developing, using and discussing nanotechnologies to ensure they communicate the science facts rather than the science fiction of nanotechnology.

The level of public awareness and understanding of nanotechnology appears to be quite low. A 2004 survey of British public opinion by the U.K. Royal Society found that only 29 per cent of respondents were aware of the term "nanotechnology" and only 19 per cent could offer any form of a definition (UK-RS/RAE, 2004). Research in Canada and the United States conducted in 2005 (Einseidel, 2005) found that 35 per cent of Canadians said they were "somewhat or very familiar" with nanotechnology. Similar polls conducted in the U.S. by the Woodrow Wilson International Center for Scholars' Project on Emerging Technologies in 2007 found that only 6 per cent of Americans polled said that they had "heard a lot" about nanotechnology, which was down from the 2006 finding that 10 per cent had "heard a lot" (PEN, 2007b).

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[12] Drexler subsequently stated that he "… now believes that self-replication — the initial source of "grey goo" fears in which nanomachines run amok and overwhelm the world — is not an essential part of the molecular manufacturing process" (Phoenix and Drexler, 2004).

Only 21 per cent of respondents in both the 2006 and 2007 poll years indicated that they had "heard something" about nanotechnology, while 70 per cent in both years indicated that they had heard "just a little" or "nothing at all" (PEN, 2007b).

These studies illustrate that at this stage of nanotechnology development, industry and government face a relatively uninformed public. How this lack of information will play out in public attitudes is unclear. Low levels of awareness or understanding can lead to apathy. But, it can also be the ground in which fear of the unknown is created and becomes a dominant factor in the way risks are perceived, with potentially significant consequences for research, development and production. Whether apathy or fear is to become the dominant attitude will depend upon many factors, but among the most important are (1) the emergence of consumer and other interest groups that raise serious questions about the safety or desirability of the technology, and (2) media reports of serious unintended consequences of a nanoproduct. Lack of public awareness provides an opportunity for informed stakeholders to engage the public *before* fear of the unknown overwhelms informed discussion. Further discussion on the role of public engagement will be presented in Chapter IV.

SUMMARY OF CHAPTER II FINDINGS

2.1 Nanotechnology encompasses the technologies used to manipulate and characterize nanostructures as well as the resulting materials and products. Nanomaterials and nanotechnology are not the same thing.

2.2 The physical, chemical and biological properties of many nanomaterials differ from those of their constituent atoms and molecules, and from those of the bulk material.

2.3 The properties of nanomaterials are very diverse due to the many possible permutations of structure, chemical composition and shape.

2.4 Nanomaterials have novel but potentially controllable properties. These allow them to be used as precursors in the development of new products and devices.

2.5 The physical and chemical properties of nanomaterials may lead to unanticipated behaviours in environmental and biological systems.

2.6 Public awareness of nanotechnology in Canada is relatively low and public attitudes are therefore vulnerable to exaggerated claims by both proponents and critics.

Chapter III – A Science Perspective on Nanomaterial Risk

As with many new technologies, one of the challenges for regulators confronting nanotechnology arises from the need to ensure public safety when introducing technologies where the knowledge of the associated risks are not well understood. The public debates over nanotechnology have seen strong arguments presented both for and against the development of nanomaterials and their incorporation into products. Concerns have been expressed that a rigid regulatory environment could stifle research and product development, that restrictions and reporting regimes may hinder commercialization of new products, and that such factors could put Canada at a competitive disadvantage and create investment uncertainty. On the other hand, it has been argued that an appropriate regulatory regime can foster commercial development by creating certainty for businesses and trust within the public at large. Meanwhile, critics of potentially uncontrolled nanotechnology development have argued that the uncertainty surrounding short- and long-term health and environmental risks, and the absence of conclusive safety information, point to a need for significant regulatory oversight. The divergent opinions among stakeholders, combined with a rising public interest/awareness, have established a need for governments to respond to the regulatory challenge.

RISK AND RISK ASSESSMENT

There are established protocols and terminology surrounding how to assess risks and what standard of proof must be met. Accepted and standardized tests and models are in place to allow for an evaluation of any processes or materials against existing benchmarks and to categorize their associated risk level. Terms such as "exposure," "dose," "hazard," "threshold" and "toxicity" have been used by scientists for decades and help elucidate the key components of assessing (and managing) new and emerging risks. In the case of nanomaterials, the central concern is whether or not these established benchmarks can be used to adequately assess nanomaterials and nanoproducts. Recently, concern has arisen that the physicochemical properties of nanomaterials — e.g., those outlined in Chapter II — may prevent them from being adequately assessed under traditional guidelines and regulations.

The terminology that has been developed in the field of risk assessment uses very standardized language and criteria. This language has developed primarily from traditional toxicology which stems from the basic assumption that there is a relationship between biological (or environmental) effect and the amount

of material to which one (it) is exposed. It is helpful to be reminded that in the 16th Century, a Swiss doctor, named Philippus Aureolus Theophrastus Bombastus von Hohenheim, (commonly called Paracelsus) stated:

> *All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.*
>
> *(Ottoboni, 1997)*

Or, in more general language, "the dose makes the poison." The toxic effect of a substance is assumed to increase as the exposure to the susceptible system increases. Thus, an "exposure limit" is derived from studies that establish adverse effect levels of a substance resulting from exposure to a given amount of substance.

Two basic conditions are required to establish adverse effect levels: (1) that the "amount" of material (however that is measured) to which an individual (or an ecosystem) is exposed is quantitatively determined; and (2) that there exists a means by which the material can be tested and biological/ecological responses measured. Thus, to determine the potential risk of nanomaterials, one must be able to measure both the exposure to the substance as well as ascertain the direct outcome of this exposure. In the past, regulatory standards have utilized experimental, clinical and epidemiological means of characterizing this relationship. Most engineered nanomaterials, however, are either relatively new in terms of their introduction to society or were previously unstudied with regard to their health or environmental effects. Thus clinical and epidemiological evidence for establishing the toxicity of nanomaterials is limited.

In the absence of sufficient clinical or epidemiological evidence, regulators will need to rely on data obtained in controlled, experimental tests to determine the health and environmental toxicological properties of nanomaterials. However, even the use of well-established *in vitro* tests and *in vivo* tests to predict nanomaterial toxicity currently faces several challenges. As noted in Chapter II, the diversity of nanomaterials is great. For instance, certain nanomaterials (e.g., carbon nanotubes) have a wide range of properties and characteristics that are unique to different forms of this nanomaterial. As an example, Colvin (2007) has suggested that — when issues such as generation processes, atomic arrangement and surface treatments are taken into account — over 50,000 different configurations of carbon nanotubes (CNT) might exist. Thus evidence garnered from one CNT may not be representative of another (apparently) similar CNT. Another challenge is the lack of knowledge

regarding if and how exposure to nanomaterials translates into biological responses as is the inability at present to accurately measure the level of exposure or dose. All of these factors need to be addressed in order to formulate an accurate assessment of the human health and environmental risks posed by nanomaterials.

RISK ASSESSMENT FRAMEWORKS

The past two decades have seen a marked increase in the number of governments using science-based risk assessment frameworks to make regulatory decisions. In 1983, the U.S. National Academies of Science (NAS) issued a pioneering report on the use of risk assessment for decision making in the federal government (US-NRC, 1983). Subsequently, various international bodies such as the World Health Organization and the European Commission, as well as individual departments and agencies within the U.S. government, have developed frameworks that they use to assess the potential risks associated with a given substance.

In 1993, Health Canada released a document entitled *Health Risk Determination: The Challenge of Health Protection* that presented a structured framework for the assessment and management of population health risks (HC, 1993). In 1997, the Canadian Standards Association released their framework as the proposed national standard for risk assessment (CSA, 1997). These two documents helped underpin the framework proposed by Health Canada in 1997 (and revised in 2000), *Health Canada Decision-Making Framework for Identifying, Assessing and Managing Health Risks* (HC, 2000). This last framework seeks to coordinate efforts across departments in applying a common approach to risk assessment in a "consistent and comprehensive manner." The Canadian framework for ecological risk follows a similar paradigm to human health. Although the analysis is differently defined, it essentially follows the same steps, so the following discussion can follow Health Canada's framework and simultaneously address ecological risk concerns.

While some of these frameworks may use different terminology, all of them are based on similar decision-making processes and information requirements, most of which were presented in the original NAS framework cited above. In general, they provide a systematic, evidence-based approach to evaluating what is known (and not known) about a given substance, a group of substances or technologies.

For clarity, this report will use the Health Canada framework (2000) as the basis for structuring an organized, scientific approach to assessing what is known (and not known) about the potential risks of nanomaterials. The application of this framework is not meant to recommend its exclusive use in assessing the risks associated with nanomaterials. It was chosen in light of the Canadian context and origins of this report. Its similarity in structure to other risk assessment frameworks speaks to its general applicability.

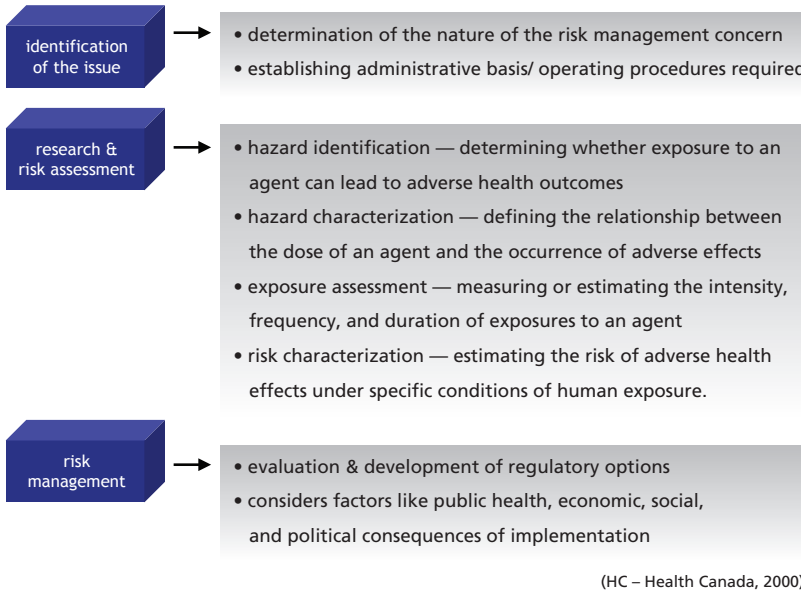

Figure 3.1
Components of a Risk Framework

The Components of a Risk Framework

Generally, there are three main divisions within risk assessment frameworks (Figure 3.1):

- Identification of the issue;
- Research and risk assessment; and
- Risk management.

These three steps in risk analysis encompass the more commonly referred to four-step process of risk assessment, with the fourth step being an explicit ongoing evaluation of the effectiveness of the risk management measures.

Issue identification involves determining the nature of the risk management concern and establishing the administrative basis and operating procedures needed to move forward. The overall analysis of the risk within its context directs and focuses both the risk assessment and risk management steps that follow.

The second element, *risk assessment*, involves the characterization of the potential adverse health and environmental effects that result from exposure to a given hazard. Risk assessment consists of four steps:

- Hazard identification — the process of determining whether exposure to an agent can lead to adverse health and environmental outcomes;
- Hazard characterization — defining the relationship between the dose of an agent administered or received and the occurrence of adverse effects in exposed populations and ecosystems;
- Exposure assessment — measuring or estimating the intensity, frequency, and duration of exposures to an agent present in the environment; and
- Risk characterization — estimating the risk of adverse effects under specific conditions of exposure.

Research, in this context, involves the generation, collection, analysis, and interpretation of biological, chemical and physical data from scientific studies. It is the fundamental underpinning of risk assessment as it provides the scientific base for evaluating risk.

The third element, *risk management*, is where regulatory options are developed and evaluated and considers factors such as public health, economic, social and political consequences of implementation. Other significant contributors include the technical feasibility of proposed solutions, the desired level of exposure control, the ability to enforce regulations, uncertainty in scientific data and the corresponding inferential bridges used to fill gaps in knowledge and public perception and level of information. Risk management also serves to focus and direct the risk assessment strategies. A comprehensive risk management approach includes the development of strategies to communicate relevant, up-to-date information about risk by those who create or hold the information to users of the information. Timely communication of risk-related information facilitates the adoption of practical and maximally relevant risk management approaches that are based on the best available scientific data.

In the context of engineered nanomaterials, the assembly and interpretation of key scientific findings that are relevant to risk management approaches are of critical importance. Though the need to systematize the assembly of risk data has been recognized for some time, the practical reality is that the challenge is significant. Effective management of any new or emerging source of risk requires a well thought-out and carefully developed communications strategy surrounding the scientific findings that underpin decision making. The various sources of uncertainty and complexity associated with nanomaterials increase the challenge.

HAZARD IDENTIFICATION

The World Health Organization (WHO) defines hazard identification as "the identification of known or potential health effects associated with a particular agent" (WHO, 2004). This step is used to determine whether or not a given agent is responsible for an adverse health or environmental outcome.

Hazards can be identified using epidemiological evaluations, animal-based bioassays, *in vitro* experiments and structural-activity comparisons. Hazard characterization requires an examination of the available science-based evidence in order to assess the relationship between the material and its adverse effects. Sometimes, the science-based evidence of a hazard is readily assessed and applied to humans. Many times, however, the data examined in hazard characterization are not definitive or transferable from one species to another. In these cases, the reliability, quality and significance of the available data are used to reach a regulatory decision. In other words, judgment is needed in synthesizing the available evidence for risk management when the data available are inconclusive.

Hazard Identification on Nanomaterials

The presence of inconclusive and sometimes questionable data surrounding a potential hazard is not unique to nanomaterials — the current issues surrounding bisphenol A are a good example (ACC, 2008; vom Saal and Hughes, 2005; Staples *et al.*, 1998). Often, it is not possible to directly study the effects of a particular agent in human and environmental systems for various practical or ethical reasons. Nanomaterials are similar to other new materials in that it is not always clear what the most appropriate test methods or benchmarks will be for assessing their potential risks.

Chapter II presented some of the properties that make nanomaterials unique and of interest to researchers. These same properties have also given rise to concern regarding the potential for increased human or environmental risks. In particular, there exists significant concern surrounding the capacity of traditional hazard identification methodologies to address two issues:

- Are the existing tools adequate to identify potentially hazardous nanomaterials compared to their adequacy for more traditional substances such as chemicals?
- Are the resultant data suitable for determining health and/or environmental risks under current frameworks?

Analytical techniques for monitoring engineered nanomaterials in real-time and on-site at a workplace, for instance, do not exist (Maynard and Kuempel, 2005). Methodologies to accurately measure the physicochemical properties (e.g., electrical, thermal and mechanical conductivities and ability to produce specific intermediate reactions that are responsible for oxidative species) do not have reference materials against which to calibrate. Ability to measure the relevant size of nanoparticles in vivo remains an urgent, unsolved need. *These examples illustrate that there is a significant gap at present in our ability to study the effects (positive and negative) of nanomaterials, reliably and accurately.* To advance our instrumentation capability and close the gap in our knowledge, the metrology — i.e., the physical measurement — of nanomaterials needs to be further developed.

Metrology of Nanomaterials

A proper assessment of the potential toxicological effects of nanoparticles requires a comprehension of both the properties and the characteristics of nanomaterials that give rise to their behaviours in biological or environmental systems. Metrology that is relevant to our understanding of biological effects of nanomaterials requires a fundamental knowledge of how materials behave inside and outside of a human being or the environment. This in turn relies on the ability to properly measure or define the materials of interest.

Currently, there are both national and international efforts underway that focus on the development of measurement and characterization tools for nanomaterials. Within the past 10 years, there has been a marked increase in the number of institutions and agencies that have instituted nanometrology programs (NIST, 2006; NCI, 2005; ISO, 2007a). University departments, government laboratories, industry and various international bodies are all

seeking to identify and develop the measurement methods, instrumentation, nomenclature, standards and reference materials — a sort of metrological infrastructure — that are needed to identify those properties of nanomaterials that influence functionality and determine biological behaviour. Specific examples of measurement tools and techniques are discussed in subsequent sections. It should be noted that for most nanomaterials there are currently no national or internationally standardized practices for performing measurements of their physicochemical properties. This in turn makes it difficult to relate a particular biological response to a specific nanomaterial property.[13]

Box 3.1 — Hazard Identification Case Study Carbon Nanotubes (CNTs)

Material Characteristics that may Contribute to Toxicity:

Human Health – CNTs are light-weight, low-density, materials that may become easily airborne or aerosolized and would likely undergo environmental, physical and chemical processes after their release into the air. Recent concerns have stemmed from the debate arising from the similarity of CNTs to asbestos. The general shape and aspect ratio of some CNTs resembles those of asbestos fibres that have been linked with various pulmonary diseases.

