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Rochester Institute of Technology
Nanotechnology:
An Assessment of Current
Occupational Health and Safety Issues
By Brian McShane, CIH, CSP

Graduate Thesis submitted in partial fulfillment of the requirements for the Degree of
Master of Science in Environmental, Health and Safety Management

Department of Civil Engineering Technology,
Environmental Management & Safety
Rochester Institute of Technology
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Nanotechnology: An Assessment of Health and Safety Issues

By Brian McShane, CIH, CSP

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Abstract

Nanotechnology is a rapidly expanding field and is expected to revolutionize many existing industries and create entirely new ones. Presently, and to a greater extent in the future, there is potential for occupational exposure to free forms of these materials in research and development labs and industrial processes. Free nanomaterials may pose a significant health risk to those exposed as described by recent preliminary data on nanomaterials but also through the work addressing exposures to ultrafine particles both in the workplace and in ambient air. There are presently no published health and safety guidelines for working with nanomaterials. This paper proposes a general frame work for classifying these materials and recommends appropriate hypothetical precautions to allow personnel to work safely with these materials.

Keywords

Carbon Nanotubes

Fullerenes

Health Effects

Manufacturing Processes

Nanomaterials

Nanoparticles

Nanotechnology

Nanotechnology Debate

Occupational Exposure

Precautionary Principle

Quantum Dots

Regulation

Risks Associated with Nanomaterials

Safety

Chapter 1.0 Introduction

This graduate thesis is a limited review of the topic of nanotechnology primarily in the scientific literature with an emphasis on the potential risks associated with occupational exposure. This review has evaluated the current information on nanotechnology toxicology, dose response data, routes of exposure, and other information related to risk characterization and analysis. The author has also interviewed or reviewed the opinions of experts in the field of nanotechnology to further elucidate occupational safety and health issues including the need for regulation and control of exposure to these materials in the workplace, concentrating in research and development laboratories and manufacturing. Included are recommendations on specific approaches to working safely with nanomaterials in the laboratory. The goal of this endeavor is to explain the health and safety issues surrounding these materials and suggest preliminary ways to work safely with them, based on the limited information available. The primary research questions asked are:

- 1.) What is the current state of knowledge concerning occupational exposure risk associated with nanotechnology?
- 2.) What are the areas of agreement and disagreement concerning nanotechnology safety in the literature and among the experts, and what additional research is required to generate a more complete picture of the health and safety problems surrounding the issue?
- 3.) What occupational safety precautionary recommendations can be made for research laboratory staff based on the current state of knowledge concerning the known risks of nanotechnology?

Nanotechnology is significant to the environmental health and safety (EHS) field and to this author for several reasons. It is an industry that is still in its infancy and there is a tremendous opportunity to proactively address potential environmental and health risks prior its use in occupational settings or by the general public rather than reacting when environmental degradation or health effects occur. While the United States government is keenly aware of the societal issues surrounding nanotechnology due to the biotechnology public relations failure of the 1990's and the associated consumer backlash, it is actively working to garner public acceptance of it (Weiss 1). However, little has been done to study and address potential environmental, health and safety issues that may arise from its use ("No Small Matter" 3). Based on a recent literature search there is no comprehensive guidance available to address working safely with these materials and it is hoped that this thesis will begin to effectively address a portion of this EHS issue and delineate areas that require additional study.

Nanotechnology is currently going through a period of rapid growth due to strategic funding supplied not only by major corporations but also from many industrialized countries. It is expected to have an effect on the world economy similar to the industrial revolution of the late 19th century. In fact, "government officials have called nanotechnology the foundation for the 'next industrial revolution' worth an estimated trillion dollars within the coming decade" (Weiss 1). It is projected to transform existing industries and also spur the creation of entirely new ones. The fields expected to be transformed by nanotechnology include material fabrication, manufacturing, medicine, healthcare, environmental protection, energy, agriculture, biotechnology, electronics, information technology and national security (Rocco and Bainbridge 2). Worldwide

several government and business alliances have been formed to address various business opportunities in the field of nanotechnology again with little emphasis on environmental health and safety. The stakes in this game are not small, the United Kingdom's Department of Trade and Industry estimates that by 2005 the market for nanotechnology applications will reach over \$100 billion dollars (Arnall 6).

Here in the United States, nanotechnology has been put at the forefront of national research and development with the National Nanotechnology Initiative (NNI) of 2001. The NNI was developed by the Clinton Administration and was approved by Congress in November of 2000. As a result of the NNI in that year a total of \$422 million dollars was spread over six departments and agencies (Roco and Bainbridge 1). The allocation of funds has increased steadily with current estimated budget for 2004 at \$961 million and a proposed budget of \$982 million for 2005 ("NNI Budget"). These allocations have grown to include both the Environmental Protection Agency (EPA) and also the National Institute of Occupational Safety and Health (NIOSH) through the National Institutes of Health (NIH) as a part of the Department of Health and Human Services. However, the emphasis is still on applications for this technology rather than the implications of its use. Even within the field of environmental nanotechnology where the science is seen as a boon to environmental remediation only now is this technology being assessed as a potential environmental threat. "Aside from worries about the direct health implications, there are concerns about how they might behave in the environment" (Kliener and Hogan 2).

The applications of nanotechnology are expected to increase significantly over the coming decade and as a result the materials arising from these new processes will

eventually present themselves to the EHS specialist. The worldwide annual industrial production in the nanotechnology sectors is expected to exceed a 1 trillion dollar mark in 10 to 15 years (Roco and Bainbridge 3) and employ about 2 million workers (Roco 1). According to Kliener and Hogan, 2.5 tons of nanomaterials are produced each year around the world with half of the sixteen producers located in the United States (3). The application of nanotechnology is so broad and the materials created are so varied that not all materials arising from it will be hazardous, but there is some recent supporting evidence, albeit preliminary, that identifies some types of nanomaterials as potentially hazardous (Borm 320; E. Oberdorster 1061; "Nanoscience and nanotechnologies" 4).

It appears that there will be few areas of the manufacturing and service industries that will not be affected by nanotechnology during the next 20 years. Thus, EHS professionals will in the near future either have to address nanotechnology exposure issues directly through new or existing commercial processes within their organizations or address use and disposal issues related to purchased materials and equipment that contain nanomaterials.

A preliminary review of the literature on nanotechnology reveals hundreds of papers and articles concerning nanotechnology, the vast majority of which address the expected benefits or damage associated with the real or imagined use of this technology. These documents are meant for the arena of public opinion and politics and provide little in the way of substantial scientific evidence. Unfortunately, very little has been written in the scientific literature on the potential for environmental damage and fewer documents exist that address risk, toxicity and the mechanisms of exposure in the occupational setting. As a result, EHS professionals should be required to take a precautionary approach when

working with nanomaterials. It was suggested in an e-mail from Dr. Andrew Maynard of the NIOSH that this lack of information on nanotechnology materials be addressed using data on ultrafine particles which have a diameter of 0.1 microns (100 nanometers) or less (“RE: Nanotechnology”). It was inferred that this information could then be applied to the issues surrounding occupational exposure to nanomaterials. Also, in July of 2004, the Royal Society and The Royal Academy of Engineering published a preliminary report, “Nanoscience and Nanotechnologies: opportunities and uncertainties” in which much of the data presented and the conclusions and recommendations reached are based on research done in large part with ultrafine particles.

The findings of the Royal Academies also validate several of the author’s predicted conclusions for this paper including applying the Precautionary Principle to occupational exposure of nanomaterials. The Precautionary Principle requires that materials be considered to be hazardous until proven otherwise and are handled accordingly in the interim. Based on the information gathered it has been possible to propose a preliminary approach to working safely with nanomaterials by applying existing precautionary control measures including engineering controls and personal protective equipment.

1.1 Definitions

Dose - the amount of a substance that will reach a specific biological system, and is a function of the amount to which the individual is exposed, namely the exposure, taking account of the fact that a proportion is eliminated by the body’s natural defenses and does not reach the target organ (“Nanoscience and nanotechnologies” 36).

Exposure - the concentration of the substance in the relevant medium (air, food, water) multiplied by the duration of contact (“Nanoscience and nanotechnologies” 36).