Environmental – Generally, CNTs are insoluble in water. Recent studies have shown, however, that natural organic matter (such as humic substance and dissolved organic carbon) can stabilize multi-walled CNTs, dispersing them and prolonging their residence time in the environment (Hyung *et al.*, 2007), thereby increasing the likelihood of bioaccumulation in aquatic species.

Identified Adverse Health or Environmental Outcomes:

Human Health – The toxicity of CNTs has been evaluated in laboratory experiments using cell and animal models. Both types of studies have found that study conditions affect whether CNTs cause biological effects. Purified and bundled CNTs present lower toxicity than unpurified and dispersed tubes (Thompson, 2007). Synthesis method and functionalization (Sayes *et al.*, 2006; Shvedova *et al.,* 2005), as well as tube length, also affect toxicity (Muller *et al.*, 2005). These factors affect bioavailability of CNTs (Helland *et al.*, 2007). Most studies evaluate the potential for CNTs to induce adverse

[13] There is a standard protocol published by the Institute of Electrical and Electronics Engineers (IEEE) for measuring electrical properties of CNTs (IEEE, 2006).

pulmonary effects (Donaldson *et al.*, 2006; Lam *et al.*, 2006). To date, few studies are comparable because of differences in tubes and study protocols. Recently, multi-walled CNTs as well as asbestos were reported to induce mesothelioma six months after intraperitoneal injection of extremely high doses in a susceptible mouse model (Takagi *et al.*, 2008). Long-fibre multi-walled CNTs as well as long-fibre asbestos have also recently been shown to induce inflammatory responses in the peritoneal cavity seven days after intraperitoneal injection of a lower dose in mice, whereas short-fibre multi-walled CNTs and short-fibre asbestos did not (Poland *et al.*, 2008). Both of these "proof of principle" studies require carefully designed follow-up experiments using relevant exposure routes (respiratory tract) and doses considering specifically translocation kinetics from the portal of entry.

Environmental – The main body of data on environmental risks of CNTs comes from studies done on aquatic species (e.g., small fish and fish embryos). Templeton *et al.* (2006) report differences in toxicity of CNT fractions in standard copepod assays.* Purified fractions were not toxic, while unpurified mixtures adversely affected population viability and reproductive success. Cheng *et al.* (2007) reported that the impact of unpurified CNTs on Zebrafish embryo development might be due to contaminants.

Considerations or Limitations to Available Data:

- Most CNT studies are being carried out on single-walled CNTs, although there are hundreds of different types of CNTs. Thus, the currently tested materials may not be representative of the specific exposures that will occur.
- Studies have been carried out at extremely high doses that do not reflect natural exposure levels.
- Peritoneal injection methods are not representative of physiological exposure routes.
- Available studies have limited interpretability because material characteristics have not been measured or reported.
- Cell-line based (*in vitro*) studies are highly controversial because of the inconsistency in the results reported in the literature and the lack of consistency with *in vivo* data.
- The variability in manufacturing and purification processes of CNTs can also influence the potential human health and environmental toxicity of the end material, limiting the comparability of available studies.

* Copepods are small crustaceans found in the sea and most freshwater habitats. They are used as bioindicators, given their dominant role in the aquatic food cycle.

Physical versus Molecular Properties

Ideally, one might seek to comprehensively characterize a nanomaterial as a means of predicting and determining its biological behaviour. In fact, the paradigms that have been used for decades in particle toxicology are also being suggested as a basis to develop the methodologies for investigating the toxicology of engineered nanomaterials (Donaldson and Tran, 2004).

As discussed in Chapter II, matter exists along a continuum between molecular and physical structures. Nanomaterials lie in the convergence zone of what traditionally has been considered as two relatively distinct features — molecular structure and physical structure. Given this convergence of molecular and physical characteristics, the effects of nanomaterials may be related to their molecular attributes, their physical attributes, or some combination that leads to unexpected and perhaps unconventional behaviour. This inter-relationship between the various properties can make it difficult to tease out actual cause-and-effect when trying to identify a potential hazard. It can also cause difficulties when trying to predict nanoscale behaviour from the equivalent bulk or macroscopic material. *Thus, nanomaterials can pose particular challenges to risk assessment and therefore to regulation because they exhibit properties based on their physical structure, their chemistry, or both.*

Nanomaterials Characterization

It has been argued that in light of the absence of definitive information regarding which properties of nanomaterials actually influence their biological effects, any attempt at characterization must be as comprehensive and broad in scope as possible (Powers *et al.*, 2006). Characterization efforts might need to go beyond those normally required to characterize the "identity" of a chemical. They may also require different approaches. Such exhaustive testing requirements are both time-consuming and complex, often to the point of infeasibility. Other researchers have proposed that the parameters investigated should be defined by the objectives of the study or intended use of the material (Stern and McNeil, 2008; ED-DuPont, 2007). In general, researchers have yet to agree on a minimum set of required material properties for hazard, exposure and risk characterization, although some (Bucher *et al.*, 2004; Oberdörster *et al.*, 2005a; Patri *et al.*, 2007; Warheit, 2008) have proposed a subset of properties that should be examined when trying to determine the toxicity of nanomaterials, as shown in Table 3.1. It is worth noting that many of these nanomaterial properties are not independent, but sometimes act in concert to produce adverse effects. The following text serves to introduce several of these properties, and how they could affect biological behaviour.

Table 3.1
Recommendations on Material Characterization

Characterization (Off-line)	Human Exposure	Toxicity Screening Studies		
		Supplied material	Administered material	Material *in vivo* / *in vitro*
Size distribution (primary particles	E (combine with agglomeration state)	E	D	D
Shape	E	E	O	O
Surface Area	D	E	D	O
Composition	E	E	O	O
Surface chemistry	D	E	D	D / O
Surface contamination	D	N	D	N
Surface charge – suspension / solution	O	E	E	O
Surface charge – powder (use bio fluid surrogate)	O	E	N	O
Crystal structure	O	E	O	O
Particle physicochemical structure	E	E	D	D
Agglomeration state	E	N	E	D
Porosity	D	D	N	N
Method of production	E	E	--	--
Preparation process	--	--	E	--
Heterogeneity	D	E	E	D
Prior storage of material	E	E	E	--
Concentration	E	--	E	D

E: These characterizations are considered to be essential

D: These characterizations are considered to provide valuable information, but are not recommended as essential due to constraints associated with complexity, cost and availability.

O: These characterizations are considered to provide valuable but non-essential information.

N: These characterizations are not considered to be of significant value to screening studies.

(Oberdörster *et al.*, 2005b)

Size — The size of a basic unit of a nanomaterial or nanostructure determines many other properties of a nanomaterial such as the surface area, reactivity and mobility. Since the size of a nanoparticle is smaller than, or at least comparable to DNA, proteins, tubules and other working biological organelles, it makes the interaction of nanoparticles with biological units potentially stronger than that of larger particles. The reduced size of nanoparticles permits them to reach places that are not accessible to their larger counterparts (Hillyer and Albrecht, 2001).

Mass — In many existing environmental safety and health (ESH) standards, mass of an agent per unit volume of air determines the trigger for regulatory action and defines the upper or permissible exposure level of the agent. In the case of nanoscale materials, many researchers argue that mass is not an appropriate metric to use (see the description below in *Surface Area*) yet it remains one of the more readily measured properties. Use of mass concentration in itself may not be an effective measure of nanomaterial exposure.

Composition — In the toxicological evaluation of nanomaterials, chemical purity is often characterized insufficiently, thereby making it difficult to ascertain the relationship between chemical composition and observed effects. The material's bulk chemical composition is important in determining its overall toxicity — e.g., silica is known as a relatively inert material while chromium salts are known for their carcinogenic properties. However, functional nanostructures are typically made from surface-modified nanomaterials. Thus, material characterization for a toxicological study must also consider the surface in addition to bulk composition. For instance, carbon nanotubes that contain transition metals (e.g., iron and nickel) have been found to exhibit significantly different toxicity than pure CNTs in many studies (Pulskamp *et al.*, 2007). In this case, the toxicity could be attributed to the very small amount of impurity (i.e., the transition metals) rather than the carbon nanotubes alone.

Surface Area — As discussed in Chapter II, a reduction in particle size results in a significant increase in the number of surface atoms relative to a particle's internal volume. These surface atoms can exhibit enhanced reactivities (Preining, 1998; Jefferson, 2000). An increase in the number of reactive atoms on the surface of a particle has been speculated to modify its biological behaviour in ways that may be important from a toxicology perspective. In studies carried out on nanotitania, it was shown that nanometre-sized particles showed an increased inflammogenic response compared to

sub-micrometre-sized particles in rats and mice — i.e., 20 nm compared to 250 nm (Warheit *et al.*, 2004). An evaluation of the response curves showed that the pulmonary inflammation was mediated by surface effects. Similar results were reported for carbon black, where an increased inflammatory effect of nanoparticles versus sub micron-sized particles was noted in rats upon correlation of the surface area instead of mass (Donaldson *et al.*, 2002). The higher surface-area to unit-mass ratio means that it takes less material for nanoparticles to provide the same surface area than it does for a larger particle.

Shape/Morphology — The toxicity induced by particles is not only correlated with the size and surface area but also the shape of the nanomaterial. Dendritic (branched) and spindle titania particles have been reported to show a higher cytotoxicity[14] than spherical particles. Similarly, nanotitania particles in the 80 nm range (octahedral in shape) showed a greater capacity to induce tissue damage than smaller (approximately 25 nm), spindle-shaped particles (Wang *et al.*, 2007). In studies carried out on carbon-based nanoparticles, CNTs have been reported to exhibit various *in vivo* effects (Lam *et al.*, 2004; Mangum *et al.*., 2006; Shvedova *et al.*, 2005; Warheit *et al.*, 2004) while single-walled carbon nanohorns[15] are reported to exhibit much milder biological effects (Lynch *et al.*, 2007). Fibre toxicology has also shown that aspect ratio and length can also drive the toxicity of a particle (Merchant, 1990). The shape similarity between CNTs and asbestos could have given rise to the recent debates over the pulmonary toxicity of CNTs (Muller *et al.*, 2006; Berger, 2007).

Crystallinity — Differences in the phase composition of nanocrystalline structures have been shown to influence their cytotoxicity. A recent study compared two forms of titanium dioxide nanoparticles and found that the anatase form of the mineral[16] was more cytotoxic and produced a larger number of reactive species than did the rutile form. Both materials were of similar specific surface area per unit mass (Sayes *et al.*, 2006).

Surface Charge — Modifying the surface chemistry of liquid-borne nanoparticles can alter their surface charge (positive and negative charge) within different environments. Altering surface charge is a common step in the

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[14] Cytotoxicity is a property of a substance's ability to damage or kill cells.

[15] Carbon nanohorns are similar in structure to carbon nanotubes but differ in shape.

[16] Titanium is found in three mineral forms: rutile, anatase and brookite. Each has its own unique structural form/crystallinity.

synthesis of nanomaterials for medical devices or drug delivery vehicles, as it can reduce or prevent particle agglomeration (see Aggregation and Agglomeration below). However, the surface charge of nanoparticles has been associated with non-favourable disruption of the cell membrane. Although research is limited, the toxicity of various nanomaterials (e.g., liposomes, nanopolymers and dendrimers) appears to be dependent on their charge state (Mecke *et al.*, 2004; Lv *et al.*, 2006).

Surface Chemistry: Reactivity — The surface reactivity of a material is determined by various factors (e.g., chemical composition, atomic structure topography). Although early studies of insoluble nanomaterials focused on the relationship between surface area and specific endpoints, it has been suggested that a combination of size, shape, surface area *and* surface reactivity dictates biological behaviour (Warheit *et al.*, 2006; Warheit *et al.*, 2007a; Warheit *et al.*, 2007b). In studies that looked at inflammation in rats caused by nano-sized quartz particles (from 12 nm to 500 nm), neither the surface area nor the size of the particles could explain differences in the increased biological response between different particles. An examination of the nanoparticle surface reactivity (as measured by the hemolytic potential)[17] showed a direct correlation between exposure and response (Warheit *et al.*, 2007a). These results mimicked those reported in a previous study with quartz nanoparticles where introduction of the nanomaterial initiated inflammation in rats (Clouter *et al.*, 2001). In each of these cases, knowledge of the size and/or surface area of the particles alone was insufficient to predict the end response.

Surface Chemistry: Coating — Surface coatings are often applied to nanoparticles to increase their overall biocompatibility and stability, but they have also been shown to cause dramatic shifts in the toxicity of the particles. In the case of cadmium-based quantum dots, treatment of the particles with a zinc-sulfide-based coating showed a marked decrease in their toxicity when examined in rat cells (Derfus *et al.*, 2004). Yet another study showed that coating quantum dots with a neutral, polymer substance (polyethylene-glycol) decreased their overall toxicity while coatings that contained charged surfaces (amine or carboxylic) exhibited cytotoxic and inflammatory effects in human cells (Ryman-Rasmussen *et al.*, 2007). Furthermore, coating of nanomaterials with certain types of proteins was found to change the interaction of the nanomaterial with cells, and influence the molecular targeting of nano-materials (Dutta and Hofman, 2004), alter the affinities of proteins for

[17] Hemolytic potential is a measurement of a substance's ability to lyse (break open) red blood cells.

nanoparticles (Cedervall *et al.*, 2007) and limit the dispersion of biogenic nanoparticles in water and in the environment (Moreau *et al.*, 2004).

Solubility — The solubility of a particle determines the release of dissolved material (atoms and ions) from its surface and, as such, will influence its potential impact on both biological and environmental systems. Dissolution rate depends on solubility and particle surface area — the larger the surface area for a given mass of material, the faster it dissolves. It is therefore likely that soluble or sparingly soluble nanoparticles will lead to much higher release rates of material into solution than larger particles.

Swiss researchers have published studies that show nanoparticle dissolution strongly influences overall toxicity, sometimes in unexpected ways (Brunner *et al.*, 2006). Low concentrations of soluble zinc oxide nanoparticles were reported to cause a sharp drop in cell metabolism and proliferation. However, at higher concentrations, toxicity was reduced. The researchers suggested that this was likely due to particle agglomeration and aggregation at higher concentrations, leading to a reduced rate of dissolution. Insoluble metal oxide particles showed virtually no effect on cell function at any concentration and uncoated iron oxide nanoparticles were particularly toxic regardless of concentration.

The solubility of a particle can also affect its rate of elimination from a biological system and its distribution throughout environmental systems.

Aggregation and Agglomeration — Aggregation (formation of strong bonds between particles) and agglomeration (weak bonding) occurs when particles adhere together, and results in an increase in particle size and a subsequent reduction in the particle number concentration. The level of aggregation and agglomeration, together with the ease or difficulty with which these collections of particles break apart (through disaggregation and de-agglomeration), affect the transport, fate, and uptake of nanoparticles. Airborne and liquid borne nanoparticles aggregate faster at higher concentrations, although even at high concentrations, nanoparticles may avoid aggregation for long enough to move from a point of generation to a point of exposure (Hinds, 1999).

Aggregates and agglomerates of up to a few hundred nanometres in diameter are less likely than smaller particles to deposit in the lungs if inhaled, and if deposited, are less likely to be transported through the body in the same way as nanoparticles. But the same mechanisms that reduce the probability of lung deposition also lead to sub-micrometre diameter aggregates and agglomerates

remaining suspended in air for longer periods than smaller particles. This leads to them potentially being transported over long distances.

Aggregates and agglomerates are often structurally complex at the nanometre scale, and may demonstrate similar properties to non-agglomerated nanoparticles. For instance, the specific surface area of agglomerates that have formed in the air can sometimes approach that of the non-agglomerated particles. These diffusion-limited agglomerates typically have a very open structure, with most of the surface area of the original nanoparticles being open to the air. If the biological activity of the nanoparticles depends on their surface area, the resulting agglomerates are likely to show a similar level of activity to the same mass of non-agglomerated nanoparticles.

Aggregates or agglomerates significantly larger than a few micrometres in diameter will only form at extremely high concentrations of airborne or liquid borne nanoparticles, or when dry powders of nanoparticles are dispersed. Aggregates/agglomerates smaller than approximately five micrometres in diameter will deposit in the sensitive alveolar region of the lungs if inhaled. Agglomerates deposit in the lungs may separate back into smaller nanoparticles, leading to the possibility of significant differences in material characteristics between inhalation and deposition. Research into de-agglomeration in the lungs remains limited although there is evidence that partial de-agglomeration might occur for some materials (Maynard, 2002). The break-up of aggregates is less likely, due to the strength of the forces holding the component nanoparticles together.

Considerations and Implications for Toxicity Studies on Nanomaterials

One of the challenges in identifying nanomaterial hazards lies in the analysis of the information once it is collected. As noted above, one of the more pressing limitations to identifying hazards arising from nanomaterials stems primarily from an inability to accurately characterize the potentially toxic agent. The lack of standardized practices for performing measurements on nanomaterials has resulted in reagents that are not always comparable between different studies. This can be the case in inhalation studies where polydispersed mixtures[18] of nano- to submicron-sized particles are introduced as the agent. In these cases, it is difficult to tell whether observed effects are due to the presence of the (often unknown) number of nanoparticles or the larger aggregates. Consideration

[18] Polydispersed mixtures are those containing a range of particle sizes (e.g., 2 nm to 50 nm) as opposed to a unique particle size (e.g., five nanometres).

must also be given to the chemical reactivity of the agents. The novel or enhanced reactivity of the nanomaterials could result in a chemical interference with certain types of hazard assessment assays. Hazard assessments for nanomaterials (as well as any other substance) must give due consideration to experimental conditions including factors such as contaminants in order to ensure that the measured toxicity is in fact representative of the material in question and not an inadvertent side-effect (Oberdörster, 2004; Zhu *et al.*, 2006; Li *et al.*, 2003; Xia *et al.*, 2004; Kagan *et al.*, 2006).

With the emergence of new analytical techniques and standards for characterization methods, it is likely that most of these concerns and limitations will be addressed. However, there remains a significant need for a more nano-specific arsenal of research tools and methodologies to allow for reliable identification of potential nanomaterial hazards.

HAZARD CHARACTERIZATION[19]

The World Health Organization (WHO) defines hazard characterization as "the qualitative and/or quantitative evaluation of the nature of the adverse effects associated with biological, chemical and physical agents" (WHO, 2004). More generally, it correlates the nature of the hazard's toxicity with its exposure route as well as identifies how the toxic effects manifest after exposure. In this way, it seeks to establish a fundamental understanding of the mechanism of action of the agent upon introduction into the system. Hazard characterization typically involves an examination of the dose-response relationship between an agent and the affected system.

Dose-Response Assessment with Nanomaterials

Traditional dose-response assessments often rely on extrapolating results obtained from *in vivo* hazard identification studies in rodent models to the human scenario. These extrapolations often have to address differences in both the magnitude and the duration of exposures used in these experimental studies to those experienced in the real world. Doses used in experimental studies (so that effects can be seen and measured) are generally much higher than those experienced via natural exposure. In addition, many studies in the

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[19] The term "hazard characterization" (as used in Health Canada's *Decision-Making Framework for Identifying, Assessing and Managing Health Risks*) corresponds to what is often called "Dose-Response Assessment." The language used herein is reflective of the Canadian terminology. It is important to note, however, that while the terminology may differ from framework to framework, the overall methodology and approach within each step remains consistent.

laboratory are short-term in nature but are used to predict doses where effects may arise from long-term exposures. In many cases, these extrapolations simply use modifying factors to account for these uncertainties — e.g., it is common to establish an "acceptable" exposure level 10-fold lower than the highest dose in a study in rodents where no effect was seen, to account for the human-rodent extrapolation. Then a further 10-fold reduction in the acceptable level is made to account for effects after long exposures, especially if the data were from a short-term study. As such the acceptable exposures for humans may be anywhere from 10 to 1,000 times lower than those established in experimental studies with other animal models.

Box 3.2 — Hazard Characterization Case Study Nano Titanium Dioxide (TiO_2)

Measurable Responses to TiO_2 Exposure:

Human Health — The biological activity of TiO_2 has been studied with respect to various biological responses both *in vitro* (lung epithelial cells and dermal fibroblasts) as well as *in vivo* (rat, mouse, guinea pig and human). Reported responses have included pulmonary inflammation and tumour induction (under lung overload conditions in mice), production of reactive oxygen species (ROS) and low levels of dermal/ocular irritation (Wang *et al*., 2007; SCCNFP, 2000; Oberdörster *et al.*, 1994; Oberdörster 2000; Warheit *et al.*, 2007a; Warheit *et al.*, 2007b; Sayes *et al.*, 2006).

Environmental — The main body of data on environmental responses to TiO_2 comes from studies done on daphnids and algae. Standard ecological toxicity tests (e.g., EPA 48-hour tox test and OECD 2002) appear adequate to examine the acute, systemic toxicity of TiO_2 and demonstrate low to moderate toxicity (Lovern and Klaper, 2006; Hund-Rinke and Simon, 2006; Wiench *et al.*, 2007; Warheit *et al.*, 2007b).

Measured Dose Dependence of Adverse Responses:

Human Health — Tests of the pulmonary toxicity of TiO_2 have yielded varied results. In dermal/ocular testing, various doses showed mild to no irritation and no evidence of irritation, sensitization, or photo-irritation/sensitization. Acute systemic toxicity studies in mice and rats revealed moderate to no toxicity with LD_{50}* values ranging from approximately 2 to greater than 5 g/kg. Human studies of TiO_2 inhalation showed low to moderate pulmonary inflammation upon inhalation of TiO_2.

Environmental — In most cases, the overall toxicity (for doses ranging from 2 mg/l to 100 mg/l) was reported to fall in the low to moderate range according to the U.S. EPA Standards. Less than half of the studies reported a quantitative LD/ED_{50} value. However, the presence of nanoscale TiO_2 bound to arsenic increased the arsenic uptake into carp (Sun, 2007).

Risk Characterization — Toxicity levels associated with some types of nanoparticle TiO_2 are well studied. However, there are several manufacturers of nano TiO_2 and the toxicity varies according to particle charge, surface coating and level of surface functionalization (Warheit *et al.*, 2007b). A detailed set of data for one commercially available product has been generated and publicly released. The comparative data above demonstrate diversity of responses in ecological test systems. U.S. EPA and Environment Canada chemicals policy characterize these aquatic toxicity levels as low to medium. This can be considered a semi-quantitative or qualitative risk assessment. The lack of data across exposure routes and types of nano TiO_2 limit the ability to define risk quantitatively. The National Institute for Occupational Safety and Health (NIOSH) has developed a risk assessment protocol for TiO_2 (NIOSH, 2005).

Considerations or Limitations to Available Data:

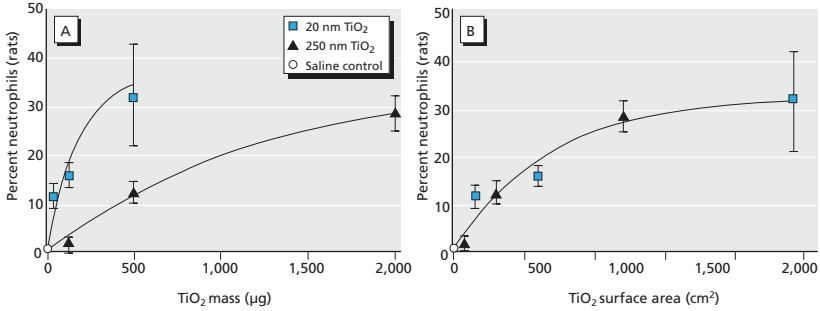
- Many studies are not clear regarding which form of TiO_2 was employed.
- Cell line-based (*in vitro*) studies are highly controversial because of the inconsistency in the results reported in the literature.
- The use of rat models has shown that this species is more sensitive than others when exposed to high doses of TiO_2 (and other particles) and may not be the most predictive model for human toxicity due to a phenomenon called "lung overload."
- Experimental results may not be comparable across various studies due to lack of consistent material reporting and/or characterization.

* The LD_{50} of a substance is defined as the dose required to induce lethality in 50 per cent of the test population. The ED_{50} is the median effective dose or, the dose required to elicit a given response in 50 per cent of the test population.

The enormous diversity of nanomaterials and their relevant properties makes it a daunting challenge to conduct *in vivo* evaluation on all those properties that may be responsible for eliciting a biological response. As such, *in vitro* methods have been proposed as a possible approach to assessing these relationships. However, preliminary tests with some nanomaterials have shown that *in vitro* testing may not always accurately predict potential hazards in more complex biological environments. Furthermore, extrapolating the dose-dependent *in vitro* response of an agent to a real world scenario is difficult due to factors such as the differences in behaviour of the nanomaterial *in vitro,* determination of appropriate dose metrics, and their relationship to observed toxicities. Measuring dose and biological response requires knowledge of the physical parameters or variables associated with the substance (e.g., physical and chemical properties of the nanomaterial) and the receptor (e.g., a cell line, an organelle, an organ or a whole animal). The inability to identify and measure the relevant physicochemical characteristics imposes a major limitation to establishing accurate dose-response relationships of nanomaterials.

The properties outlined in the previous section could facilitate meaningful data comparisons provided that there is consistency or intercomparability in characterization of the property (e.g., size distributions, shape or particle number) and a determination of an appropriate response-metric for each material. It is important to remember, however, that these parameters do not address the issue of *dynamic* change in properties once the nanomaterials are introduced into biological or environmental systems.

Ascertaining Appropriate Dose Parameters — As presented in earlier sections, the selection of appropriate dose and response parameters is not straightforward when attempting to characterize the potential hazards of nanomaterials. Studies of different nanomaterials have shown that the metric used to define the observed response will need to be specific to the material being evaluated. One example of the difficulty in predicting appropriate dose metrics are studies carried out on rodents using two different forms of titanium dioxide (Oberdörster, 2000).



- y-axis is plotted as the per cent neutrophils measured in rats. Neutrophils are a type of white blood cell generated by the immune system to fight infection.

(Oberdörster *et al.*, 2005a)
Reproduced with permission from National Institute of Environmental Health Sciences.

Figure 3.2
TiO_2 Induced Inflammatory Response in Rodents

In these studies, it was observed that ultrafine anatase TiO_2 (20 nm) generated a much greater pulmonary-inflammatory response than fine anatase TiO_2 (250 nm) upon exposure to equal mass doses (Figure 3.2A). Likewise, expressing the dose as a function of particle number also showed huge differences in the dose-response curve of the two materials. However, when the dose was expressed in terms of particle surface area (Figure 3.2B), both forms of TiO_2 followed a similar dose-response curve. These results suggest that particle surface area (for agents of the same chemistry) may be a better dose metric than particle mass or number. It should be noted that surface area/dose-response curves will vary as a function of material (e.g., less reactive TiO_2 nanoparticles will exhibit a different dose-response curve than more reactive copper nanoparticles). However, other studies have not demonstrated a close association with surface area when evaluating biological response to nano-sized TiO_2 quartz and other particles (Warheit *et al.*, 2006; Sayes *et al.*, 2007). Such conflicting results become problematic when trying to establish generic dose parameters for all classes of nanomaterials and indicate that identification of an appropriate dose metric may need to be done on a case-by-case basis for classes of nanomaterials.

Another difficulty in evaluating appropriate, material-specific dose metrics stems from inconsistent reporting of the measurements used to describe the physicochemical properties of nanomaterials. With the exception of size, almost all reported studies of nanomaterials describe the properties of the tested substances in a different way (Hagens *et al.*, 2007; Hansen *et al.*, 2007).

In a review by Hansen (2007), over 400 studies were examined that reported on a total of 965 nanomaterials. These limited studies addressed the mammalian toxicity, the cytotoxicity and (in a few cases) the ecotoxicity of the various materials. In general, the findings showed that "it was impossible to link specific properties of nanoparticles to the observed effects," and recommended that "future research strategies must have a strong focus on characterization of the nanoparticles tested." The lack of a standardized approach to nanoparticle measurements makes difficult a comparison of results across various studies, which in turn limits the capacity to begin identification of material-specific dose metrics. It is likely that many, if not all, physicochemical parameters discussed previously will be both relevant and necessary to accurately predict biological responses. *The diversity of possible nanomaterials is vast and the tolerances of a biological system to changes in the physicochemical properties of the nanomaterials that determine their behaviour are poorly understood.*

A database of standardized dose parameters (and their resultant biological responses) could help facilitate a more comprehensive understanding of the toxicity of nanomaterials as a function of physicochemical properties, even though this may be technically challenging. Establishing a unified classification system for nanomaterials could also alleviate inconsistency in naming a nanoagent under investigation and would advance the toxicology of nanomaterials. The development of reference nanomaterials and test protocols would contribute to the clarification of currently available scientific data and, at the same time, serve to underpin the development of nano-specific hazard characterization techniques.

Determining Biological Response — Common physiological responses that are used to describe the adverse impacts of a material are strongly dependent on the expected method of exposure. In the case of respirable contaminants, common response metrics include endpoints such as animal death (e.g., LD_{50}), change of body weight, development of fibrosis and granulomas, cardiovascular disease and the reduction of lung function. Given our current understanding of toxicological sciences, there are no new biological endpoints caused by the exposure of nanomaterials.

Beyond endpoint studies, a judgment on the biological response of nanomaterials could also be described at the molecular, cellular, tissue, organ, or even whole animal level. These studies would allow one to analyze the subtle response of a biological system to nanomaterials, which can provide more direct evidence of toxicity. In order to correlate the physical-chemical relationship of a nanomaterial with a biological response, it is important to conduct ADME (absorption,

distribution, metabolism and excretion) studies. As stated in Chapter II, an ADME study will provide the location of the biological interaction, which then can be further evaluated for a detailed understanding of molecular and cellular mechanisms in the targeted organ. Biodistribution and kinetic studies are a first route in determining toxicity of a nanomaterial. At the current time, there are a limited number of reports (less than 10 papers) that have investigated the *in vivo* biodistribution and kinetics of nanomaterials in a systematic format. A broad conclusion from these studies is that many of the nanomaterials studied (e.g., quantum dots, fullerenes and carbon nanotubes) appear to be taken up by organs (e.g., liver or spleen) that are part of the reticuloendothelial system.[20] The blood clearance appears to be related to the surface chemistry of the nanomaterials. Fischer *et al.* (2006) showed that quantum dots that possessed different coatings exhibited different half-lives (i.e., 59 minutes for an organic acid-based coating and 39 minutes for a protein-based coating). Both of these quantum dots were above 20 nm. However, they demonstrated that these quantum dots were not excreted from the body (Fischer *et al.*, 2006). Other studies have shown that the blood clearance half-life of carbon nanotubes is three hours. In contrast to the quantum dot in the Fischer study, these carbon nanotubes were excreted from the body (Singh *et al.*, 2006). Based on these biodistribution and kinetic studies, researchers are targeting the specific organs and cells involved in nanotoxicity. *Nevertheless, based on the current understanding of toxicological sciences, there are no new biological endpoints caused by the exposure to nanomaterials. The mechanisms by which nanomaterials are transported or translocated in the human body and the environment may be substantially different, but no scientific studies thus far have shown new endpoints to the biology or ecology.*

Overall Assessment of Toxicity

Based on the previous discussion, the traditional approaches and methodologies that have been established for routine toxicological characterization of chemicals are likely to be sufficient to examine the toxicological properties of nanomaterials. The physicochemical properties of nanomaterials do not appear to result in the manifestation of novel biological responses. While the biological endpoints will remain the same, it is likely that these endpoints may be reached via novel and/or unpredicted pathways. However, this must be

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[20] The reticuloendothelial system is part of the immune system and consists of a widely distributed collection of macrophages (cells possessing the ability to break down and eliminate pathogens) located in various connective tissues throughout the body (e.g., thymus, lymph nodes, tonsils and spleen).

qualified by the recognition that these studies are inherently limited by the current lack of standardized characterization and reporting. The presence of over 400 studies on the health and environmental risks of nanomaterials and the persistent lack of definitive evidence for novel, nano-specific biological responses supports this view. These limitations were observed in the final report of a workshop held in 2004, where it was stated in the summary that: "The use of currently available analytical techniques to detect and quantify nanoscale structures in biological systems was considered critical for both guiding the selection of the specific toxic endpoints of interest, and for following the movement of nanoscale materials in biological systems" (NIEHS, 2004). The inherent limitations to these techniques exist for all substances and are not specific to engineered nanomaterials. *To date, there are no unique biological effects associated with exposure to nanomaterials, but there is still a poor understanding of how specific nanomaterials lead to specific endpoints.*

EXPOSURE ASSESSMENT

A hazard can only cause harm if there is an exposure pathway to enable it to reach a receptor, be it human, an organism or an environmental medium (e.g., air, water and soil). There are both biological and environmental aspects of exposure to consider in an exposure assessment. The transport and fate of a nanomaterial defines how it moves in the environment and determines the extent to which environmental exposure occurs. Biological exposure considers what happens when a receptor comes in contact with the substance, determining how much is absorbed into the body (or ecological population) and defining the level of contact where it may cause harm. Both biological and environmental aspects of exposure require consideration with regard to nanomaterials.

Box 3.3 — Exposure Assessment Case Study Nanocerium Oxide (CeO_2)

Likely Sources of Exposure throughout the Life-Cycle:

- *Production and Manufacturing* — Occupational exposure might occur during extraction and refinement processes as well as product manufacturing. Accidental exposure during shipping, handling and/or storage could also occur.
- *Non-Consumer* — Public and environmental exposure could result from exposure to exhaust fumes from automobiles.
- *Consumer* — Consumer exposure could result from the use of cosmetics and/or household items containing CeO_2.