Fullerenes – a form of carbon having a large spheroidal molecule consisting of an empty cage of sixty or more carbon atoms (“Hyperdictionary.com”).

Hazard - the potential to cause harm: hazard is typically assessed by toxicology, for example testing harmful potential on cultured cells or isolated organs (*in vitro*) or directly on laboratory animals or humans (*in vivo*). Another hazard is the potential for clouds of combustible nanoparticles to explode (“Nanoscience and nanotechnologies” 36).

Nanobots – self replicating nanomachines used to create materials one atom at a time in precise order and configuration (Arnall 16).

Nanometer – one billionth of a meter.

Nanoscience - the study of phenomena and manipulation of materials at atomic, molecular and macromolecular scales, where properties differ significantly from those at a larger scale (“Nanoscience and nanotechnologies” 5).

Nanotechnology - the design, characterization, production and application of structures, devices and systems by controlling shape and size at the nanometer scale (“Nanoscience and nanotechnologies” 2).

Nanotubes – carbon based structures composed of a single layer of atoms in a cylindrical arrangement about 1.5 nm wide and up to 1 millimeter in length, multiple concentric rings may also form, creating tubes of a much larger diameter (Maynard, et al. 88).

Quantum Dots - nanoscale crystals made of a semiconductor material which can emit light in a multitude of colors (“Cancer Nanotechnology” 11).

Risk - a quantification of the likelihood of such harm occurring: risk is assessed from consideration of the likelihood of exposure, the dose and the inherent toxicity of the substance to which people or other organisms may be exposed. Sometimes, in the case of materials to which exposure has already occurred, risk may be measured directly by the techniques of epidemiology (“Nanoscience and nanotechnologies” 36).

Ultrafine particles – particles with a diameter of less than 100 nm which are ubiquitous in the indoor and outdoor ambient atmosphere and originate from many anthropogenic and natural sources (G. Oberdorster, et al. 438).

Chapter 2.0 Background

The root of the word nanotechnology is nanos which comes from the Greek word for dwarf. The word nanotechnology was coined by K. Eric Drexler in 1986 in his book Engines of Creation: The Coming Era of Nanotechnology. In that book Dr. Drexler describes a world with tremendous wealth, where in an unpolluted environment; every need is met by nanotechnology. This idyllic world vision has been embraced by the industrialized world with countries and companies vying for position as the world's leader in nanotechnology.

The concept of nanotechnology has been on the minds of scientists for centuries. The Scottish physicist, James Maxwell in 1871 imaged tiny demons that could move atoms (Keiper 2). It was not until December 29, 1959 when the concept of nanotechnology was clearly defined in a speech given by the Nobel Prize winner Richard Phillips Feynman. In that speech, entitled "There's Plenty of Room at the Bottom," Dr. Feynman talks of a class of minute materials beyond the scale of miniaturization in which atoms are rearranged to make small switches and machines.

Nanotechnology is

based on the recently developed ability to measure, manipulate and organize matter on the nanoscale – 1 to 100 billionths of a meter [...] The nanoscale is not just another step toward miniaturization, but a qualitatively new scale. The new behavior is dominated by quantum mechanics, material confinement in small structures, large interfacial volume fraction and other unique properties, phenomenon and process. (Rocco and Bainbridge 1)

It has been found that materials composed of elements that are considered to be either inert or otherwise innocuous, such as gold, develop unexpected properties, such as altered reactivity, and optical properties when their unit size is reduced to nanoscale particulates

(Weiss, "For Science" A01). It is these new observed and theorized behaviors of materials that are of particular concern to the EHS specialist for their potential to cause harm to humans and the environment.

3.0 Methodology

The purpose of this literature review was to organize information pertaining to nanotechnology and the occupational safety and health issues surrounding it. The information was gathered for this thesis from various sources including bound literature, periodicals, newspapers and published articles accessed either on the world wide web, through the Rochester Institute of Technology document retrieval system or from review of popular literature. Additionally, the author also reviewed information on nanoparticles found on various websites. Information from a limited number of interviews with leading experts in this field or reviews of their published opinions was also used. Preliminary questions asked pertained to requesting information concerning the risk and/or toxicological impact of nanomaterials as well as the any health and safety studies that have been done on any aspect of this technology. Later questions to nanotechnology and particulate experts from NIOSH included inquires related to the best available technology via engineering controls that can effectively control nanoparticulates in the work place. Additional opinions from leading experts in the field of nanotechnology were ascertained from existing interviews or editorials making actual interviews unnecessary.

3.1 Literature Review

This literature review was a distillation of the findings from current and past scientific studies concerning nanotechnology with an emphasis on information pertinent to occupational exposures. There was also a limited review of bound literature. The subjects addressed in these books include ultrafine particles, toxicology and containment technologies. The acquired information was organized and compared to identify areas of agreement and areas where information is either lacking or contradicted. The primary

purpose of the review was to identify within the literature information that provides a basis to complete a scientific risk assessment and risk analysis of the occupational exposures to nanomaterials and propose a mechanism of regulation and control of exposures in the workplace.

3.2 Expert Interviews

Telephone and e-mail interviews were conducted with several experts or their representatives in the field of nanotechnology (or their published opinions were reviewed) in an effort to answer questions concerning the use of proper engineering controls and personal protective equipment, regulatory issues and to provide insight into those areas where information is lacking. The interview candidates included Dr. Andrew Maynard, Ph.D. of the NIOSH Division of Applied Research and Technology and Vincent Castranova, Ph.D., NIOSH Nanotechnology Safety and Health Research Coordinator. They were asked questions about available information concerning the known health hazards and risks associated with nanomaterials, the existence of any EHS guidelines concerning their use as well as the effectiveness of existing engineering controls and personal protective equipment. Anticipated questions for other leading experts in the field of nanotechnology including Vicki Colvin, Executive Director of the Center for Biological and Environmental Nanotechnology at Rice University, Tim Harper, the founder of CMP Cientifica and Executive Director of the European NanoBusiness Association and Pat Mooney, founder and Executive Director of Erosion, Technology and Concentration (ETC), were to include to what degree, if any, regulation was needed to ensure that this technology is used safely. However, the author was able ascertain these opinions from existing published interviews or editorials making actual

interviews unnecessary. Dr. Colvin was also asked about the availability of EHS guidelines. Appendix B contains a list of questions asked or that were intended to be asked of these experts. Their answers are included in the Chapter 4.0 Literature Review and Chapter 5.0 Results and Discussion.

Chapter 4.0 Literature Review

4.1 Introduction

In the international rush for supremacy in the field of nanotechnology there appears to have been little thought given to investigating how this technology will impact the environment and also the health and safety of researchers, manufacturing employees and others who may face significant occupational exposures to these materials now and in the future.

Nanoscale materials, primarily in the form of nanoparticles, have already been used commercially in products intended for the general public. These materials have been used in existing applications including sunscreens, cosmetics, tennis racquets and other commercial products (“Nano’s Troubled Waters” 1). At this point the author is unable to find any reports of adverse reactions due specifically to these materials but it has been hypothesized that nanoparticles made of titanium dioxide which are commonly used in transparent sunscreens become photo-reactive upon exposure to sunlight and may cause oxidative stress to the skin (“No Small Matter” 7). Additionally, it has been found that particles less than 1 micron (μm) in diameter can penetrate far enough into the skin to be taken up by the lymph system (Howard). However, a recent study on the application of nanoparticulates of titanium oxide to intact skin indicates that this material does not fully penetrate viable skin tissue (Lademann et al. 247).

4.2 Nanotechnology Defined

Nanomaterials by definition do not exceed 100 nms. To put this into perspective one nm is approximately the width of 10 hydrogen atoms (Feder 2). Cold viruses are

generally 50 nms in length (Rotman 72). This technology therefore approaches the size limits of matter.

As predicted in Dr. Feynman's lecture this technology is now driven by mankind's recent ability to visualize measure and physically manipulate matter on the atomic scale. The watershed moment occurred in 1981 when a team of scientists from IBM invented the scanning tunneling microscope. The device uses a fine needle and extremely low electric current to detect the height of individual atoms. This microscope was able to not only visualize molecules but also contact, move and precisely place individual atoms (Keiper 3). Since then man's ability to visualize and manipulate matter on the atomic level has steadily improved.