- *Post-Consumer* — Secondary exposure may occur from use as a fuel additive. Releases to air from exhaust could deposit on land and water, while accidental releases of fuel could introduce ceria to ground water. Disposal of products containing ceria via landfill, incineration or other pathways could include release to air from incineration, and releases to land, food and plants from waste water treatment (including from solid waste landfill leachate). These pathways may or may not include nanoparticulate forms of ceria.

Likely Routes of Exposure:

As produced — Inhalation and Dermal
Cosmetics — Dermal
Medicinal — Ingestion
Fuel Additive — Inhalation, indirect environmental exposures (deposited on soil)

Current Environmental Levels:

Concentrations in surface water and sea water are at or below the part per trillion range. In groundwater contaminated by a landfill in California the concentration was approximately 1 mg/L (or 1 ppm). Ceria was not detected in waste water or landfill leachate in a U.S. survey, but concentrations from sewage sludge ash in Japan were 35 ppm (NTP, 2006). Ambient air concentrations are generally less than 10 ng/m^3. In California, concentrations were less than 1 ng/m^3 in fine and ultrafine particles. Soil concentrations in Great Britain were in the 47 ppm to 136 ppm range near roadways, and 38 ppm in rural areas (HEI, 2001).

Available and Needed Analytical Techniques:

Standard analytical techniques for measuring ceria are useful for measuring the total mass and concentration. These techniques may be supplemented with microscopic visualization to assess the particle-size distributions. However, real-time measurements of nanoparticle CeO_2 are not currently available.

Exposure can generally be grouped into three categories: workplace exposure, consumer use and environmentally mediated exposure (EPA, 2007), and has been defined as the contact over time and space between a person and one or more biological, chemical or physical agents. Exposure assessments serve to identify and define the exposures that occur, or are anticipated to occur, in human populations (IPCS, 1993) or ecological environments, and can be a quantitative or qualitative

evaluation of the degree of intake likely to occur (WHO, 2004). As in the case of hazard identification, a determination of "zero exposure" would mean that no risk is present — thus, risk requires the simultaneous presence of both a hazard (or multiple hazards) and exposure. People are exposed to a variety of potentially harmful agents everyday such as natural background low-level radiation, gas and particulate pollutants in the air they breathe, the liquids they drink, the food they eat, the surfaces they touch and the products they use. Environmental receptors may be exposed by intentional (e.g., the use of nanoparticles for environmental remediation) and incidental exposures via air, water, soil and food.

The primary considerations in exposure assessment are the likelihood, magnitude and route(s) of exposure along with the population or sub-population (e.g., hypersensitive group of the population) that could be exposed. The likelihood of exposure addresses the probability that contact between a potential hazard and a human or environmental receptor can occur and requires identification of the potential pathways through which this could happen. The magnitude of exposure involves knowledge or estimation of both the amount (e.g., volume or concentration) of exposure as well as the duration of the exposure. Potential routes of human and animal exposure to nanomaterials include inhalation, absorption through eyes, absorption through the skin and ingestion. In medical applications, for example, a patient could also be exposed to nanomaterials and nanomedical devices through needle injection or ingestion. For an ecological pathway, an entire ecosystem may be exposed through one or more routes. For example, a substance introduced into a wetland could result in exposure to organisms via ingestion (at all levels of the food web) or dermal absorption.

Performing Exposure Assessment on Nanomaterials

The uncertainty regarding appropriate metrics for quantifying the exposure of nanomaterials in the workplace causes difficulties when attempting to identify monitoring techniques for exposure to these potential hazards. These difficulties are compounded by the limited availability of analytical tools and techniques that are sensitive and/or specific enough to study nanomaterial exposure. For example, commercially available particle counters are capable of detecting the presence of nanoparticles as small as a few nanometres in sphere-equivalent diameter in seconds. However, engineered nanoparticles may only be a tiny fraction of the detected nanoparticle count. Thus, use of the particle count data without any discrimination against the real subject may significantly overestimate the presence of, and therefore exposure to, engineered nanoparticles. That could likely lead to ineffective exposure control

mechanisms. The ability to detect specific exposure against background (or incidental) exposure could require new analysis techniques (Maynard and Aitken, 2007). These new methodologies will need to use not only traditional benchmarks such as mass concentration (e.g., in the units of mg of target agent per m^3 of air), but also establish new ones by considering those physicochemical properties of nanomaterials that may affect their ultimate, biological and environmental behaviour. Thus, it is unlikely that a general measurement criterion can be applicable to all nanomaterials. *Prevailing human and ecological risk assessment frameworks are robust, but their application to nanomaterials requires new ways for measuring exposure, dose and response.*

Routes of Exposure — A Life-Cycle Approach

Figure 3.3 illustrates the complex and interconnected pathways that link the various aspects of both human and environmental exposure. Toxicologists study the biology of materials in order to ascertain how a substance gets into the body, how much can enter and what happens once it is inside. Consideration of environmental sources of exposure requires the study of more indirect pathways such as workplace, consumer or environmentally-mediated exposure — i.e., how a substance gets to a location where human or non-human exposure could occur.

Experience with chemical substances demonstrates the need to broadly consider the potential for exposure throughout a product life-cycle. Brominated flame-retardants, for example, were discovered to be widespread in the environment when they were detected in polar bears in arctic waters, far from the consumer products they originally coated. Such exposure levels were not predictable from their management in occupational environments, or their incorporation into furniture, computer equipment and a host of other home-use products. While not specific to nanomaterials, the nature of exposure is also likely to vary throughout the product life-cycle for emerging substances. Therefore, in order to fully understand all the possible sources and modes of exposure, a product or material must be examined throughout its entire life-cycle (from the point of manufacture to post-disposal stages). An understanding of the life-cycle of a product/material can provide information regarding what environmental routes are likely (e.g., water, air), and consequently what biological routes are important (e.g., ingestion or inhalation).

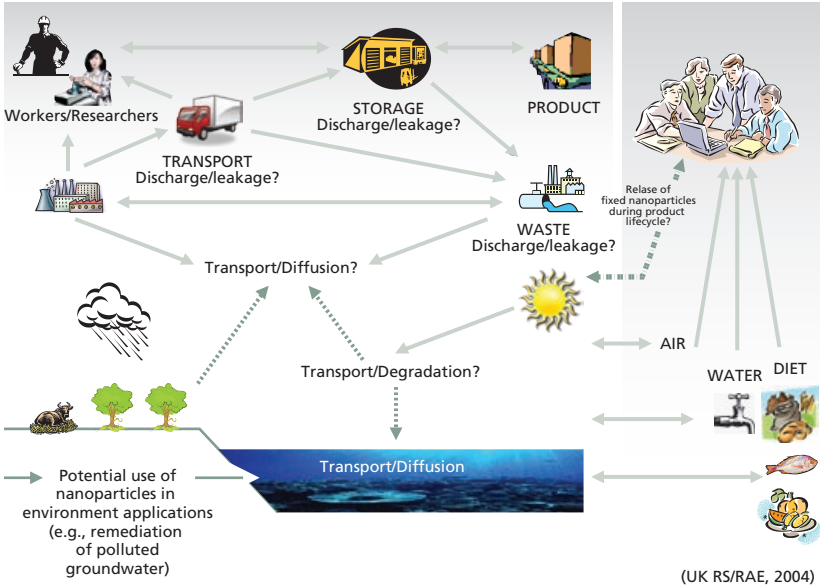
A life-cycle approach to exposure assessment is not a new concept. It has been advocated for use in all types of general risk assessment, particularly for new and emerging substances (Davis, 2007; Shatkin, 2008; EPA, 2007; EC, 2003). Past examples of the introduction of new substances into the environment — e.g., PCB's, brominated flame-retardants, halogenated refrigerants — have demonstrated that simply looking at manufactured products and their immediate uses is not sufficient to predict long-term health and environmental outcomes. Systematic life-cycle approaches allow for identification and prioritization of points of exposure such that risk management steps can be taken at appropriate points during the product's lifespan to minimize exposure to a potentially hazardous material. *Changes in the potential for nanomaterials to cause harm at different stages in their life-cycle imply a need for a life-cycle approach to risk assessment.*

Risk Characterization

Risk characterization is defined as, "the integration of hazard identification, hazard characterization and exposure assessment into an estimation of the adverse effects likely to occur in a given population, including attendant uncertainties" (WHO, 2004). For a known risk to exist, there needs to be both a known hazard *and* known exposure. Once a hazard has been identified and potential exposure has been characterized, then characterization of the risk involves looking at the data behind each step and determining what the overall risk will be. In general, there are two types of risk assessment or characterization that can be done. A quantitative assessment is based on collection and quantitative analysis of data sufficient to adequately characterize the risk (DiNardi, 2003). A qualitative assessment is the estimation of the risk based on integration of available information and professional judgment. In the absence of definitive data, methodologies for assessing the uncertainty surrounding a hazard are developed and applied. Such measures generally employ conservative assumptions of risk — the following section and Chapter IV will address this issue in further detail.

Risk Characterization with Nanomaterials

The lack of understanding regarding what levels of exposure constitute a potential hazard adds another layer of complexity to the issue of assessing human and environmental risks. While many household products come labeled with recommended precautions or usage instructions, these data remain largely unknown for nanoproducts. This lack of metrological capacity (both in terms of measurement and dose estimations) represents a limiting factor when evaluating the potential risks of nanomaterials.



(UK RS/RAE, 2004)
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Figure 3.3
Graphical Depiction of Possible Exposure Pathways Throughout a Product Life-Cycle

Existing risk characterization methodologies often employ a comparative approach — i.e., the likening of a new material and its properties or behaviours to another material that is already regulated. This method would involve looking at nanomaterials as smaller versions of existing substances and drawing analogies and predictions based on the parent material. Given the known properties of some nanomaterials, this method will not prove effective for all nanomaterials. For example, gold (in bulk or macroscale quantities) has been regulated for decades and is one of the most inert materials in use. On the macroscale its properties have been well characterized: metallic yellow in colour, excellent conductivity properties, non-magnetic, relatively low melting point, etc. In nanoparticle form, however, it can vary in colour from red to black in solution (depending on its size), it can act as either a conductor *or* a semiconductor, it can become highly reactive, and can even be magnetic. These changes in physicochemical properties suggest that comparisons of nanogold to its larger-scale counterpart may not serve as an accurate, predictive model (Rosi and Mirkin, 2005). While most materials are likely to undergo some changes in the transition from macroscale forms to nanoscale forms, unusual scale-specific properties may only manifest themselves at the smallest sizes in some cases. Such properties are not well understood and confound the ability to confidently produce quantitative risk estimates.

Eventually, it is reasonable to expect that the relationships between properties and toxicity will be measureable, allowing quantitative risk estimates. However, it is currently more reasonable to consider less quantitative determinations that assess, for example, high, medium or low environmental risk. Such qualitative, or ranking, exercises are commonly found in risk analysis. Overall, the lack of definitive data limits the risk assessment of most nanomaterials to a qualitative assessment. *There are inadequate data to inform quantitative risk assessments on current and emerging nanomaterials. At most, only qualitative risk assessments are feasible, given the current state of knowledge.*

Despite the lack of sufficient data to inform a quantitative risk assessment on engineered nanomaterials, the work of the panel has not identified any evidence that the existing nanoproducts currently in Canadian trade and commerce present hazards and/or routes of exposure to humans or the environment that cannot be addressed through available risk management strategies. This lack of evidence arises in large part from the limitations in the research to date identified above, and so priority should be given to a strategic research agenda to address these limitations as quickly as possible. The implications to risk management of this situation are discussed more fully in Chapter IV.

Strategic Risk Research

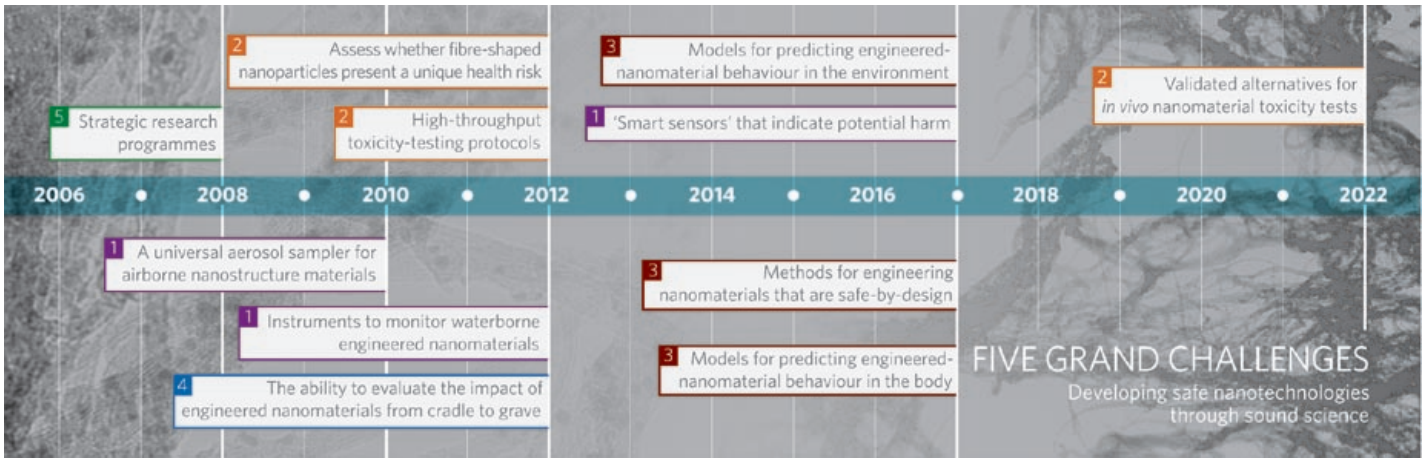
Given the current gaps in knowledge that prevent quantitative risk assessments to be conducted on current and emerging nanomaterials, a number of organizations have made recommendations on research that is needed to fill the gaps. Perhaps the first authoritative such set of recommendations appeared in the 2004 Royal Society/Royal Academy of Engineering report (UK-RS/RAE, 2004). Since then, notable contributions to the debate over what research is needed, and by when, include publications from the U.S. Environmental Protection Agency (EPA), the U.S. National Institutes for Occupational Safety and Health (NIOSH), the American Chemical Society, the U.K. government and the European Commission. Most recently, the National Nanotechnology Initiative (NNI) released a long-awaited research strategy for nanotechnology-related environmental, health and safety research in the United States (NNI, 2008).

In 2006, the journal *Nature* published an article written by 14 internationally respected scientists that outlined their list of the five "grand challenges" to ensuring the safety of nanotechnology (Figure 3.4) (Maynard *et al.*, 2006). These addressed overarching research needs in the areas of exposure monitoring, instrument development, toxicity testing, predicting nanoscale

material impact, developing life-cycle approaches to using nanotechnologies safely and implementing targeted research strategies. Since publication of this paper, there has been a move towards more focused research programs, particularly in Europe and the United States. In addition, the Organisation for Economic Cooperation and Development (OECD) has begun the process of coordinating research initiatives in member countries through the Working Party on Manufactured Nanomaterials. However, there remains a dearth of research strategies that lay out a clear roadmap to filling essential knowledge gaps, especially in the Canadian context.

In July 2006, Maynard published a comprehensive assessment of short, medium and long-term research needs (Maynard, 2006a). The argument is made that research in the short-term should be a balance between targeted research addressing immediate needs, and early investment in exploratory (but still goal-oriented) research addressing longer-term issues (Table 3.2). More importantly, the case is made for developing a strategic research plan that provides a clear path towards generating knowledge that will underpin safe use of nanotechnologies, complete with funding and mechanisms (including international collaboration) that will enable the plan to be executed.

While no previously published research agenda is a substitute for developing a Canada-specific strategy, together these agendas from other jurisdictions provide a clear starting point for identifying what is important to address, and by when, in order to underpin the development and commercialization of safe and successful nanotechnologies. *In all cases, it is clear that systematically targeted research is needed to fill the knowledge gaps and reduce uncertainty.*



(Maynard *et al.*, 2006)

Figure 3.4

Five "Grand Challenges" Identified by Leading Scientists to Ensuring the Development of Safe Nanotechnologies

Table 3.2
Comprehensive Assessment of Short, Medium and Long-term Research Needs

Category	Research Needs
Immediate research needs	• Appropriate measurement methods • Best practices for working with engineered nanomaterials • Engineering controls • Exposure routes • Instrument-based exposure metrics • Personal protective equipment and respirator development and evaluation • Potential release routes • Process-based controls • Responsive and effective methods of doing risk research • Toxicity screening tests
Early investment in medium-term research	• Control and management of spills • Dose-metrics relevant to target testing • Health outcomes associated with exposure • Life-cycle analysis • Measurement standards • Nanomaterial characterization • Predictive toxicology — role of physicochemistry and mechanisms of toxicity • Risk assessment • Routes for entry into the body • Safety (risk of physical harm) • Toxicity evaluation, including identification of appropriate endpoints and testing methods
Early investment in long-term research	• Computational toxicology • Control — substitute materials • Dispersion, transformation, fate, persistence and bioaccumulation in the environment • Ecotoxicity — toxic mechanisms • Informatics • Nanomaterials release into the environment • Standards — terminology, reference materials • Structure activity relationships • Transport, transformation and fate in the body

(Maynard, 2006a)
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SUMMARY OF CHAPTER III FINDINGS

3.1 Nanomaterials can pose particular challenges to risk assessment, and hence to regulation, because they exhibit properties based on their physical structure and their chemistry.

3.2 The diversity of possible nanomaterials is vast and the tolerances of a biological system to changes in the physicochemical properties of nanomaterials that determine their behaviour are poorly understood.

3.3 To date, there are no unique biological effects associated with exposure to nanomaterials, but there is still a poor understanding of how specific nanomaterials lead to specific endpoints.

3.4 Prevailing human and ecological risk assessment frameworks are robust, but their application to nanomaterials requires new ways of measuring exposure, dose and response.

3.5 Changes in the potential for nanomaterials to cause harm at different stages in their life-cycle imply a need for a life-cycle approach to risk assessment.

3.6 There are inadequate data to inform quantitative risk assessments on current and emerging nanomaterials. At most, only qualitative risk assessments are feasible, given the current state of knowledge.

3.7 Systematically-targeted research is needed to fill the knowledge gaps and reduce uncertainty.

Chapter IV – Underpinning Regulatory Perspectives on Nanomaterials

The previous chapter describes properties of nanomaterials that are relevant to the determination of their safety in products, in workplaces and in the environment. While engineered nanomaterials have attractive properties making them a high priority for those seeking to realize their potential benefits, those same properties present a challenge to their regulation. These include, for example, their non-scalable effects on chemical reactivity, their dynamic nature and their ability to exhibit properties based on their chemical structures, their physical structures or both. How these nano-specific properties translate into biological or environmental behaviours is still poorly understood, making it more difficult than in the case of currently regulated chemicals to evaluate dose and toxicity *in vivo*; a situation complicated by the limited understanding of appropriate metrics for animal models and the unavailability of reproducible studies.

Beyond the uncertainties in our understanding of nanomaterial properties, there is a lack of clarity and precision with respect to the identification of standards for measuring and evaluating the effects of exposure to nanomaterials. In particular, because of the limited ability to measure and quantify nanomaterials, there is insufficient understanding of the initial pathways by which exposure might occur. Regulators require quantitative tools to conduct science-based risk assessment of emerging technologies. At present, they do not have a complete or reliable toolkit to answer fundamental questions about nanotechnology because the basic scientific research needed to develop and defend an efficient and effective risk management strategy has yet to be completed.

It is neither unusual nor unexpected for an emerging field of science and technology to raise more questions than it answers. Similar situations have been encountered with other technologies; most notably (but not limited to) biotechnology and nuclear technology. Thanks to the experience with and study of those prior technologies, regulators are better placed to develop regulatory management strategies appropriate to the early stages in the development and implementation of new technologies. We are in a position to better understand the complexities involved in regulating novel technologies in the public interest, in the absence of the science that supports a reliable system of risk assessment and risk management. These complexities are outlined in the following text.

The findings of Chapters II and III lead to the following three conclusions: (1) there is a lack of information about nanomaterials in general because there are limited studies providing material characterization adequate to draw solid conclusions with respect to the materials studied; (2) the mechanisms by which nanomaterials might yield adverse biological and environmental effects are not well understood; and (3) there is a lack of well-accepted metrics by which to measure the effects of nanomaterials in human and natural environments. Based on the findings in Chapter III, it can be concluded that the current state of science regarding nanomaterials is insufficient to provide a comprehensive understanding of their behaviours or to arrive at quantitative characterizations of the risks they may impose upon human health or the environment.

The three conclusions just drawn show that there are different sources of uncertainty about nanotechnology. Box 4.1 gives the definition of certain terms associated with the principle of uncertainty. Some of this uncertainty is due to simple *ignorance* — gaps in understanding that can be filled by the development of new scientific tools and more research. Some of it is a form of *ambiguity* — where the appropriate "yardstick" or "metric" is missing or disputed. Sometimes, uncertainties exist as a result of disagreement with respect to the disputed frameworks with which scientists attempt to understand underlying physical or biological systems.

Where these uncertainties remain in science and technology it is not possible to reach definite conclusions about the risks posed by these new materials and products. In these circumstances, regulators therefore need to make choices that cannot be based upon firm assurances that the potential risks fall well within established standards of safety. Instead, they will need to depend upon a broader set of considerations related to public values and perceptions. In some cases the strong weight of public opinion will support the pursuit of the benefits promised by the technology. In other cases, aspects of the technology and the profile of its potential risks may engender more cautious attitudes. These choices in turn will shape the future development of the technology by fixing standards, identifying areas in which to pursue greater research effort and developing communities of practice in the regulatory agencies. Uncertainty in science and regulation can inhibit technology development and undermine public confidence in the ability to adequately protect human health and environmental quality. *Uncertainty in science can be offset by clarity and certainty in the terms and conditions under which such materials may enter trade and commerce.*

Box 4.1 — Different Qualities of Uncertainty

Risk: under which we know both the probabilities of possible harmful events and their associated kinds and levels of damage. This is where the various techniques of risk assessment are most usefully applicable.

Uncertainty: where we know the types and scales of possible harms, but not their probabilities. This is the best established "strict" definition of the term "uncertainty," under which "risk assessment" is strictly not applicable.

Ignorance: where we don't have complete knowledge over all the possible forms of harm themselves. Where we "don't know what we don't know" — facing the possibility of surprise. This renders problematic even the questions that we ask at the outset in risk assessment.

Ambiguity: where the problem at hand is not one of the likelihood of different forms of harm, but where the measurement, characterization, aggregation or meanings of the different issues are themselves unclear, disagreed among specialists or contested in wider society. For example, how exactly do we define "harm" or "risk"?

Indeterminacy: where the possibilities for different social "framings" depend "reflexively" on complex interactions and path dependencies in the co-evolution of social, technological and natural systems. In other words, not only do our commitments and choices depend on what we know, but what we know is conditioned by our preferred or expected commitments, values and choices.

Adapted from European Commission, 2007

From the perspective of an innovator, under-regulation can be just as detrimental to getting products approved as over-regulation. Under-regulation leads to increased risk for the innovator by opening up multiple avenues of direct and indirect regulation (i.e., by provinces, through the courts or through other specialized tribunals) as actors struggle to establish the ground rules. It also leads to uncertainty as regulators themselves attempt to determine, based on inadequate rules, what their jurisdiction is and how it can be exercised. Further, public confidence in the technology may erode if there is a perceived absence of regulation, leading to fewer sales and the possibility of political intervention. Industry generally prefers certainty over uncertainty, even where that means greater regulation. One need look only at industry's reaction to climate change to see this (Little, 2006; Gelbspan, 2000). Industry does not, by and large, resist

new regulations — in fact, many participants call for them — but wants to avoid having to comply with multiple sets of regulations from different provinces and states, and wants to ensure that the rules are clear and binding on all. *Evidence from other industries suggests that the private sector prefers to have regulatory certainty even if the level of precaution invoked is relatively high.*

The preferred option for the regulator is to be able to set out science-based, transparent regulatory pathways for new product approvals that safeguard the public's interest without stifling innovation. Uncertainty in nanotechnology makes the job of regulators more difficult because they lack the knowledge upon which to make evidence-based decisions. But it does not make it impossible, since regulators can use the very fact of uncertainty as the evidentiary basis for regulation. Although this may seem paradoxical, uncertainty in science and technology need not generate uncertainty in regulation because a regulatory framework responds to uncertainty by taking a precautionary approach (see precautionary approach below). What this means is that regulatory processes are able to handle various degrees of evidence and changing balances of uncertainty. In fact, the same regulatory processes can handle new technologies, adapting to increasing levels of evidence (and reduced levels of uncertainty). *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 the risk and the selection of standards of safety.*

That nanotechnology is currently associated with high levels of scientific uncertainty need not deter the development of new products. Nor should it prevent these products from entering the Canadian markets. This chapter reviews the challenges that nanomaterials will pose to the regulatory system. In particular, this chapter examines three central questions that regulators must address:

1. How does one undertake to assess and manage risk in a precautionary manner under conditions of scientific uncertainty?

2. How should the question of acceptable risk be decided under the current state of scientific knowledge about nanomaterials and products?

3. How can the policy and regulatory system adopt foresight mechanisms to identify new regulatory triggers, regulatory paths, evidentiary standards and capacity for the evaluation of evidence?

These three questions cannot be analyzed in isolation from one another. For example, determinations of what types and levels of risk are acceptable will depend on the nature and depth of current evidence. On the other hand, the types of evidence one considers and how one analyzes it will depend in turn on the level and type of risks that are considered acceptable. Further, knowing the nature and implications of the decision one must take will identify gaps in knowledge or in skill that would assist decision making. In what follows, each of these questions will be discussed in depth to reveal these connections.

A PRECAUTIONARY APPROACH TO RISK ASSESSMENT

As with many new technologies, one of the challenges for regulators confronting nanotechnology arises from the need to ensure public safety when new products and materials are introduced. To achieve this, it has become best practice to perform a risk assessment of new products, identify potential areas of concern for human health and environmental integrity, and implement appropriate risk management strategies. In Chapter III, it was concluded that despite the lack of sufficient data to inform a quantitative risk assessment on engineered nanomaterials, the available evidence regarding existing nanoproducts currently in Canadian trade and commerce suggests that they present no known hazards and/or routes of exposure to humans or the environment that cannot be addressed through existing risk management strategies. This lack of evidence is in part a function of limited data and points to the need for further examination of these (and emerging) nanomaterials. The preceding text identified three questions that regulators will need to address in order to manage the safe and effective incorporation of nanomaterials into society. This section addresses the first of these three questions: How does one undertake to assess and manage risk in a precautionary manner under conditions of scientific uncertainty?

Precaution in Regulation

The Canadian regulatory system is based upon the principle that where there are significant levels of uncertainty in the scientific assessment of risks it is appropriate to exercise caution in favour of protecting human health and the environment (PCO, 2003). This presumption in favour of safety is commonly referred to as the application of precaution, or the "precautionary approach."

The precautionary principle has become a widely recognized component of national and international environmental law. It is cited in more than twenty international laws, treaties, protocols and declarations. It is also clearly invoked

in international agreements affecting the regulation of plant and animal biotechnology in trade. For example, the *Cartagena Protocol* on Biosafety authorizes the use by importing countries of the precautionary principle as a basis for excluding plants and food products from their markets (CBD, 2000). The language of Articles 10.6 and 11.8 of the Protocol has been appropriated in many other national and international regulations. *The Canadian Environmental Protection Act* (CEPA) provides, for example, that "the Government of Canada is committed to implementing the precautionary principle that, where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation." Other Canadian statutes, including the *Canadian Environmental Assessment Act* and the *Oceans Act* also refer specifically to the use of a "precautionary approach."

Table 4.1
Five General Principles of Application & Five Principles for Precautionary Measures

Five General Principles of Application	Five Principles for Precautionary Measures
The application of precaution is a legitimate and distinctive decision making approach within risk management.	Precautionary measures should be subject to reconsideration, on the basis of the evolution of science, technology and society's chosen level of protection.
It is legitimate that decisions be guided by society's chosen level of protection against risk.	Precautionary measures should be proportional to the potential severity of the risk being addressed and to society's chosen level of protection.
Sound scientific information and its evaluation must be the basis for applying precaution; the scientific information base and responsibility for producing it may shift as knowledge evolves.	Precautionary measures should be non-discriminatory and consistent with measures taken in similar circumstances.
Mechanisms should exist for re-evaluating the basis for decisions and for providing a transparent process for further consideration.	Precautionary measures should be cost-effective, with the goal of generating (1) an overall net benefit for society at least cost, and (2) efficiency in the choice of measures.
A high degree of transparency, clear accountability and meaningful public involvement are appropriate.	Where more than one option reasonably meets the above characterization, then the least trade-restrictive measures must be applied.

(PCO, 2003)

In a 2003 report entitled "Framework for the Application of Precaution in Science-Based Decision Making About Risk," the Government of Canada elucidated 10 key principles — "five general principles of application" and "five principles for precautionary measures" (Table 4.1) (PCO, 2003). Departmental and agency officials are expected to consider these guiding principles in decision making and to work together — in consultation with the relevant stakeholders — to develop guidance for the application of precaution in their particular areas of responsibility.

The precautionary approach is the subject of many criticisms. Most of these claim that the approach involves a decision to move away from a rigorous "science-based" approach to risk management by introducing extra-scientific social and political considerations into the regulatory system. For example, it is often argued that the principle involves a concession to social concerns and fears about the safety of a technology when there is little or no scientific basis for such concerns, thus permitting irrational fears, induced by media sensationalism and interest-group propaganda to determine public regulatory policy. This constitutes a misunderstanding of the principle, which is, in fact, based solidly on science-based regulation.

Burden of Proof

Under conditions of scientific uncertainty, precaution is an unavoidable aspect of decision making. This is easily understood in terms of the traditional problem of the Type I and Type II error in the handling of scientific uncertainty. The Type I errors occur when a scientific hypothesis is affirmed which ought to have been rejected in the light of future evidence. Type II errors occur when a hypothesis is rejected which later turns out to be true in light of future evidence. Regardless of the current level of scientific information, a decision must still be made as to which hypothesis will be accepted.

In the context of assessing the potential risks of nanomaterials, one could state the hypothesis to be that nanomaterials pose no risks to human and environmental safety. Thus, a Type I error would result in future scientific results showing that nanomaterials *do* in fact, pose human and or environmental health risks. If, however, this hypothesis was not accepted (i.e., it was decided that nanomaterials did pose health and environmental risks) a Type II error would mean that the hypothesis was rejected and nanomaterials would be treated as potential risks until future results showed otherwise. In this context, a Type II error is less serious than a Type I error. If one fails to affirm a hypothesis that turns out to be true, this can be cited as evidence that one has

adopted an attitude of fallibilism towards the scientific hypothesis. This type of fallibilistic approach could be described as "precautious" in its attempt to avoid an error of Type I. Such an approach often requires a high standard of proof to overcome the rejection of the hypothesis (Schrader-Frechette, 1991).

In Canada, as in many regulatory regimes, the burden of proof is often given to the producer to provide evidence of the safety of a product or technology. In effect, this means that the product is presumed to be "risky until shown to be safe." In this context, scientific investigation is required to overcome the hypothesis that the product or technology may pose unacceptable risks to human health or the natural environment. The requirement that the scientific data provide full confidence that the product does not involve unacceptable risk can be difficult, if not impossible, to meet (it involves the task of "proving the negative") (Salter *et al.*, 1988).

Such a rigorous scientific requirement is highly precautionary with respect to human and environmental safety. It would keep products off the market unless producers could prove them to be safe, with full scientific evidence of their biological behaviour and interaction within human organisms and natural ecosystems. Essentially, it would be next to impossible to place new products on the market. Few Canadians would argue in favour of this extreme level of precaution with respect to all technologies and products as it would deprive of us of the benefits of technology. Moreover, we learn from our experience and apply that knowledge to how we handle emerging technologies (Einsiedel, 2008). At the same time, many Canadians might support such a high level of precaution with respect to hazards that could be potentially catastrophic and irreversible.

It would thus be unwise to require the "proof of the negative" with high levels of confidence with respect to many or even most technologies. Such a requirement would necessitate subjecting every new product to a rigorous, time consuming and costly scientific assessment process regardless of its known chemical and biological character, the theoretical scientific reasons for suspecting potential associated hazards, and the nature and severity of the hazards themselves. Thus, the claim often heard that precaution always requires a proof of the negative is largely a straw man describing only the most extreme demand for a particular kind of proof. Moreover, a demand for a proof of the negative would be inconsistent with the Canadian regulatory system and its use of the precautionary approach.

For these reasons, science-based regulation of new technologies requires risk assessors to exercise a series of discretionary judgments about how to carry out risk assessment. One of the most important of these judgments involves the level of confidence in the available data to establish that the technology is safe. For many products, and with respect to many types of hazards, the appropriate level of precaution would be obtained by requiring a "preponderance of evidence" or a "weight of evidence" standard of proof. For other, lesser hazards a mere prima facie case that the product is safe might be sufficiently precautionary.

DETERMINATION OF "ACCEPTABLE" RISK

The absence of unequivocal evidence (either for or against) the potential hazards associated with nanomaterials, and the current and ongoing introduction of nanomaterials and nanoproducts into the Canadian market, means that regulators will need to formulate governance strategies in the current climate of uncertainty. The foregoing discussion outlined how the application of precaution in regulation should consider both the potential hazard and the level of proof surrounding a new product or technology such that an appropriate level of precaution is invoked. This issues raises the following question: "How should the question of acceptable risk be decided under the current state of scientific knowledge about nanomaterials and products?" In other words, how does one determine the "appropriate level of precaution" and/or define an "acceptable risk?"