There are many ways to classify the various facets of the nanotechnology field. For the purposes of this thesis a useful classification system relies on how materials are made on the nanoscale (1 to 100 nanometers) whether it is from the top down versus the bottom up. Top down technology is not new and can be termed a more refined version of chemical engineering involving more sophisticated and precise tools (Keiper 3). The top down method is really a form of miniaturization and is currently how most nanomaterials are manufactured "producing very small structures from larger pieces of material, for example by etching to create circuits on the surface of a silicon microchip" (Nanoscience and nanotechnologies" 3). Examples of this include industrial processes in the semiconductor and microchip industries which are continually striving for more effective methods of miniaturization and mechanical attrition processes such as grinding, milling and alloying (Aitken, Creely, and Tran 26).

The bottom up method involves using atoms or molecules to arrange themselves into a structure due to their natural properties (“Nanoscience and nanotechnologies” 3). Atoms can now be moved manually but while this ‘positional assembly’ offers greater control over construction, it is currently very laborious and not suitable for industrial applications (“Nanoscience and nanotechnologies” 3). Other scenarios which have yet to be realized involve using nanomachines to create materials one atom at a time in precise order and configuration (Arnall 16). This bottom up approach has also been termed molecular manufacturing. It is expected in the coming years that bottom up manufacturing will dominate this field as new, more precise and intricate manufacturing processes are developed. It is also where the more exciting properties of nanomaterials are seen due to the effect that quantum mechanics has at the atomic and molecular level which “gives them bizarre but useful physical properties” (Akin 134). Currently the bottom up approach has only been used to make a limited number of types of nanoparticles. The manufacturing processes are not optimized; in particular, the manufacture of carbon nanotubes has proven difficult due to inherent deficiencies in the manufacturing processes which are currently unable to produce a uniform product in discreet units (“Nanoscience and nanotechnologies” 3). It is currently in the bottom up approach where most of the innovation and rapid technological development is taking place.

The bottom up approach is also where the presently imaginary nanobots reside. It is in relation to these entities in which the dire doomsday warnings appear and also which have captured the imagination of the public, for good or bad. In this scenario, which K. Eric Drexler cites in his 1986 book Engines of Creation: The Coming Era of

Nanotechnology, molecular manufacturing occurs by which self replicating nanomachines are used to make anything desired. The machines would simply need the necessary elements to be supplied as raw materials to build atom by atom finished products, both biological and inert, without waste or any other form of pollution (Baum37). It is the fear of self replicating nanobots gone wild, as described by Drexler, consuming everything on earth as they proliferate geometrically, that has caught the public's imagination and has spawned the specter of the earth and everything in it being reduced to 'gray goo' at the hands of these nanobots. Currently the state of the art is nowhere near this level. To put the progress of this technology in perspective, in August of 2001 scientists from the University of Osaka built a nanoscale spring, the first and smallest micromechanical system ever. While this is a significant achievement, it is far from the complex molecular factory envisioned as a basis for this technological approach (Arnall 33).

It is generally assumed that molecular manufacturing is years or possibly decades away. There is also a school of thought which maintains that building such machines is physically impossible. Chief among these detractors is Richard E. Smalley of Rice University, a Nobel Prize winner for the discovery of fullerenes. Dr. Smalley believes that not only are nanofactories physically impossible to create but that the concern generated by the threat of molecular assemblers (nanomachines or nanobots) threatens the entire field of nanotechnology (Baum 37).

4.3 The Debate

The public debate surrounding nanotechnology has a familiar ring to it. When asked about nanotechnology, those who were aware of it in Great Britain compared it with

genetically modified organisms (“Nanoscience and nanotechnologies” 6). In the 1990’s the biotechnology community and its genetically modified foods went through a public relations crisis (Eichenwald A1). Much of the policy making for this technology was performed in a vacuum where regulators and industry leaders formed policy without the input of other concerned stakeholders (Eichenwald A1). The biotech industry was unable to prove that their products were risk free and have since allowed the anti-biotech activists to set the agenda for the debate. As a result, Susan Huttner, the vice provost for research for the University of California system states, “We have become slaves to the [continuing] controversy” (Hesman C8). The nanotech industry along with supporting governments are attempting to not repeat the mistakes of the biotech industry and are seeking to include all stakeholders in the public policy process in order to foster acceptance of the technology by the general public.

The commercial participants in the debate include the current nanotechnology industry leaders such as Dupont and industrial organizations such as the NanoBusiness Alliance which includes Lockheed Martin, Praxair, Zyvex, NanoFilm, venture capitalists, lawyers and also a representative from the U.S. EPA. The Alliance has been formed to address and prevent the extreme views of a nanotechnology nightmare as proclaimed by anti-nanotechnology activists from impacting the current debate (Feder 2).

The governments providing funding for further research and involved in the debate include the United States through its National Nanotechnology Initiative (NNI), Japan with its Expert Group on Nanotechnology through their Ministry of Economy, Trade and Industry and the European Commission which funds nanoscience research through its Framework Programme (Arnall 19). Most of these national programs are actively

seeking the input of stakeholders in order to incorporate environmental concerns into the policy making process. Significantly, only limited amounts of funding from these governmental entities has been allocated for research and development of environmental applications of nanotechnology, and only recently have endeavors to explore environmental risks arising from the use of this technology surfaced.

On the other side of the debate lies the non-governmental organization (NGO) the Action Group on Erosion Technology and Concentration (ETC) under its former name of Rural Advancement Foundation International was responsible in large part for fomenting the backlash to the use of biologically engineered crops in Europe. The Group's Executive Director, Pat Mooney, has called for a temporary moratorium on commercial production of nanomaterials until the risks are better elucidated and regulations are promulgated to control environmental, health and safety impacts (Weiss "For Science" A01).

Given the strategic economic importance of nanotechnology, it is highly unlikely that a world-wide ban on nanomaterials will occur. In fact one other significant NGO, Greenpeace, has proclaimed a more moderate approach than ETC on the issue. In that report Greenpeace author, Alexander Arnall, states "an externally imposed nanotechnology moratorium seems both impractical and probably damaging at present" (41).

The issues surrounding the debate primarily have to do with the anticipated benefits and environmental costs of this technology. According to the promoters of the technology, it will cause nothing short of a transformation in the way people live.

Simply put it will affect almost every aspect of our lives,
from the medicines we use, to the power of our computers,

the energy supplies we require, the food we eat, the cars we drive, the buildings we live in and the clothes we wear. More importantly, for every area where we can imagine an impact, there will be others no one has thought of – new capabilities, new products, new markets. (Holister 5)

Since this technology is thought to have such a potential impact on daily life, the worldwide economic potential and the wealth derived from it are expected to be tremendous. Thus, the strategic positioning and funding for this field is of utmost importance, and there has been little thought given to what other consequences can occur as a result of its use.

On July 29, 2004 the Royal Society and the Royal Society of Engineering published “Nanoscience and nanotechnologies: opportunities and uncertainties” which is a comprehensive report on the state of the industry and the societal, environmental and health issues it raises. The committee work group was composed of experts in the field of nanotechnology in both industry and academia including ethicists, scientists, engineers, health, environment and consumer affairs (“Nanoscience and nanotechnologies” 2). This report stated that a case for a moratorium (as proposed by ETC) has not been made, and that while the nanotechnology industry does need to be regulated, the regulation must be appropriate to the, as yet unproven, risk.

The middle ground for the debate is not quite as clear cut. Stakeholders all agree that there needs to be more research on the risks of the technology, but they disagree on whether regulation is needed and how these regulations or recommendations should be promulgated. Vicki Colvin stated in an interview published in April of 2003 that “in the next few years, the answer is no (to regulation of nanomaterials).” However, she does feel in the future “that eventually there will be a regulatory component to this industry”

(Rotman 72). As Tim Harper of CMP Cientifica (a nanotechnology industry information company) states:

From a business standpoint, we simply want to know what the rules are, or will be. Nobody wants to risk investing in the production of materials that may be banned at some stage in the future, or may be subject to the same sort of regulation as pharmaceuticals, which would dramatically affect the viability of a whole sector of industry. (Harper)

As part of the “Nanoscience and nanotechnologies” report, the public in the United Kingdom was polled on the public’s awareness and general attitude toward nanotechnology which is crucial to societal acceptance of this technology. The report found that:

Public awareness of nanotechnologies is low in Great Britain. In the survey of public opinion that we commissioned, only 29% said they had heard of ‘nanotechnology’ and only 19% could offer any form of definition. Of those who could offer a definition, 68% felt that it would improve life in the future, compared to only 4% who thought it would make life worse. (“Nanoscience and nanotechnologies” 6)

Currently the majority of the concerns expressed by stakeholders involve the impact this technology will have on the environment and public health.