Precaution in the Face of Uncertainty

The level of precaution appropriate to the type of technology and hazard involved will be reflected in the safety standards applied to the risk (how much risk is acceptable?) and in the kind of management strategies adopted to maintain the risk within acceptable levels. High levels of precaution are exercised when "zero-risk" safety standards are invoked.[21] Lower levels are exercised with various "threshold" standards of risk acceptability.[22] Risk/benefit standards, which permit any level of risk as long as it is outweighed by the benefits to be gained, are generally the least precautionary with respect to

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[21] An example of a "zero-risk" safety standard is the "No Observable Adverse Effect Level" standard (NOAEL) used in the management of carcinogenic substances in many regulatory systems.

[22] The "Natural Background Level" standard, often used with respect to exposures to hazards naturally present in the environment (e.g., radiation) is an example of a "threshold" safety standard.

human and environmental health risks, but are obviously more cautious to avoid depriving us of the benefits derived from a technology or product. Similarly, different risk management strategies adopted by a regulatory agency involve different levels of protection hence, precaution. Allowing industry to self-regulate — that is, make its own decisions with respect to the safety of its own products — falls on the less precautionary side of the spectrum of regulatory strategies for conflict of interest reasons. Pre-market approval strategies, in which industry is required to conduct rigorous scientific risk assessments before licensing or registration, fall on the other end of the spectrum. That is, they are much more precautionary of human and environmental health. Post-market surveillance strategies fall in the middle of the spectrum insofar as they accept the possibility of potential harm to the public or environment, relying on surveillance mechanisms to identify those harms before they can cause too much damage. In combination with pre-market approval strategies, however, they may be the most precautionary of all.

The choices inherent in the application of risk assessment and management illustrate that science-based regulation cannot avoid judgments about which elements among the risks and benefits of a technology are to be given priority. The combination of choices about these issues — burden of proof, standards of proof, safety standards and regulatory mechanisms — will reflect a certain balance of precaution with respect to one set of elements or another. In this sense, precaution is an unavoidable aspect of science-based regulation wherever there is less than complete scientific understanding and certainty about the risks associated with the product or technology.[23]

The higher the levels of scientific uncertainty surrounding a technology, the more pressing the issue of precaution becomes. If there is reason, even of the most preliminary and theoretical kind, for believing that a product or technology could pose potentially serious hazards to health or the environment, in the absence of scientific tools for assessing which of these might actually pose these hazards and of what the levels of exposure and harm might be, then there is warrant for leaning to the more precautionary side of the spectrum described earlier. In such circumstances, regulators are faced with

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[23] For a full explication of the factors involved in the precautionary tradeoffs in the face of uncertain science, see Barrett, K. and C. Brunk, "A Precautionary Framework for Biotechnology." Iain E.P. Taylor (eds.) Genetically Engineered Crops: Interim Policies, Uncertain Legislation. Binghamton, New York: Haworth's Food Products Press, 2007.

the difficult choice about whether those products should be permitted onto the market, and if so, under which risk management strategy and safety standard. Given the absence of reliable tools for pre-market assessment of risk and for post-market monitoring or surveillance, it would be misleading to claim that these products have been deemed safe "on the basis of science." In the extreme case, where the knowledge base for risk assessment is virtually non-existent and the risks potentially high, precaution might very well require that the products be kept off the market until more data are available.

On the other hand, the more scientific tools, data and understanding we have available through sustained research and experience with new products, the greater the potential for lowering uncertainties around the risks and benefits of these new products. In these circumstances, the regulatory system can establish less restrictive barriers to product introduction in order to retain the appropriate level of precaution. As the knowledge base expands and the risks become more readily assessable and manageable, the stronger the case becomes for streamlined procedures in moving products to market. At the same time, it would be the more reasonable to then shift to less onerous risk management and governance strategies, such as voluntary measures, labelling, and post-market monitoring or surveillance. *A transparent and robust precautionary approach normally includes prior approval before allowing entry into commerce any material over which there is the type of uncertainty displayed by nanomaterials and nano-enabled products.* It should be noted, however, that saying all nanomaterials should be subject to regulation does not prescribe the specific measures that can be taken for addressing each product. For example, in some cases, a product may be placed on the market with conditions attached — e.g., an obligation on the manufacturer/distributor to set out a monitoring strategy. Thus, a requirement for regulation should not inherently be seen as a barrier to entry in terms of the introduction of new products to market.

The Role of Public Participation in the Governance of Nanotechnology

A critical aspect of the management of risks in a regulatory context is the involvement of the public — not only those who define themselves as specific stakeholders, but also the broader public, acting as citizens and consumers. This is referred to in most risk analysis frameworks as the task of *risk communication*. This task can be as critical to the development and implementation of technologies as that of solving the underlying scientific, technical and economic challenges. The level of acceptance of a technology within a society can depend upon how the task of risk communication is handled.

A significant challenge for the future of nanotechnology will be its reception by the public. Experience with biotechnology suggests that an emerging technology with unknown potential and consequences may face hostility among the public and that its future development may, as a result, be significantly inhibited (Einsiedel, 2005; Kulinowski, 2004; Mehta, 2004). Whether that inhibition is positive or negative will obviously be a subject of dispute. Nevertheless, the degree and nature of public acceptance of nanotechnology depends crucially on the attitudes of the public and the ways in which its values influence judgments about this emerging technology. Indeed, as Maynard notes, "relatively recent technologies such as nuclear power and genetically modified organisms have led to increased skepticism within society over the ability of industry and governments to ensure their safety. And the power of people to decide — whether based on real or perceived risks or benefits — which technologies succeed and which do not has become a significant factor" (Maynard, 2007b).

The Importance of Public Participation in Technology Regulation – It is increasingly recognized that not only are public perceptions of the benefits and risks of new products critical to the acceptance of those products in the marketplace, but more importantly, that the public has a legitimate claim to democratic participation in the formulation of public policies related to the governance of these products and their underlying technologies. When the policies governing the approval and regulation of new technologies are perceived by large publics as having been negotiated behind closed doors by those standing to benefit the most from their development, resentment and alienation can arise. Interested publics often perceive themselves as among those who are most likely to bear the potential risks of a new product and they may feel that the product's benefits are outweighed by its risks.

There is, however, an important nuance often lost in the rush to include the public. Government officials may wish to satisfy the laudable democratic ideal of public participation but leave undefined and uncertain the actual role that public participation will play in decision making. An appropriate participatory process will involve a bilateral exchange of information between hosts and participants at an event, such as a focus group or town hall meeting. One way to conceive of the push and pull of information is to *involve* the public in participatory events that require an exchange of information. Most public participation events are of this variety, but are often described as "consultations." The public is *consulted*, but only in cases where the push and pull of information is tied directly to a time-constrained decision to be made by the relevant authority. In a consultation, the participating members of the public also know that their views are going to inform the decision (Castle and

Culver, 2006). True public consultation is allied with democratic ideals of the value of direct public participation in decision making.

The three dominant questions of public concern in relation to the risk-based regulation of new technologies are: (1) What is the level of risk posed by the product? (2) what level of risk should be considered "safe"? (i.e., what level of risk would be considered as an *acceptable* level), and (3) for *whom* is the level of risk acceptable? The answer to this last question would seemingly include those who are the potential bearers of the risks, whatever those risks may be. Such individuals would claim that they ought to be meaningfully involved in the process.

Public perceptions of the risks and benefits of new technologies ought not to be viewed as purely "political" constraints on an otherwise science-based regulatory regime. They are an integral part of such a regime because, as noted above, there are essential non-scientific aspects of risk regulation in which the public, in a democratic society, has the right to participate. There are ways of engaging "informed publics" in the formulation of public policies governing the regulation of new technologies that can — and should — be utilized.

One need only look at the case of biotechnology to understand the importance of public engagement to the successful regulation and introduction of a new technology into society. Biotechnology was introduced into the North American market with little public debate. It shared with nanotechnology similarly low levels of understanding and awareness. It also shared a public perception that the scientific understanding of the risks posed by the technology was inadequate to guarantee human and environmental safety. The products introduced were seen to offer no benefit to consumers and significant benefit to producers. Regulators and scientists will need to utilize various methods of public engagement in order to avoid a repetition of the circumstances that surrounded biotechnology.

Uncertainty in the science necessary for effective risk management is not the only reason for the need for public participation, but it is sufficient on its own. Because the current state of scientific understanding does not support a traditional science-based regulation of the potential risks that may be posed by some nanomaterials and products, it is doubly important that the public be consulted on the question of how to approach the issue of the introduction of these products into the marketplace. The question of how precautionary we should be in the face of the scientific uncertainties is ultimately a political question that can be answered through an appropriate political process.

Without such a process, public confidence in the regulatory system, and ultimately in the technology itself, will be seriously undermined. *The establishment of meaningful avenues for public participation in the formulation of regulatory policies governing nanotechnology is essential to the establishment of public confidence in the governance of the technology.*

Options for Public Engagement – It is easy to say that the public, or publics, should be involved in participatory exercises with government in order to have input into the development of regulation and policy. It is more difficult to say what kinds of engagement and consultative processes are effective and appropriate. The difficulty lies in finding processes that can be said to be representative of the "public" or of the relevant "publics," and then engaging them in ways that elicit useful information. There is always the problem of deciding "who should be at the table" and it ought not to be only the parties who are most vocal or extreme in their positions. Neither is it useful to query people randomly, regardless of their level of understanding of the technology or concern about the issues surrounding it. These difficulties are not insurmountable, however. There are many examples of public engagement and consultation instruments, that have been used in regard to nano- and other technologies that the Canadian government could usefully investigate and employ in its own communication and consultation efforts.

In 2004, the U.K. government commissioned a report on *Nanoscience and Nanotechnologies: opportunities and uncertainties* by the Royal Society and the Royal Academy of Engineering in the U.K. The report underlined the importance of public and stakeholder dialogue at the early stages in the development of nanotechnologies (UK-RS/RAE, 2004). In particular, the report recommended: "a timely and very broad-based debate … before deeply entrenched or polarised positions appear." The government endorsed the call for public dialogue and initiated an Outline Programme for Public Engagement on Nanotechnologies (OPPEN) under which it funded three public participation projects: Small Talk, Nanodialogues and the Nanotechnology Engagement Group. The latter group was charged with the task of assessing the public participation projects sponsored by the government. The report of this group, *Democratic Technologies? The Final Report of the Nanotechnology Engagement Group (NEG)* provides an excellent description of the processes engaged in, and their strengths and weaknesses. It emphasizes the importance of "upstream" participatory processes that take place ahead of the implementation of governance procedures for new technology and thus ahead of the rancorous public debates and negative reactions that can occur if the public is not engaged early on (Kearnes and Wynne, 2007).

One of these experimental approaches was adopted to convene deliberations between scientists, policy-makers and members of the lay public in order to reach mutual understanding about the interface between facts and values (Stigloe *et al.*, 2005). These "Nanodialogues" aimed to improve citizens' understanding of nanotechnology and the current state of knowledge about nanomaterials while simultaneously affording citizens an opportunity to express their values and concerns to scientists and policy-makers.

One of the potential benefits of a deliberative approach[24] to public engagement, as illustrated by the Nanodialogues, is that it can help to repair misunderstandings on the part of scientists, policy-makers and citizens (Stigloe *et al.*, 2007). Scientists and policy-makers learn that most citizens seek to understand genuine risks and to make informed decisions about how to balance potential benefits against potential risks. At the same time, scientists and policy-makers are able to deliver the message that they are genuinely motivated to improve the lives of all people. But there are also risks with a deliberative approach. If participants regard themselves as defenders of a position, rather than sincere interlocutors, then interactions between perceived friends and enemies can serve to reinforce unreasonable positions rather than improve relationships and understanding (Sunstein, 2002; Mendelberg, 2002).

To date there has been little in the way of formal public consultation on the governance of nanotechnology by governments in North America. There is a great need for these governments to learn from the well-developed models of public participation in continental Europe and the United Kingdom. There are also public engagement models that have been developed and tested in Canada by various academic researchers — primarily in the area of agricultural and biomedical biotechnology. Among these are projects at the University of British Columbia, led by Michael Burgess, and at the University of Calgary, led by Edna Einseidel. *Until such time as a robust, science-based risk management regime is feasible, it is especially critical to involve the widest spectrum of stakeholders in the determination of the approach to regulating the introduction of new nanomaterials and products to the market, especially with respect to the desired level of precaution with respect to potential human health and environmental risks.*

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[24] A deliberative approach to decision making allows participants to consider relevant facts from multiple points of view, discuss the issues and options and develop their thinking together before coming to a view.

The Task of Risk Communication — The temptation on the part of those who favour or oppose the implementation of new technologies is to perceive the risk communication task as similar to or even identical with effective marketing strategies, where the goal is to persuade the public and consumers that the technology is, or is not, beneficial, safe and desirable. When risk communication is handled in this way, it is often viewed with suspicion by those informed members of the public who are likely to have strong influence on public opinion. Government agencies charged with the regulation of new products in the public interest need to avoid this kind of "persuasive" communication. Rather, their proper task is to assist in the fostering of an open and informed public debate. This involves several tasks:

- Helping to make available to the public a range of scientifically informed opinion of the technology, both pro and con;
- Creating avenues for informed and concerned stakeholders in the technology to communicate interests and concerns to the regulator, as well as recommendations for the managing of risks. This includes, most importantly, the process of discerning public levels of risk acceptance, and the management strategies most likely to maintain public trust in the regulation of the technology;
- Making available to the public clear and transparent descriptions of the regulatory approach taken to new products of the technology, including candid discussion of the anticipated benefits, costs, risks, and unknowns; and
- Explaining what steps are being taken or anticipated to deal with the risks and to close the gaps in the knowledge.

All of this illustrates that risk communication is a two-way, reciprocal activity, in which essential information is communicated to the public in the most objective, fair manner possible, and avenues for the communication of public and stakeholder opinion on the regulatory policies related to the technology are made available and taken seriously in the formation of policy (Castle and Culver, 2006).

The first part of this chapter established that given the findings from Chapter III, the management of nanomaterials will need to occur within a climate of uncertainty. In light of this, and given the current Canadian regulatory precedence, it is clear that any measures taken regarding nanomaterials will need to incorporate an appropriately precautionary approach. Given the diversity of nanomaterials and nanoproducts (outlined in Chapters II and III), such an approach will require regulators to determine what an "acceptable" risk for a given material or product would be (i.e., a case-by-case approach).

USING FORESIGHT TO "FILL IN THE GAPS"

There are a series of critical factors that should be taken into account in determining how to regulate nanomaterials and nanoproducts. Among the most important of these are the following:

- What are the levels of uncertainty in the science at the current time, and what are the critical questions that need to be answered to have reasonable assurances of safety?
- Does the existing scientific understanding (both empirical and theoretical) provide reasons to believe that a product (or technology itself) poses serious hazards?
- What is the profile of the hazards? That is, what are the potential magnitudes and other features of these hazards (e.g., detectability, available controls, reversibility/irreversibility or vulnerable populations)?
- What scientific tools are available to monitor the occurrence of adverse effects of a product and to trace them to the product as a contributory cause?
- What are the factors involved in the vectors of exposure to the potential hazards that affect the overall risk (e.g., physical, biological and social conditions or the reliance on human conduct)?
- How reliable are the available mechanisms for maintaining the risk within acceptable levels?

Chapter III outlined the traditional methodology used in risk assessment frameworks and concluded that prevailing human and ecological risk assessment frameworks are robust, but their application to nanomaterials requires new ways for measuring exposure, dose and response. Regulators will need to identify means of filling both management-related and science-related knowledge gaps (Box 4.2). Some of these questions fall outside of the mandate and expertise of this panel and are best left to the regulators to address. The following draws from the information presented throughout this report to identify the knowledge and capacity "gaps" that are likely to pose the biggest challenges to the regulation of nanomaterials.

Science-centred Regulatory Challenges

Classification — Given the diversity of nanomaterials and their potential use in a vast array of products and processes, it is clear that various laws and regulatory departments will be implicated in discussions over the regulation of nanomaterials. Regardless of whether specific laws and/or regulations will apply to these materials, or the products that contain them, regulators require

an unequivocal definition of what does (and what does not) constitute a nanomaterial or a nano-enabled product. As discussed in Chapter II, there is no nationally or internationally recognized definition of nanotechnology; nor is there a system of nomenclature for the categorization of nanomaterials. Work is currently underway through organizations like the American Society for Testing and Materials (ASTM), the Organisation for Economic Co-operation and Development (which has two working parties: the Working Party on Nanotechnology — WPN, and the Working Party on Manufactured Nanomaterials — WPMN) and the International Standards Organization's Technical Committee 229 (ISO TC229). These efforts, while critical to the advancement of international standards for the development of safe and productive nanotechnologies, will not yield rapid solutions to immediate regulatory challenges. *Interim terminology and classification are needed to help regulators effectively oversee this emerging group of materials and products.*

Regulatory "Triggers" — It was concluded in Chapter III that nanomaterials are a heterogeneous class of materials and that, in the near-term, each material will require independent assessment criteria. This situation is not novel within the current regulatory framework. Industrial chemicals, pharmaceuticals and medical devices are all treated on a case-by-case basis to evaluate each material's impact on human health and the environment. Evaluation of a new substance or product currently falls to Health Canada and Environment Canada (EC and HC, 2007).