Almost all of the concerns expressed to us, in evidence and during our workshop on health and environmental impacts of nanotechnologies, related to the potential impacts of manufactured nanoparticles and nanotubes [in the free rather than fixed form] on the health and safety of humans, non-human biota and ecosystems. (“Nanoscience and nanotechnologies” 35)

While how these materials will be regulated environmentally was a concern of the public, unfortunately, either no question was asked or no opinion was expressed specific to the health impact occupational exposures will have on workers where airborne

concentrations of nanomaterials would presumably be orders of magnitude higher than any found in the ambient environment.

4.4 Types of Nanomaterials

Currently the most ubiquitous types of nanoparticulates are finely scaled particles of single elements or molecules such as carbon or titanium dioxide. Nanoparticulates also include constructs such as quantum dots which can act as semiconductors, are a “promising nanoscale tool for laboratory diagnostics” (“Cancer Nanotechnology” 11) and can be as small as 2 nm in diameter (“Nanoscience and nanotechnologies” 10). Another type is a ball-shaped latticework of 60 carbon atoms called buckminster fullerenes, fullerenes or bucky balls named for Buckminster Fuller, the inventor of the geodesic dome. Fullerenes, which are hollow, can be used in the pharmaceutical industry for drug delivery, for energy production in fuel cells, for environmental remediation and lubrication, and for catalytic nanoparticles which are used in various commercial chemical reactions. The size of these particles varies; fullerenes are 1 nm in size and nano catalysts are 1 to 10 nms in length (Arnall 15).

There are currently two types of nanotube constructs. The first is a single-walled construct and the second is a multilayered design. These constructs typically have an interior diameter of 5 nm and an outer diameter of 10 nms (Arnall 15). A smaller diameter tube of 1.5 nm and up to 1 millimeter in length was also reported by Maynard, et al. (88). Nanotubes exhibit high tensile strength, high conductivity, large surface area, unique electronic properties and may have high molecular storage capacity. The fields potentially impacted by this technology are electronics, high strength materials, quantum wire and mechanical memory (Maynard et al. 88). The production process for these

materials involves the use of a transition metal particle as a catalyst in the presence of molecular carbon at high temperature or pressure. The two processes described in Maynard, et al., involve the use of lasers or high pressure carbon monoxide.

4.5 Current Manufacturing Processes

Currently there are four general types of publicly known manufacturing processes for nanomaterials, “all of which may potentially result in exposure by inhalation, dermal or ingestion routes [...] to agglomerated particles during recovery, powder handling and product processing” (Aitken, Creely and Tran 57).

The first bottom up approach is gas phase synthesis in which the raw material is evaporated using a furnace, laser or plasma evaporation “followed by a homogenous nucleation and a further condensation and coalescence of particles” (Gleiche and Hoffschulz 29). Of the four manufacturing processes “only the gas-phase processes have the potential to cause exposure to primary nanoparticles by inhalation during the synthesis phase” (Aitken, Creely and Tran 57). Gas phase synthesis includes flame pyrolysis used in the production of fumed silica and ultrafine titanium dioxide. Two gas phase synthesis processes were described by Maynard et al. for the production of carbon nanotubes. They are the laser ablation process and the high pressure carbon monoxide process (HiPCO). “The laser ablation process involves formation of a carbon plug, which contains an intimate mixture of catalyst (usually Iron (Fe) and/or Nickel (Ni)), and its ablation by laser in an inert gas stream. The resulting material is collected downstream in a cold finger trap [...] the collected product is fairly compact and its fibers are relatively difficult to separate” (89). The carbon plug provides the raw material and needs regular replacement making this is a batch process. The second process, HiPCO,

involves (the) introduction of ultrafine Fe or a combination of Fe and Ni metal catalyst particles into a high pressure/high temperature carbon monoxide (CO) gas stream. The product is collected onto a filter and since it is produced in the gas phase, forms a much expanded mat of fibers. (89)

Colloidal methods, another bottom up process, involve wet chemistry precipitation reactions which are relatively inexpensive to perform and are a reliable and well established means of producing nanomaterials (Aitken, Creely and Tran 25). The sol-gel process which “is a wet chemical procedure based on an initial liquid and colloidal ‘sol’ is one such method in which the product of the process is a solid structure “gel”.” “Different drying procedures will form a glassy or ceramic structure, whereby thin coatings, fibers, aerogels and powders can be obtained” (Gleiche and Hoffschulz 29).

The vapor deposition method, the last bottom up approach, is a process in which “vapour is formed in a reaction chamber by pyrolysis, reduction, oxidation and nitridation ... to deposit thin films of silicon and other semiconductors on to semiconductor wafers” (Aitken, Creely and Tran 25). Colloidal methods may also involve the use of ultrasound radiation used to induce chemical reactions (Aitken, Creely and Tran 26).

Attrition methods involve top down processes in which smaller particles are produced from larger ones. The processes primarily involve wet milling of materials such as clays and metals. The suspensions can be produced at the rate of tons per hour which must be stabilized to prevent agglomeration (Aitken, Creely and Tran 26).

This survey of manufacturing processes is by no means exhaustive. There may be other types of manufacturing processes in use in the nanotechnology industry today, but specific information on the processes was not found by the author and may be proprietary.

4.6 Risks Associated with Nanomaterials

The United States Environmental Protection Agency (EPA) defines risk using the following formula:

$$\text{Hazard} \times \text{Exposure} = \text{Risk}$$

Risk is a function of the “hazardousness of the substance and expected exposure to it” (“Assessing Risk” 1). Based on this definition the literature does not currently address the occupational risks associated with exposures to nanomaterials. However, there are only a few studies that have been completed which begin to address the toxicity hazards specific to manufactured nanomaterials in laboratory animals as well as effects on various target organs in anticipation of identifying routes of exposure in the occupational setting.

Nanoparticulates are of special concern because by virtue of their size, they exhibit significantly greater hazardous properties than larger particles consisting of the same material (“Nanoscience and nanotechnologies” 80). It is the same properties that make this material an item of interest to industry, such as surface reactivity and the ability to cross cell membranes that also make it a safety and health risk. After a skin or inhalation exposure, for instance, it is thought that these materials may end up in areas of the body relatively distant from the exposure site and cause harm through inflammation and other disease causing mechanisms. As a result, materials originally thought to be inert have drastically different and generally harmful properties on the nanoscale (“Nanoscience and nanotechnologies” 4).

The literature cites in several places that nanotechnology is not new nor is man’s exposure to nanoscale particulates. The production of metal colloids dates back several

centuries (Aitken, Creely and Tran 26). Dr. C. Vyvyan Howard notes that there have always been ultrafine particles and exposure to them, mainly consisting of minute crystals of salt which become airborne through the action of the oceans' waves and with the advent of the use of fire, the exposure to the products of combustion ("No Small Matter Annex").

It would be logical at this juncture to mention the issue of nanoparticles versus ultrafine particles. The previous historical examples refer primarily to ultrafine particles which like nanoparticles occur in the size range of less than 100 nms. The difference, however, may be significant in that true nanoparticles are engineered atom by atom and may exhibit different properties from ultrafine particulates which are generally found in ambient exposures as a by-product of one of many processes including combustion, aerosol generation, welding, etc.

A review of the literature concerning nanoparticulates has revealed a very preliminary body of work on the health effects of nanotubes, fullerenes and quantum dots. The majority of information on the potential health effects of nanoparticulates in general resides in the work performed by researchers working in the field of particulate toxicology and, in particular, revolving around their work with ultrafine particles. The use of ultrafine particle studies as surrogates to extrapolate the potential effects of engineered nanoparticulates has been validated by the work that The Royal Society and the Royal Academy of Engineers has done for their report "Nanoscience and nanotechnologies: opportunities and uncertainties." This committee of experts has based their preliminary conclusions concerning nanomaterials in large part on the investigational work done with ultrafine particles. In this report the committee makes no

real distinction between ultrafine and nanoparticulates. “Few studies have been published on the effects of inhaling free manufactured nanoparticles and we have had to rely mainly on analogies with results from studies on exposure to other small particles – such as the pollutant nanoparticles known to be present in large numbers in urban air, and the mineral dusts in some workplaces” (4).

Whether it is an ultrafine or a nanoparticulate, Dr. Vyvyan Howard, an aerosol expert from the University of Liverpool, reported in the Annex to the ETC article “Size Matters” that the size of the particulates more than properties of the element itself are what seem to determine toxicity. These nanoscale particles appear to cause inflammation to the tissues to which they are exposed and produce free radicals that cause cellular damage. Also, due to their exceedingly small size, they also have the ability to enter the body through various pathways including intact skin.

4.7 Routes of Exposure

It is the unfixed or free forms of nanomaterials that are of concern and pose a potential occupational exposure risk to laboratory researchers and workers manufacturing them. Since the risk of harm depends upon a hazardous material reaching the target organ (“Nanoscience and nanotechnologies” 36) the exposure mechanisms by which these materials can get into the body are of utmost importance.

Inhalation is identified as the major route of exposure in the occupational setting for free nanoparticles; skin contact follows as the next most common route of exposure (“Nanoscience and nanotechnologies” 36). One exception to this statement may be unrefined carbon nanotubes. Evidence has been reported that skin contact from nanotubes rather than inhalation may be a more significant route of exposure in

occupational settings (Maynard, et.al 106). Future ingestion issues for food and drink were also cited should such materials be added to food. Injection may also occur as these materials are used in medical procedures (“Nanoscience and nanotechnologies” 36). Overall very little is known about the actual routes of exposures for nanomaterials.

Several recent papers address exposure issues related to handling nanotubes, cytotoxicity of human skin cells and the exposure of bronchial cells to nanotubes. Exposure of human skin cells to unrefined nanotubes produced oxidative stress (Shvedova et al., “Keratinocyte” 1924) and bronchial epithelial cells were adversely affected through the mechanism of oxidative stress when in contact with nanotubes (Shvedova et al., “Bronchial” 91) which may lead to disease caused by the toxicity of this material to the skin and lungs of exposed workers.

4.8 Target Organs

The target organs for inhalation exposures are the lungs and respiratory system. Particles and aerosols larger than 5 micrometers (um) in diameter are captured in the nasopharynx and tracheobronchial regions of the respiratory system. The main defenses against particulates and aerosols in these upper regions of the respiratory system are impaction and capture in mucous. The mucous covered airways of the tracheobronchial region are where cilia rhythmically beat to move impacted particulates up and out of the respiratory system in a bed of mucous to the throat. Generally, particles less than 5 um, especially 1 to 3 um size particulates, are deposited deep inside the lung in the pulmonary (alveolar) region where gas exchange occurs and macrophages work to remove impacted particulates (Sobsey).

Deposition of ultrafine particles within the three regions of respiratory system is essentially size dependent with

about 90% of inhaled UFP [ultrafine particles] around 1 nm in size deposit in the nasopharyngeal region (Swift, et. al. 1992, Cheng et al. 1996), whereas only about 10% of this size deposit in the tracheobronchial and essentially none in the alveolar region; in contrast, 5 to 10 nm UFP deposit equally in all three regions with about a 20-30% efficiency, whereas 20-nm UFP are predicted to be deposited in the alveolar region up to 50% and only about 10 % each in the nasopharyngeal region and tracheobronchial regions (ICRP, 1994). (qtd. in G. Oberdorster et al.)

Nanoparticles or ultrafine particles, which deposit deep inside the lung in the alveoli, are removed by macrophages which move to the site of impaction, engulf and carry the particles up to the ciliary escalator or transport the particles through the lung interstitium to the lymph system where they are carried to the lymph nodes.

Both mechanisms tend to remove the particles from areas where they have the potential to cause harm and to neutralize their toxicity. However, an overwhelming dose may lead to excessive inflammation, scarring (fibrosis) and destruction of lung tissue, as exemplified by bacterial pneumonia or industrial lung diseases such as asbestosis. (“Nanoscience and nanotechnologies” 38)

Another target organ of concern is the skin. The skin, the largest organ of the body, is made up of a thin outer layer (called the epidermis) and a thicker outer layer (called the dermis). The dermis contains glands that produce sweat and the protective secretion, sebum. The blood supply to the dermis layer

allows recruitment of inflammatory cells when the skin is attacked by bacteria or otherwise damaged, enabling protective inflammation and tissue repair. Prolonged or repeated inflammation such as may be induced by certain chemicals or by sunlight, may lead to skin damage and cancer. (“Nanoscience and nanotechnologies” 39)

While nanoscale titanium dioxide does not penetrate viable skin, other nanomaterials are known to move through the skin, because of that cosmetic products are being developed to take advantage of this process. “Some toxicologists are alarmed by the trend. The skin is a barrier for a reason - to keep harmful substances out. If nanoparticles can penetrate will they end up in the bloodstream and brain? Will they do damage?”

(Boseley). The answers to these questions have yet to be fully explored.

The ingestion of nanomaterials and their effects on the gastrointestinal tract may also be an issue, but little research has been done on this with the exception of lead exposures involving hand to mouth exposure and contamination of food stuff in certain industries (Aitken, Creely and Tran 15). As a result, ingestion exposure is expected to be directly related to skin exposure, food storage and personal hygiene practices in the workplace.

4.9 Physical Characteristics of Ultrafine/Nanoparticles

The physical characteristics of ultrafine particles are important to understand in order to comprehend their interactions with target organs and cells. As previously stated, nanoparticles approach the size of molecules and atoms. “They are smaller than human cells (10,000 to 20,000 nanometers in diameter) and organelles and similar in size to large macromolecules such as enzymes and receptors [...]Nanoscale devices smaller than 50 nanometers can easily enter most cells” (“Cancer Nanotechnology” 6). Howard has described a ‘passageway’ between organs for nanoparticles to move into and around the body. These ‘caveolar’ openings are thought to be involved in the transport of proteins and other macromolecules around the body and are the correct size for transporting nanoparticulates (“No Small Matter Annex”).

Also, because of their small size nanoparticles “account for a major portion of the numbers of particles within PM [ambient particulate matter], and have a high surface area to mass ratio” (Brook, et.al. 2657). For example, “to obtain 10 $\mu\text{g}/\text{m}^3$ [micrograms per cubic meter] of 2 μm [micron] diameter particles you only need 1.2 particles per ml of air and a total surface area of 24 $\mu\text{m}^2/\text{ml}$; the same airborne mass concentration of 20 nm particles requires 2.4 million particles with a surface area of 3,016 $\mu\text{m}^2/\text{ml}$ ” (Donaldson and Stone 406).

Jefferson and Tilley state that it is the relatively high proportion of surface atoms that makes these particles so interesting; for instance for a 50 nanometer single particle one in six atoms will be at the surface (64). “Such a high proportion of surface atoms ensures that, in general terms, nanoparticles of this size regime display vastly increased reactivity” (Jefferson and Tilley 64) because more atoms and their molecular bonds are exposed and available for interactions with adjacent atoms. Thus the increased surface reactivity coupled with the large numbers of particles and their large surface area to mass ratio may account for the enhanced inflammation and other adverse effects observed from exposure to these materials. In their conclusion Jefferson and Tilley state “we cannot regard these nanoparticles as small crystals of bulk material, and the physical and chemical properties of the latter can no longer apply” (81). They further state that contrary to popular belief these are not crystalline in structure but are rather “large inorganic macromolecules with molecular rather than crystalline properties” (82).

4.10 Health Effects of Ultrafine Particles

Ultrafine particles (less than 100 nanometers) are ubiquitous in the atmosphere arising from many different sources - both man made and naturally occurring - and have been

implicated in causing respiratory and cardiovascular disease in susceptible subjects and on a particle count basis account for the largest amount of ambient particulates (Brook, et.al. 2657). Initially ultrafine particle exposures were generally confined to the work place; however due to the increase in ambient concentrations of these particles, toxicologists have explored the relationship between ambient exposure to these materials and death and disease in susceptible populations. There has been a significant body of work done on ultrafines and some of the information gleaned from these studies may be useful in predicting the behavior and potential consequences of exposure to nanomaterials where information on this subject is generally lacking.