Chemical Substances: Whether or not a chemical substance requires submission of a notification to regulatory authorities is determined by various factors, often labelled "triggers." Currently, substances being introduced to Canada are regulated jointly by Health Canada and Environment Canada under the *Canadian Environmental Protection Act* (EC, 2006). Under the provisions of CEPA, the Ministers of the Environment and of Health are required to conduct environmental and human health risk assessments and manage appropriately any risks arising from the introduction of new substances to the Canadian market (EC, 2007). In general, a substance must submit notification if it meets one of the following criteria:

- The substance does not currently appear on the Domestic Substance List (DSL); [25]

[25] The DSL is an inventory of approximately 23,000 substances manufactured in, imported into or used in Canada on a commercial scale. It is based on substances present in Canada, under certain conditions, between January 1, 1984 and December 31, 1986 (EC, 2007).

- The substance represents a unique structure or molecular arrangement of an existing material; or
- The substance is being manufactured/imported at quantities greater than an established mass quantity (SOR, 2005).

In the case of nanomaterials, the unique and diverse properties of this new class of materials means that these triggers are unlikely to be sufficient if the goal is to assess *all* new nanomaterials entering the market. For example, many of the metal-based nanomaterials (e.g., silver, titanium dioxide) already exist as registered substances under the DSL. And since their nanoscale counterparts do not represent a unique molecular or structural arrangement of the material, they *would not* be considered "new" under current regulation. However, many of the carbon-based nanomaterials (e.g., fullerenes, carbon nanotubes) are not currently listed on the DSL and, as such, *would* need to undergo the assessment process. The reduced size of nanomaterials generally results in lower overall production masses than is typical for industrial chemicals. While use and production of some nanomaterials (e.g., carbon nanotubes or titanium dioxide) may result in significantly large production masses to trigger regulatory measures, it is unlikely that all of these materials would reach the threshold to trigger assessment via the regulatory notification process. The foregoing statements suggest that some nanomaterials will not meet either the unique structure trigger or the mass trigger and, as such, are likely to not undergo regulatory scrutiny.

Consumer Products: As with chemical substances, the various divisions of Health Canada and Environment Canada work together to regulate new products being introduced into the Canadian market. New products must register as such, regardless of whether or not they contain a new substance. In the absence of standardized terminology however, it will be difficult for regulators to assess the product information submitted — e.g., manufacturing processes and/or material composition. Product manufacturers and suppliers will need a clearly defined set of terminology in order for regulators to be able to consistently and effectively identify those products entering the market that may appropriately be classified as "nanoproducts." *Current regulatory triggers are not sufficient to identify all nanomaterials entering the market that may require regulatory oversight.*

Box 4.2 — Nanosilver — Regulatory Challenges

In Chapter II, several nanomaterials were presented to provide a general understanding of what types of nanomaterials are being produced and where these materials are likely to be used. An examination of these materials and usages reveals that it is likely that the development of these materials could result in both human and environmental exposure. Thus, in Chapter III, several of these materials were examined with respect to the three stages of risk assessment in order to determine the capacity of current frameworks to assess their potential risks. It was concluded that the current state of knowledge surrounding these materials allows only for a qualitative, and not a quantitative, risk assessment. Chapter IV has examined how the regulatory system deals with assessing the risk of new materials in the face of scientific uncertainty. As noted in earlier discussions, this is not a new phenomenon. The fact remains, however, that each of these new materials will need regulatory oversight until such a time as the level of uncertainty has decreased.

Such an approach is not a trivial task, particularly when it comes to nanomaterials. This box uses nanosilver to illustrate some of the specific regulatory challenges posed by nanomaterials.

Definitional Difficulties:

Safety standards surrounding the manufacturing, handling and distribution of silver already exist and are implemented daily in occupational settings. Thus, in the absence of a novel definition/classification, nanosilver would likely be treated in the same manner as bulk forms regardless of the potential differences between the two.

"Triggering" a Risk Assessment:

Further to the previous statement, the ability to define a nanomaterial as "new" poses difficulties in terms of regulating the products as well. Based on current regulatory triggers, nanosilver would not be assessed as a new substance under CEPA.

Cross-Jurisdictional Issues:

Nanosilver is used in a variety of products as an additive or component. Given the wide range of products (e.g., cosmetics, food stuffs, pharmaceuticals, household appliances) and product claims, interdepartmental and interagency cooperation (e.g., IC, HC, EC, PMRA, CFIA, NSD*) would be needed to identify all the products that would need assessment.

Public Perceptions:

The introduction of products containing nanosilver into the market without regulatory oversight could lead to regulators needing to reconsider previous decisions in the face of public concern. This was best evidenced by the EPA revocation of an initial decision that washing machines containing nanosilver were not pesticides but rather devices and as such did not fall under the U.S. Federal Insecticide, Fungicide and Rodenticide Act. After receiving feedback from the silver industry workers and environmental groups, the EPA has now reconsidered this decision.

Interim Measures:

Regulators face the pressure of having to implement regulatory measures in the current climate of scientific uncertainty. Recently, the International Center for Technology Assessment (CTA), based in the U.S., and a coalition of consumer, health and environmental organizations filed a legal petition with the EPA, calling for the agency to exercise its authority to regulate pesticides and halt the sale of commercial products containing nanosilver.

Regulatory Foresight:

While current initiatives and measures must be put in place to address the safe and effective management of nanomaterials, regulators must also be looking towards the time when the level of uncertainty will not be as high as it is today. Regulatory measures that restrict the development of nanosilver-enabled technologies today (e.g., drug development) could limit the availability of safe and beneficial products and services in the future.

* IC – Industry Canada; HC – Health Canada; EC – Environment Canada; PMRA – Pest Management Regulatory Agency (HC); CFIA – Canadian Food Inspection Agency; NSD – New Substances Division (EC).

Reporting — Current reporting requirements regarding nanomaterials differ depending on the jurisdiction. In Canada, Health Canada and Environment Canada released a report that proposes a voluntary reporting structure (EC and HC, 2007). In the United Kingdom, a Voluntary Reporting Scheme has been established for industry and research organizations that seek to provide government with information relevant to understanding the potential risks posed by free engineered nanoscale materials (DEFRA, 2007). The scheme was subject to a full public consultation and began in September 2006. In the Unites States, the Environmental Protection Agency (EPA) has also supported a voluntary

reporting structure under the *Toxic Substances Control Act* (TSCA), called the Nanoscale Materials Stewardship Program. To date, no national jurisdiction has implemented mandatory reporting regimes for nano-related activities and/or products. However, regardless of whether it is mandatory or voluntary, in the absence of standardized terminology, the information being acquired is likely to be inconsistent in its descriptions and limited in its usefulness.

Occupational Health and Safety — Nanomaterials have specific implications for occupational health and safety as well as safe laboratory practices. In these settings, worker safety relies on the availability of standardized information sources regarding the safe handling of potential hazards. For example, in Canada, the Workplace Hazardous Materials Information System (WHMIS) references the use of Material Safety Data Sheets (MSDS) as a primary source for worker information on substances in the workplace (HC, 2008). Currently, however, MSDS provides information for bulk scale materials only — not their nanoscale counterparts — thereby preventing access to standard practices for occupational handling of nanomaterials. The current lack of monitoring tools capable of detecting nanoparticles means that workers and employers do not have access to detection equipment for monitoring worker exposure. Issues such as these are important not only for ensuring safe occupational environments for researchers and workers, but they also provide early indications for overall population health issues. *In the absence of standardized terminology, information being acquired from monitoring systems is likely to be inconsistent and limited in its usefulness. In the context of occupational settings, standardized information regarding the proper handling of nanomaterials is required to ensure proper worker safety. New tools are needed to accurately monitor worker exposure.*

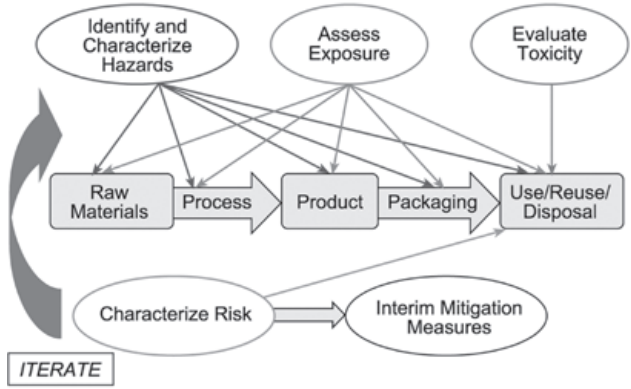
Surveillance — The physicochemical properties of nanomaterials and their increasing presence in both the workplace and general society serve to underscore the need for proper surveillance of nanomaterial exposures and effects. Focused surveillance of worker exposure over time can provide information about potential long-term harm as a result of exposure to nanoparticles. Having said this, the surveillance of nanomaterials in the general population or environment is a daunting proposition. Materials or products that were originally identified as "nano" may or may not retain their "nano-ness" once they are released into biological systems or the environment. The dynamic nature of these materials (as discussed in Chapters II and III) will require a behavioural understanding of both the starting materials, as well as the end products (e.g., decomposition products). Furthermore, teasing out confounding factors — e.g., cumulative effects,

population susceptibility — remains a difficult exercise for existing substances and is further exacerbated by the limited metrological capacity for nanomaterials. This limited capacity also hinders the current ability to ensure adequate surveillance of nanomaterials; items which are not identified as nanomaterials (or products) cannot be subsequently tied to any future adverse response. *The current metrological capacity for nanomaterials is insufficient to ensure the surveillance of their effects on consumers, workers and the environment. This is further limited by the inability to ensure adequate identification of existing and future nanomaterials and products containing them.*

Management-centred Regulatory Challenges

This report has focused primarily on the science-based challenges surrounding nanomaterials (e.g., metrology, toxicology and exposure). Based on the findings of Chapter III, it is clear that if regulatory measures are to be put in place, it will need to be done in an environment of high scientific uncertainty. The introductory sections of this chapter presented a precautionary approach that would allow governments to introduce a degree of "certainty" for all stakeholders. This approach requires a targeted research plan for addressing the science-based knowledge gaps as well as a knowledge management strategy that would go beyond the physical sciences. Various approaches are already being used around the world to try to do just this (Box 4.3). The following sections address some of the management issues that arise from the current state of knowledge regarding the potential human health and environmental risks of engineered nanomaterials.

Life-Cycle Approach and Adaptive Management — Earlier discussions of a life-cycle approach (Chapter III) examined the necessity of following a product from its original point of manufacture all the way through its lifespan to its eventual introduction into society and the environment, and to its ultimate, post-disposal fate. If risk assessments are to evaluate and identify the potential risks of a product at any given point in its cycle, then risk management strategies can be informed by the evaluation at each of these stages and respond accordingly. Just as products have life-cycles, from conception to disposal; so also do regulatory systems, but of a different kind — in effect, a series of adaptations. Once a regulatory process is implemented it begins to accumulate experience. At the same time, the activity being regulated is inevitably also evolving, partly under the influence of technology and factors in the market, but also in reaction to the regulatory environment itself. Eventually, the original regulatory rules and procedures (which normally tend to be rather inflexible) become less well aligned with their original objectives



(Shatkin, 2008)

Figure 4.1
Life-Cycle Risk Assessment Framework

and must therefore be rethought and updated in light of an evaluation of the effectiveness of the earlier decisions, how they were implemented and whether new issues have arisen. In Canadian regulation, there have been different approaches to life-cycle based regulatory measures including Health Canada's 2000 Decision-Making Framework, and work undertaken by the former Canadian Biotechnology Secretariat. This adaptive approach to management informs subsequent decisions as new information becomes available.

Shatkin, a leader in developing a life-cycle approach to risk assessment and management for nanotechnology, highlights three main elements of a life-cycle risk assessment framework (Figure 4.1): life-cycle thinking and screening level, qualitative risk assessment and adaptive management (Shatkin, 2008). This approach allows for the identification and continual reappraisal of concerns related to nanomaterial hazards with a focus on ensuring product safety in light of limited evidence for evaluating human and environmental risks. The framework focuses on exposure potential and highlights priorities for human and environmental protection. Finally, while the life-cycle approach discussed here applies to regulatory systems focused on products, others have suggested that the entire innovation cycle might benefit from the same treatment. *An adaptive, life-cycle approach explicitly allows for regulatory adaptation to scientific and technological uncertainties by revising earlier decisions as new information arises.*

Horizontal and Intergovernmental Coordination — The preceding text outlines a broad range of needs in order to develop a framework that will address the current regulatory challenges posed by nanomaterials. The diversity of nanomaterials and their potential uses alone will create a need for governments both within Canada (Table 4.2) and internationally (Box 4.4) to work collaboratively to identify those products and substances entering the market that require a more focused regulatory oversight. The international position of Canada as a major importer of goods means that there is a vested interest in the development of internationally accepted standards for the testing and manufacturing of nanomaterials and nano-enabled products. Research and development initiatives in Canada will require direction for the development of appropriate occupational health and safety standards. Consumers will need to be engaged and informed of the regulatory decisions being made with respect to existing — as well as future — nanomaterials and products. *The diversity in both material type and usage of nanomaterials, the magnitude of scientific research that is needed and the increasing presence of nanomaterials in both Canadian and international products will require governments to work collaboratively. High levels of intra- and inter-governmental coordination will be needed.*

Box 4.3 — International Landscape for Risk Management of Nanomaterials

The growing presence of nanomaterials in daily consumer products has heightened the pressure on governing bodies to respond. Regulations are required that will protect both consumers and the environment from potential risk while still allowing access to this new class of products. Several countries have adopted — or are considering adopting — voluntary measures such as Codes of Conduct, Risk Management Systems (e.g., CENARIOS, Nano Risk Framework) and certificates or disclosure agreements as interim approaches to the management of nanomaterials. Others are investigating ways in which current regulations might be refined or adapted to address nanomaterials. To date, no governing authority has implemented nano-specific regulations.

Country or Governing Body	Type of Management Approach	Description
United States	Voluntary Reporting Regime	Administered by the EPA, The Nanoscale Materials Stewardship Program (NMSP) was established to help provide a firmer scientific foundation for regulatory decisions by encouraging submission and development of information including risk management practices for nanoscale materials.
European Commission	Code of Conduct for Research	A European Code of Conduct for Responsible Nanosciences and Nanotechnologies Research is part of the EC's ambition to promote a balanced diffusion of information on nanosciences and nanotechnologies, and to foster an open dialogue involving the broadest possible range of interested parties. It follows on the safe, integrated and responsible strategy for nanotechnology, which the EU Member States endorsed in 2004, and on the nanosciences and nanotechnologies Action Plan 2005-2009, which proposes, *inter alia*, the adoption of a code of conduct for the responsible development and use of nanosciences and nanotechnologies.

Country or Governing Body	Type of Management Approach	Description
United Kingdom	Voluntary Reporting Scheme	The Voluntary Reporting Scheme is for industry and research organizations to provide government with information relevant to understanding the potential risks posed by free engineered nanoscale materials. The scheme is voluntary and will not replace existing legislation. It is intended to run from September 2006 to September 2008. The scheme was subject to a full public consultation.

(Council of Canadian Academies)

Table 4.2

A Non-exhaustive List of Canadian Regulatory Measures that are Potentially Relevant to Nanotechnology

Environment Canada
Canadian Environmental Protection Act, R.S.C. 1999, c. 33:
• *New Substances Notification Regulations (Chemicals and Polymers)*, S.O.R./2005-247;
• *Persistence and Bioaccumulation Regulations*, S.O.R./2000-107.
Canadian Environmental Assessment Act, R.S.C. 1992, c. 37.
Fisheries Act, R.S.C. 1985, c. F-14.
Agricultural Products Act, R.S.C. 1985, c. 20.
Feeds Act, R.S. 1985, c. F-9.
Fertilizers Act, R.S. 1985, c. F-10.
Pest Control Products Act, R.S.C. 1985, c. P-9.
Oceans Act, S.C. 1996, c. 31.
Arctic Waters Pollution Prevention Act, R.S.C. 1985, c. A-12.
Canada Water Act, R.S.C. 1985, c. 11.
Health Canada
Food and Drugs Act, R.S., c. F-27, s. 1:
• *Food & Drugs Regulations, C.R.C. c. 870;*
• *Medical Devices Regulations, S.O.R./98-282;*
• *Cosmetics Regulations, C. R.C., c. 869;*
• *Natural Health Products Regulations, S.O.R./2003-196.*
Consumer Packaging and Labeling Act, R.S. 1985, c. C-38.
Hazardous Products Act, R.S.C. 1985, c. H-3:
• *Controlled Products Regulations, S.O.R./88-66;*
• *Ingredient Disclosure List, S.O.R./88-64.*
Health of Animals Act, 1990, c. 21.
Workplace Health and Public Safety Program:
• Work Hazardous Materials Information System (WHMIS).
Human Resources and Social Development Canada
Canada Labour Code, R.S.C. 1985, c. L-2., H-3.3:
• *Canada Occupational Health and Safety Regulations, S.O.R./86-304;*
• Provincial Labour Codes & Occupational Health and Safety Codes.