Several factors were identified as determining particle toxicity of ultrafines. In the case of mineral dusts, the morphology (aspect ratio), surface area surface activity and persistence in the body determine the toxicity of the particulate. “Whereas studies of mineral dusts and asbestos have shown the importance of particle size, surface reactivity and dose in the causation of lung disease, the most direct evidence on nanoparticles comes from studies of air pollution” (“Nanoscience and nanotechnologies” 38). “The most significant finding from research into air pollution particles for the hazard of nanoparticles is that cells and organs may demonstrate toxic responses even to apparently non-toxic substances when they are exposed to a sufficient dose in the nanometer size range” (“Nanoscience and nanotechnologies” 40). Studies of ultrafine particulates have led to the general conclusion that the factors determining toxicity are

the total surface area presented to the target organ; the chemical reactivity of the surface [including any surface components such as transition metals and coatings], and particularly its ability to take part in reactions that release free radicals; the physical dimensions of the particle that allow it to penetrate to the organ or cells or that prevent its

removal: possibly, its solubility, in that soluble particles such as salts may disperse before initiating a toxic reaction (“Nanoscience and nanotechnologies” 41).

4.10.1 Epidemiology

Epidemiological studies have shown that exposure to ambient airborne particulates is associated with heart and lung disease, including atherosclerosis and cardiovascular abnormalities and exacerbation of bronchitis and asthma (Borm 316-318). It is likely that a portion of the removal of nanoparticles from the lung may be via the bloodstream which then affects the cardiovascular system in general. Donaldson and Stone hypothesize that there are two main ways that particulates can affect the heart. In the first, the heart rate is changed electrically as the particles stimulate the autonomic nervous system thereby stressing the heart or causing damage to the heart either directly or indirectly. The second is that the particles affect the blood supply to the heart muscle causing increased “clotting, haemostasis and atheromatous plaque rupture” (Donaldson and Stone 409) leading to ischemic stroke events.

There have also been observations linking cardiac events to increases in ambient particulates. A recent letter from the CDC and FDA entitled “Nanoparticles Pose Greater Cardiopulmonary Risk than Thought” addresses the health risk of ultrafine particles. “Recent evidence in scientific literature suggests that a relatively small increase in particulate matter of 10 micrometers or less [...] results in a small but consistent increase in death rates and illnesses caused by impact on the cardiopulmonary system” (Cheng, “Air Pollution” 4). An American Cancer Society cohort study estimated that for every increase in annual average exposure to 10 micrograms (μg) of fine particles ($<2.5 \mu\text{m}$) per cubic meter of ambient air, there is a

6% increase in cardiopulmonary mortality rates (Brook et al. 2655). “Nanoparticles behave aerodynamically like gas molecules and have a larger surface area, per unit mass, than large particles. As a result, environmental nanoparticles can penetrate deeper inside human lungs and cause more harm than larger particles because of the increased particle surface area” (Cheng, “Air Pollution” 4).

In 1985, a severe air pollution episode occurred in Europe with elevated particulate levels and other gaseous components. Higher than normal heart rates were observed in the general population when adjusting for cardiovascular risk and weather. “An elevated resting heart rate is a risk factor for death and fatal heart disease, and may signal changes in the autonomic control of the heart, that might partially account for the adverse health effects observed in association with air pollution” (Peters et al. 1094). Peters has suggested that an increase in blood plasma viscosity may account for this effect which may modify the autonomic control of the heart at least contributing to the adverse health effects seen.

Oberdorster’s 2001 review entitled “The pulmonary effects of inhaled ultrafine particles” organizes various sources of information to make a case for the hypothesis that ultrafine particles are a cause of disease in humans susceptible to their effects. The reviewed studies, particularly those designed to mimic the characteristics of susceptible portions of the human population, support the hypothesis that ultrafine particles are responsible for the effects seen. “A number of epidemiological studies have consistently shown an association of adverse effects on sensitive parts of the population, with slightly elevated ambient particulate pollution” (1); the portion of the population

identified as sensitive were elderly individuals with compromised cardiovascular and respiratory systems.

4.10.2 Phagocytosis

The significantly larger surface area per unit of mass of ultrafine particles versus larger particles may also account for their increased effectiveness. “Thus although inhaled mass concentrations of ultrafine particles may be very low, numbers of ultrafine particles depositing in the alveolar region are extremely high” (G. Oberdorster 5). Particles in the alveolar region are not as readily removed by phagocytes as well as larger particles are. Renwick, Donaldson and Clouter found that ultrafine particles had a greater negative impact on alveolar macrophage phagocytosis than did their fine counter parts. The increased surface area, greater numbers of particles, the smaller sizes of the ultrafine particles and the surface associated free radical generation [from both ultrafine particles and phagocytes] may cause the impairment of macrophage phagocytosis observed resulting in decreased clearance of particles from the alveoli leading to greater concentrations of particles collecting in these areas (125).

Also, the smaller the inhaled particle, the more likely it was to reach the alveolar surface of the lung and penetrate into the interstitium (Ferin et al. 383) from where it can be transported through the blood stream or lymph system to other parts of the body. It was found that effective phagocytosis prevents such penetration but that macrophage breakdown or death “promotes translocation (of particulates) from the alveoli to the interstitium” (Ferin, et al. 383).

Evidence has also been found that the particulates work their way into the interstitial lung space and are transported via the blood circulatory system to other

locations within the body where they may cause harm. Preliminary studies done with ultrafine platinum have found that approximately 8 % of the material introduced into the lung found its way into the liver within 6 hours of exposure. However, there is some question as to whether a portion of the platinum used in this study may have become soluble and then filtered out by the liver (G. Oberdorster 5). Such studies point out the potential for nanomaterials to cause damage to extra pulmonary organs when the route of exposure is inhalation.

4.10.3 Inflammation

When compared on an equal mass to mass basis between fine and ultrafine particles “the ultrafine particles produced free radicals to a much greater extent than their fine counterparts” (Renwick et al 125) due to the larger surface area of the ultrafine particles. This oxidative stress is then transmitted directly to the lung tissue in contact with the reactive particle. “Furthermore, reactive oxygen species are generated during phagocytosis of the particles, leading to enhancement of oxidative stress” (Donaldson and Stone 407).

Additional studies of ultrafine platinum and carbon particles (~20 nm in diameter) inhaled by healthy and emphysematous mice showed a very mild pulmonary-inflammatory response. However, using a model of rats exposed to endotoxin or lipopolysaccharide (LPS) to mimic the early stages of a respiratory tract infection, ultrafine and fine titanium dioxide (TiO₂) exposure “confirmed that only the ultrafine TiO₂, not the fine TiO₂, induced a significant pulmonary inflammatory response which was greater than the LPS or with ultrafine TiO₂ alone” (G. Oberdorster 6). A similar model used in a study with LPS and ozone demonstrated statistically “that ultrafine

carbon particles have an inflammatory effect of their own and that co-exposure to LPS and ozone increases the response even more” (G. Oberdorster 7).

These studies have demonstrated that ultrafine particles cause a greater inflammatory response than do fine particles.

Surface properties (surface chemistry) appear to play an important role in ultrafine particle toxicity. Contributing to the effects of ultrafine particles is their very high size-specific deposition when inhaled as singlet ultrafine particles rather than as aggregates. It appears also that inhaled ultrafine particles deposited in the lung largely escape alveolar macrophage surveillance and gain access to the interstitium. Inhaled low doses of carbonaceous ultrafine particles can cause mild inflammation in rodents. Age and compromise/sensitized respiratory tract can increase the susceptibility to effects of ultrafine particles. (G. Oberdorster 7)

“Inflammation plays a key role in many diseases from Alzheimer’s disease to heart disease to cancers as well as pulmonary fibrosis” (“Pulmonary Fibrosis” 98). Studies have shown that people who take non-steroidal anti-inflammatory drugs have a reduced incidence of cancer (Roan F3). However, the direct link between inflammation and cancer while thought to be obvious has only been proven recently. In two experiments, researchers at the University of California have deactivated a protein called I-kappa-B kinase beta (IKK-beta) inside cells and stopped cancer progression in its tracks. Apparently IKK-beta promotes inflammation and inhibits cell death allowing tumors to grow in older cells. Many cancers of the digestive tract are involved with inflammation but it’s not clear that inflammation plays a role in other types of cancer (Lock 117). The effect of the generation of proinflammatory compounds by canines exposed to chronically polluted air and its possible relationship to neurodegenerative disease such as

Alzheimer's disease has also been hypothesized by researchers (Calderon-Garciduenas et al. 534).

4.10.4 Pathways to the Brain

The transport of macromolecules from the bloodstream to the brain is thought to be limited or regulated by the blood-brain barrier. Recent findings suggest, however, that nanomaterials can get into the brain through the barrier or by other available pathways.

In one study, the metals nickel (Ni) and vanadium (V), characteristic of Mexico City's urban air pollution primarily from the burning of fossil fuels, were found post mortem in the brains of resident dogs. "There was a gradient in the concentration of both Ni and V going from higher concentrations in the olfactory epithelium to lower, but still detectable levels in the frontal cortex" (Calderon-Garciduenas et al. 527) suggesting transport of these materials through the olfactory neuron to the brain. Higher levels of these materials were also found in the peribronchial lymph nodes suggesting transport of these materials through the lung interstitium to the lymph system. The researchers state that this metal uptake to the brain "could be through olfactory neurons and axons, peripheral sensory nerves, direct passage of inhaled particles into the systemic blood circulation, and through lung intravascular macrophage-like cells that ingest ultrafine PM and are capable of reaching the brain" (Calderon-Garciduenas et al. 532).

In a recent study by Oberdorster et al. published in July 2004 entitled "Translocation of Inhaled Ultrafine Particles to the Brain," evidence has been found that ultrafine particles, particularly those on the lower end of the nanoscale, are readily taken up by the olfactory bulb in rats and transported to the brain. The hypothesis for this study was based on an earlier study where inhaled ultrafine particles of C₁₃ were found to be

concentrated in the olfactory bulb of laboratory rats. In a subsequent experiment C₁₃ ultrafine particles were used with a central mean distribution of 37 nm and 35 nm in diameter. The investigators “found significant and continuous increases of C₁₃ in the olfactory bulb throughout the 7 day post-exposure period following a 6 hour inhalation exposure to ultrafine elemental C₁₃ particles” (441). C₁₃ was also found in the cerebrum and cerebellum (441). The investigators concluded “that inhaled ultrafine particles are to a significant extent translocated to the CNS [central nervous system]” (444) via the olfactory bulb and associated neurons “circumventing the tight blood–brain barrier. This generally unrecognized clearance pathway from the nasal mucosa to the CNS could be of significance for induction of neurotoxic effects following acute or chronic inhalation exposures to environmental or occupational UFP [ultrafine particles]” (444). The authors also state “it appears, therefore, that UFP size and chemistry (e.g., carbon vs. metal) are important determinants for extrapulmonary translocation of UFP” (438).

4.10.5 Transition Metal Coatings

One ultrafine study of note, “Increased inflammation and intracellular calcium caused by ultrafine carbon black is independent of transition metals or other soluble components,” was undertaken with the expressed purpose of determining whether reactive compounds such as transition metals, which are thought to coat ultrafine particles, or the particle itself, in this case ultrafine carbon black, are responsible for the lung inflammation found in rats exposed to this material. Comparisons were also made between ultrafine carbon black (UFCB), 4 nm in diameter and fine carbon black (CB), 320 nm in diameter, and each’s ability to cause lung inflammation. In addition, sets of each were coated with desferrioxamine mesylate (desferal) which deposits Fe (III) on the

surface of the particles. The four types of particles were then instilled into the lungs of rats. The results of the study indicated that the both types of UFCB caused significant lung inflammation versus both types of CB. However there was not a statistically significant difference in proinflammatory action between the treated and untreated types of UFCB. The authors concluded “the increased inflammogenicity of the UFCB compared with CB cannot be explained by soluble transition metals released from or by the accumulation of iron on the particle surface. Differences may be accounted for by the increased surface area or particle number” (Brown et al. 685). These findings are in direct contradiction from the findings of Maynard, et.al cited below. Additional research may be necessary in order to resolve the conflicting study results.

4.11 Nanomaterials

While the body of research on engineered nanoparticles is not as extensive as those on ultrafine particles, significant strides have been made in identifying toxicity and health effects as well as preliminary work on target organs and the anticipated routes of exposure in the workplace. Basically similar health issues have been identified with nanoparticles as those found with ultrafines.

The evidence suggests that at least some manufactured nanoparticles will be more toxic per unit of mass than larger particles of the same chemical. This toxicity is related to the surface area of nanoparticles (which is greater for a given mass than that of larger particles) and the chemical reactivity of the surface (which could be increased or decreased by the use of surface coatings). It also seems likely that nanoparticles will penetrate cells more readily than larger particles (“Nanoscience and nanotechnologies” 4).

“The greatest potential for exposure therefore over the next few years will be in the workplace, both in industry and in universities” (“Nanoscience and nanotechnologies”

42). Also, according to the Royal Society and Royal Academy of Engineers, a substantial amount of nanoparticles, such as those potentially found in the workplace, will have to be inhaled to negatively impact a healthy individual (“Nanoscience and nanotechnologies” 4).

4.11.1 Carbon Nanotubes

Carbon nanotubes are an interesting prospect from a safety and health standpoint because of their fiber-like characteristics (aspect ratio), low solubility in the lung and extremely small size. Because of their fibrous shape, they have been described in the popular press as the next asbestos and have been singled out as something to handle with particular caution (“Nanoscience and nanotechnologies” 4). Currently, there are two gas phase synthesis production processes that have been partially investigated by researchers interested in the health effects of unrefined single walled nanotubes. Maynard et al. investigated single walled carbon nanotubes and the potential for exposure during two production processes, the laser ablation process and the high pressure carbon monoxide process (HiPCO) which were described in more detail in the Manufacturing Processes section above.

Materials produced by both processes end up with significant amounts of catalyst metal in and on them and, therefore, would have to go through secondary processing to remove the metals from the nanotube construct. Unfortunately, not all of the catalyst can be removed without destroying a significant amount of the formed nanotubes. Both processes end up with a “very low density material comprised of nanometer-diameter catalyst metal particles, carbon nanotubes and other forms of elemental carbon. This material is manually handled prior to further processing, and has the potential to release

SWCNT [single walled carbon nanotube] particles into the air as an aerosol” (Maynard et al. 89).

Measurements were taken at the National Aeronautics and Space Administration (NASA) Johnson Space Center in Houston, Texas at the laser ablation facility, and a simulation of manual handling after the HiPCO process was carried out at Rice University in Houston, Texas. Both processes were also simulated at Carbon Nanotechnologies, Inc. in Houston, Texas. The results of the study suggest “that respirable nanotube aerosol generation from production powders is an inefficient process” (Maynard et al. 99). In fact, while the laboratory studies do indicate that nanomaterials can be made airborne with sufficient agitation, “the aerosol concentrations generated while handling unrefined material in the field at the work loads and rates observed were very low” (Maynard et al. 106). These results indicate that, dependent upon agitation and disturbance of these materials, exposure by inhalation may not be a significant route of exposure.

However, there may be a significant dermal exposure risk. “Glove deposits of the SWCNT during handling were estimated at between 0.2 milligrams (mg) and 6 mg per hand” (106). Also because large clumps of this material can become airborne and although not considered to be respirable, the release of these materials may “lead to dermal exposures in less well protected areas” (106).

Since the skin was identified as a main route of exposure to carbon nanotubes, studies were designed which looked at the effect unrefined (prior to catalyst removal) single walled carbon nanotubes had on the viability of human epidermal keratinocyte (HaCaT) cells. Since, as previously mentioned, iron and nickel are used as catalysts in each manufacturing process, “the health risk associated with nanotube materials prior to the

removal of catalyst is therefore likely to be associated with both the carbonaceous and metallic components. Transition-metal complexes as well as free iron and nickel are known catalysts of biological free radical reactions” (Shvedova et al., “Keratinocyte” 1910).