(Council of Canadian Academies)

Box 4.4 — International Initiatives: Filling in the Knowledge Gaps

Filling the knowledge gaps surrounding the potential risks of nanomaterials will require coordinated efforts at both the national and international levels. Various initiatives are already underway that will serve to fill in these knowledge gaps and facilitate a more uniform and productive approach to the regulation of nanomaterials. The following table identifies some of these initiatives and their goals.

Initiative	Description
OECD Working Party on Manufactured Nanomaterials (WPMN)	Established in September 2006. Objective: This group will focus on the implications for the safety for human health and the environment of the use of nanomaterials (focusing on testing and assessment methods). Launched a "sponsorship program" in which countries will share the testing of specific nanomaterials. See: http://www.oecd.org/department/0,3355,en_2649_37015404_1_1_1_1_1,00.html.
ISO – TC 229	Established in November 2005. Objective: developing standards for: terminology and nomenclature; metrology and instrumentation, including specifications for reference materials; test methodologies; modelling and simulations; and science-based health, safety, and environmental practices. See: http://www.iso.org/iso/standards_development/technical_committees/ list_of_iso_technical_committees/iso_technical_committee.htm?commid=381983.

Initiative	Description
OECD Committee on Scientific & Technological Policy (CSTP)	Established in March 2007. Objective: promote international cooperation that facilitates research, development, and responsible commercialization of nanotechnology in member countries and in non-member economies. A work program is currently being launched to start addressing some of the main policy challenges. This program will include work on statistics and indicators of nanotechnology; examination of the business environment for nanotechnology; work to foster international collaboration in nanotechnology research; work on public perceptions towards nanotechnology and the engagement of stakeholder communities in the debate on nanotechnology; as well as a dialogue on policy strategies to spread good policy practices towards the responsible development of nanotechnology. See: http://www.oecd.org/document/30/0,3343,en_2649_34269_40047134_1_1_1_1,00.html.

(Council of Canadian Academies)

Capacity — The pressing demand upon governments has resulted in a heightened state of urgency surrounding regulation of nanomaterials. American agencies such as NIOSH and the EPA have diverted regular operating funds to establish nano-focused initiatives that will address what they have identified as the immediate needs within this field (NIOSH, 2007; EPA, 2007). However, while such efforts are a beginning, they do not adequately address either the human or monetary resources needed to answer the many uncertainties posed by nanomaterials. An ongoing challenge for regulators will be to keep the state of knowledge and regulatory capacity in sync with the development of nanomaterials and the products containing them. Even with the development of appropriate tools, the undertaking of transversal social science research and the adoption of a life-cycle approach to understanding the risks of nanotechnology, regulation will depend on the skills, knowledge set and knowledge sharing among regulators, scientists, industry and the public. A successful regulatory environment will thus depend on the production and distribution of a significant amount of knowledge.

Products that contain nanomaterials are already entering Canada, most without any regulatory review. With the likely rapid increase in entry and sales of these products, one can only expect that the Canadian regulatory system will soon find itself overburdened unless institutional and human resources are directed at the risks posed by nanomaterials. As discussed in Chapter II, some Canadian funding is available for basic science. However, little is available to develop the technologies and scientific and social understandings of nanotechnology necessary to underpin regulations and their implementation. Without local knowledge production, it will be difficult to train the individuals who will take on responsibility for administering the regulatory system. The lack of this capacity, if not addressed, thus threatens the entire enterprise of nanotechnology and the regulation of nanomaterials in Canada. *The safe introduction of nanomaterials into trade and commerce will require a targeted research approach to both risk assessment and risk management. Additional human and monetary investments will be required to respond to the increasing knowledge and management demands being posed by nanotechnology.*

The precise combination of decisions regarding these different questions is something the regulators will need to define, in response to different types of materials with different known characteristics and different levels and types of uncertainties. Because nanomaterials and nanoproducts differ widely and dramatically, it would be inappropriate for this report to recommend any general answer to these various questions for the whole range of products and materials that fall under the classification of "nano." Appropriate decisions about how to manage them in accordance with the precautionary approach must therefore be made on a case-by-case basis. *As scientific research fills in the knowledge gaps, the decisions respecting the precautionary measures applied to nanoproducts can be revised.*

Filling in the Knowledge Gaps

The question addressed to the panel asked, in part, for a description of the state of knowledge "which could underpin regulatory perspectives on needs for research, risk assessment and surveillance." The previous section discussed how regulators are to deal with the current state of knowledge. This section will deal with how the regulatory system should move towards more robust forms of evidence. There are advantages to doing so. As new knowledge is gained, the precautionary approach evolves into more traditional forms of evidence-based risk assessment. The precautionary approach facilitates this evolution by identifying the specific types of knowledge that are needed to move toward a more traditional form of risk assessment. Industry, regulators and government, preferring such traditional forms of assessment, therefore

have an incentive to conduct the very type of research that is needed to underpin a mature regulatory system. An examination of the information provided in Chapters II and III reveals three key areas of research (metrology, toxicology and exposure) that need further development in order to reduce the level of uncertainty when conducting risk assessments on nanomaterials.

Metrology Research — Traditionally in materials research, studies are conducted using a "known quantity"; that is to say, the material in question has been — or at the very least, can be — well characterized with regards to its physicochemical properties. Standardization of measurement techniques and materials ensure that quantitative results are comparable and that reagents are consistent in their physicochemical characterization. In the case of nanomaterials, such characterization is often unknown and/or unavailable to the researcher. In the absence of standards, a comprehensive reference base of nanomaterial properties and behaviours can not be compiled. Further, the characterization of nanomaterials depends on consistent manufacturing parameters that reliably yield consistent product materials, again something that is currently lacking. *Validated measurement methods and standards, along with nano-capable instrumentation, are needed in order to provide researchers with consistent methodologies and criteria for evaluating nanomaterial properties and behaviours.*

Toxicology Research — The rising interest in the potential risks associated with nanomaterials has given rise to a burgeoning interest in the study of the toxicological profiles of nanomaterials. Two criteria are required for evaluating the toxicity of these materials: (1) that the material can be accurately characterized in terms of its biologically relevant properties and (2) that known and measurable responses exist and can be attributed to the aforementioned properties. As discussed in Chapter III, studies on the toxicity of nanomaterials are hindered by a lack of appropriate dose and response parameters. As such, it remains difficult to assess adequately the toxicity and potential health/environmental risks of nanomaterials. *Research is needed to identify the properties of a nanomaterial that enable it to elicit an adverse biological response. Further research is needed to identify appropriate regulatory responses regarding nanomaterial exposure.*

Exposure Research — As discussed in Chapter III, for a risk to exist there must be both an identified hazard and human or environmental exposure. There are currently no national or international consensus standards on measuring general exposure to nanomaterials, although information and guidance for monitoring nanoparticle exposures in the workplace have recently been developed by the International Organization for Standardization (ISO, 2007b). The current science suggests that people will in fact become

exposed to engineered nanoparticles and that the magnitude and significance of exposures will depend on various factors — e.g., the material, the production process, handling, transport and disposal (Maynard, 2007a). Research, monitoring and surveillance (over the entire life-cycle of the material) will all need to be carried out in order to assess where and how these exposures are most likely to occur.

It is evident from the numerous international initiatives that have already been put in place that the gaps identified above represent a significant challenge; and these gaps are not likely to be resolved by any one institution or country. There is a pressing need for international and intra-jurisdictional cooperation to divide up the work and develop the multi-national machinery that can provide recommendations to national regulators based on the best scientific evidence that can be marshaled worldwide. A multi-national cooperative approach is also called for in light of the increasing prevalence of nano-enabled products in world trade. The challenge for regulators at the national level then becomes maintaining their support and engagement in these important endeavours while identifying and meeting the interim regulatory needs that are imposed by nanomaterials. As presented earlier, ideal management of these new substances and materials would see an evolution from the current state of uncertainty to a more traditional assessment of their potential human and environmental risks.

SUMMARY OF CHAPTER IV FINDINGS

4.1 Uncertainty in science and regulation can inhibit technology development and undermine public confidence in the ability to adequately protect human health and environmental quality. Uncertainty in science can be offset by clarity and certainty in the terms and conditions under which such materials may enter trade and commerce.

4.2 Evidence from other industries suggests that the private sector prefers to have regulatory certainty even if the level of precaution invoked is relatively high.

4.3 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.

4.4 A transparent and robust precautionary approach normally includes prior approval before allowing entry into commerce of any material over which there is the type of uncertainty displayed by nanomaterials and nano-enabled products.

4.5 The establishment of meaningful avenues for public participation in the formulation of regulatory policies governing nanotechnology is essential to the establishment of public confidence in the governance of the technology.

4.6 Until such time as a robust, science-based risk management regime is feasible, it is critical to involve the widest spectrum of stakeholders in the determination of the approach to regulating the introduction of new nanomaterials and products to the market, especially with respect to the desired level of precaution as it concerns potential human health and environmental risks.

4.7 Interim terminology and classification are needed to help regulators effectively oversee this emerging group of materials and products.

4.8 Current regulatory triggers are not sufficient to identify all nanomaterials entering the market that may require regulatory oversight.

4.9 In the absence of standardized terminology, information being acquired from monitoring systems is likely to be inconsistent and limited in its usefulness. In the context of occupational settings, standardized information regarding the proper handling of nanomaterials is required to ensure worker safety. New tools are needed to accurately monitor worker exposure.

4.10 The current metrological capacity for identifying and monitoring nanomaterials is insufficient to ensure the surveillance of their effects on consumers, workers and the environment. This is further limited by the inability to ensure adequate identification of existing and future nanomaterials and products containing them.

4.11 An adaptive, life-cycle approach explicitly allows for regulatory adaptation to scientific and technological uncertainties by revising earlier decisions as new information arises.

4.12 The diversity in both material type and usage of nanomaterials, the magnitude of scientific research that is needed and the increasing presence of nanomaterials in both Canadian and international products will require governments to work collaboratively. High levels of intra- and inter-governmental coordination will be needed.

4.13 The safe introduction of nanomaterials into trade and commerce will require a targeted research approach to both risk assessment and risk management. Additional human and monetary investments will be required to respond to the increasing knowledge and management demands being posed by nanotechnology.

4.14 As scientific research fills in the knowledge gaps, the decisions respecting the precautionary measures applied to nanoproducts can be revised.

4.15 Validated measurement methods and standards, along with nano-capable instrumentation, are needed in order to provide researchers with consistent methodologies and criteria for evaluating nanomaterial properties and behaviours.

4.16 Research is needed to identify those properties of a nanomaterial that enable it to elicit an adverse biological response. Further research is needed to identify appropriate regulatory responses regarding nanomaterial exposure.

4.17 Research, monitoring and surveillance (over the entire life-cycle of the material) will all need to be carried out in order to assess where and how these exposures are most likely to occur.

Epilogue

Nanomaterials and nanoproducts do present exciting new opportunities for improving the quality of life of Canadians. At the same time, the scientific knowledge on which one can quantitatively assess the risks associated with these materials is limited, especially given the diversity of nanomaterials and their potential applications. Many of the uncertainties associated with risk assessment and risk management are not unique to nanomaterials, but have been present in the introduction of other new technologies, such as biotechnology and nuclear technology. These uncertainties have been managed in the Canadian regulatory frameworks by taking a precautionary approach, giving priority to ensuring the safety of health and the environment.

Given the current limited state of scientific knowledge regarding many nanomaterials, the panel identifies the need to give priority to the development and resourcing of a strategic research agenda to better improve our understanding of the risks associated with each specific class of nanomaterials. Research into metrology, the properties of nanomaterials that are linked to biological responses, and effective monitoring and surveillance strategies should be given high priority.

Although the panel believes that it is not necessary to create new regulatory mechanisms to address the unique challenges presented by nanomaterials, existing regulatory mechanisms could and should be strengthened. First, an interim classification of nanomaterials should be developed. Second, the current regulatory "triggers" — i.e., the criteria used to identify when a new material or product should be reviewed for health and environmental effects — should be reviewed, as existing mechanisms will not identify all nanomaterials and nanoproducts. Third, standardized approaches to the proper handling of nanomaterials should be developed to ensure proper worker safety. Finally, the current metrological capacity for nanomaterials should be strengthened to ensure effective surveillance of their effects on consumers, workers and the environment.

The panel also focused on specific management-centred regulatory challenges. It identified an adaptive, life-cycle approach to the risk assessment and risk management of nanomaterials as most appropriate. The large number of classes of nanomaterials and the need to make case-by-case assessments of health and environmental risk mandates a coordinated approach across agencies within government, among levels of government and with international partners in order to avoid duplication of effort and the creation

of inconsistent or conflicting regulatory regimes. A critical aspect of the management of risks in a regulatory context is the involvement of the public, which includes not only self-identified stakeholders but the broader public who act as citizens and consumers. The establishment of meaningful avenues for public participation in the formulation of regulatory policies governing nanomaterials is essential to the establishment and maintenance of public confidence in this technology.

The existing Canadian regulatory approaches and risk management strategies are appropriate to the challenge presented by nanomaterials, provided that a greater investment is made into strategic research associated with the risk assessment of these materials, that attention is paid to addressing issues of classification, regulatory triggers and regulatory capacity, and that regulatory agencies coordinate their activities with each other, among federal and provincial levels of government and with the regulatory agencies of other countries.

The panel recognizes that by the very nature of the charge, it has not addressed a host of issues that reasonably could be included in a broader agenda. It has not made specific recommendations regarding which regulatory tools would best manage the risks presented by nanomaterials. It has not provided a detailed, prioritized research agenda most appropriate to develop Canadian capacity to innovate and regulate in this arena. It has not made specific recommendations regarding next steps for the sponsoring agencies, as it believes that the presentation of its conclusions in the form of findings most readily provides the sponsors with the necessary flexibility to move ahead following appropriate consultation and coordination. It has not considered the implications of the development of speculative "next-generation" nanomaterials and nanoproducts, especially those involving the convergence of multiple technologies. It has not addressed specific challenges to regulatory practice, such as how to best collect proprietary information to support regulatory decision making. Finally, it has not abstracted its findings, specific to engineered nanomaterials, to other new and potentially disruptive technologies. These are important issues that are best addressed by the agencies responsible for the stewardship of Canada's science and technology strategy, its regulatory mechanisms and capacity for innovation.

In conclusion, the panel thanks the sponsors of the study and the staff of the relevant agencies for the assistance and time they have given the panel throughout its deliberations. It also thanks the staff of the Council of Canadian Academies, without whom the panel would not have been able to complete this work.

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Appendix A – List of Respondents to Public Call for Evidence

On October 16, 2007, the Expert Panel on Nanotechnology issued a call for written evidence for the nanotechnology assessment.

The following is a list of organizations and individuals that gave evidence to the assessment in writing. The views of individuals do not necessarily represent those of their organizations.

ORGANIZATIONS

American Chemistry Council Nanotechnology Panel
BC Nanotechnology Alliance

Canadian Institute for Environmental Law and Policy

Canadian Manufacturers and Exporters, jointly with
Canadian Standards Association

Consumers Council of Canada

École de technologie supérieure, Université du Québec

Government of Alberta (Alberta Advanced Education and Technology; Alberta Employment, Immigration and Industry; Alberta Environment; and Alberta Health and Wellness)

Government of British Columbia – Ministry of Environment

Government of Nova Scotia – Department of Health

Government of Nova Scotia – Department of Environment and Labour

Government of Ontario – Ministry of Labour

Greenpeace

Institut de Recherche Robert-Sauvé en santé et en sécurité du travail

Laurentian University

NanoQuébec

Ontario Centres of Excellence – Centre for Photonics and Centre for Materials and Manufacturing

L'Oréal Canada

Ryerson University

INDIVIDUALS

Carter, David	Ministère du Développement durable, de l'Environnement et des Parcs, QC
Kapustka, Larry	Golder Associates
Lennox, Bruce	Dept. of Chemistry, McGill University
Roa, Wilson	Alberta Laboratory for Environmental Cancer Risk and Assessment (jointly with James Xing)
Schriemer, Henry	Dept. of Physics, University of Ottawa
Xing, James	Cross Cancer Institute (jointly with Wilson Roa)