The results from this study indicate that the presence of iron (up to 30%) encased in the carbonaceous structure of the unrefined SWCNT is associated with the adverse effects observed on the keratinocytes in vitro. “Exposure of the HaCaT cells to the SWCNT induced oxidative stress, which was confirmed by the presence of free radical species, accumulation of peroxidative products, reduction of low molecular weight thiols and a decrease of vitamin E and total antioxidant reserves” (Shvedova et al. “Keratinocyte” 1922), which resulted in loss of cell viability. In addition to the loss of cells, “in vitro studies with tumor cells have demonstrated that oxygen free radicals are involved in the development of skin cancers” (Nogues et al.).

“Additionally, exposure to SWCNT resulted in ultrastructural and morphological changes in cultured human cells. Data indicate that unrefined SWCNT exposure can result in accelerated oxidative stress and may produce dermal toxicity in exposed workers” (Shvedova et.al. “Keratinocyte” 1924). Thus, not only can the carbon based nanotubes potentially have an adverse reaction on the skin cells, this effect can be accelerated by the presence of process catalysts in unrefined nanotube product.

Also, while inhalation is not recognized as a major route of exposure, it may become significant with enough disturbance of the unrefined nanotubes; as a result, the researchers investigated the effects of SWCNT on cultured human bronchial epithelial cells. Again the investigators used unrefined SWCNT containing up to 30% iron. They

also state that they question an earlier finding from Brown et.al, 2000 “that transition metals were not shown to be primarily involved in ultrafine-particle-mediated generation of free radicals” (Shvedova et al., “Bronchial” 100). Using reducing agents to neutralize the oxidative properties of the embedded iron, they found “remarkably reduced cytotoxicity indicating redox active iron within the SWCNT matrix was primarily responsible for SWCNT-induced cytotoxicity” (100). In the conclusion of this paper, the authors call for further research to separate the cytotoxic effects of the transition metals from those of the carbon nanotubes; thus more work on refined carbon nanotubes is needed.

Nanotubes from other materials other than carbon are being developed. “Perceived similarities with asbestos and other disease causing fibres have led to concern about their safety” (“Nanoscience and nanotechnologies” 42). “Technology exists that allows production of nanotubes that can have remarkable predicted dimensions of a few nanometres in diameter and micrometres in length [although currently they can only be produced as agglomerates, not as single nanotubes]” (“Nanoscience and nanotechnologies” 42). Because of their fibrous shape, ability to penetrate deep into the lung, low solubility and the presence of transition materials on the surface of these constructs, nanotubes could present a significant hazard to workers (“Nanoscience and nanotechnologies” 42). However, these constructs may tend to clump together make their entrance into the deeper portions of the lung more difficult. “Little is known of their aerodynamic properties and indeed whether they can present a risk in the air in sufficient numbers to constitute a risk” (“Nanoscience and nanotechnologies” 42).

Presently, the production of individual nanotubes that do not bind together to form clumps has not occurred. It is considered unlikely that these materials will be readily made airborne anytime in the near future. However,

given previous experience with asbestos, we believe that nanotubes deserve special toxicological attention [...] In the meantime, we believe that there is sufficient concern about possible hazards to those involved in research and early industry development of nanotubes to control their exposure. (“Nanoscience and nanotechnologies” 43)

4.11.2 Fullerenes

Fullerenes have the potential to act as drug delivery systems and also have been found to have anti-oxidant effects. In order to make them biocompatible which would allow them to reach certain target organs and cells, it is thought that the fullerenes or other types of nanoparticles would be bound with proteins or other materials to allow transport within the body (Borm and Kreyling 2).

One study performed by Eva Oberdorster of Southern Methodist University demonstrated that largemouth bass showed brain damage when exposed to moderate levels, 0.5 parts per million (ppm), of Carbon 60 (nC60) fullerenes. Fish exposed to a 0.5 ppm concentration of nC60 fullerenes showed “a significant increase in lipid peroxidation in [...] exposed fish compared with controls. The difference between the brain, gill and liver are striking. The gill and liver showed a trend toward decreased lipid peroxidation, whereas the brain had significantly elevated lipid peroxidation” (E. Oberdorster, 1060-1061). In addition to describing another instance of transporting these materials to the brain, these findings raise questions about the environmental impact these

materials will have and also if health and safety issues will arise from exposure to these materials as injectable therapeutic agents.

The toxicity of water-soluble polyalkylsulfonated C60 in rats by various routes of exposure has also been assessed. Rats were exposed to polyalkylsulfonated fullerenes (FC4S) using oral and injection (intravenous and intraperitoneal) routes of exposure. The FC4S introduced orally were found to be non-toxic to the rodents. Both intravenous and intraperitoneal injections of FC4S, however, were eliminated through the kidneys, which were damaged by the exposure causing phagolysosomal nephropathy. The authors state that the observed changes to the kidney may serve as a biological marker of exposure in toxicity tests for this class of nanoparticles (Chen et al. 150).

4.11.3 Quantum Dots

Quantum dots are “semiconductor nanoparticles that can be ‘tuned’ to emit or absorb particular light colours for use in solar energy cells or fluorescent biological labels” (“Nanoscience and nanotechnologies” 3). While quantum dots can be used as labels and assays without doing apparent harm to cells in-vitro, researchers at the University of California in San Diego have found that quantum dots can be cytotoxic under certain circumstances. Quantum dots with a core of cadmium selenide capped with a zinc sulfide (ZnS) or bovine serum albumin (BSA) coating proved to be toxic in vivo. Toxicity was due to the release of cadmium ions from the cores of the quantum dots when exposed to air and/or ultraviolet radiation. While the coatings were found to inhibit the release of cadmium overall, enough was emitted to cause injury. “Long-term ultraviolet (UV) exposure [to mimic phagocytosis] resulted in high levels of cadmium-

ion formation and cytotoxicity in hepatocytes (liver cells), even with an inorganic ZnS and organic BSA capping layer, cadmium release still occurred” (Kalaugher 1).

4.11.4 Sunscreens and Cosmetics

Currently the general public is dermally exposed to nanoparticles through the use of sunscreens containing nanoscale titanium dioxide particles. Iron oxide is used as a base in some cosmetics as well. “It is clear that nanoparticles have different properties to the same chemical on a larger scale, and the implications of these different properties for long term toxicity to the skin require rigorous investigation on a case by case basis” (“Nanoscience and nanotechnologies” 43). In Europe, the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) states that “titanium dioxide is safe for use in cosmetic products at a maximum concentration of 25 % in order to protect the skin from certain harmful effects of UV radiation” (“Opinion” 1). The evaluation and opinion from the SCCNFP in June of 2003 for the use of micronized zinc oxide in sun block and cosmetics requires further study (“The Scientific Committee” 28). There is insufficient information about whether other nanoparticles used in cosmetics (such as zinc oxide) penetrate the skin, and there is a need for more research into this.

If nanoparticles penetrate the skin they might facilitate the production of reactive molecules that could lead to cell damage. There is some evidence to show that nanoparticles of titanium dioxide (used in some sun protection products) do not penetrate the skin but it is not clear whether the same conclusion holds for individuals whose skin has been damaged by sun or by common diseases such as eczema. There is insufficient information about whether other nanoparticles used in cosmetics (such as zinc oxide) penetrate the skin and there is a need for more research (“Nanoscience and Nanotechnologies” 5).

4.11.5 Medical Applications

Nanoparticulates are thought to be the next vehicle for transporting therapeutic agents to the proper organ or cells by injection of these materials into the body. However, particulates smaller than 7 μm are generally taken up by macrophages of the liver and spleen, and larger particles are trapped mechanically in the capillary network of the lungs (Illum et.al. 367). By selecting the proper biologically active coating for the nanoparticulates, the scavenging of these materials by the liver or spleen may be reduced permitting the particle to be selectively transported to organs or cells of choice depending on the coating type (Illum, et al 368).

While the “Nanoscience and nanotechnologies” Report expresses concern for the effects these materials would have on patients, the exposure to these materials especially those that are coated with biologically active substances used to target certain organs or cells would almost certainly present a hazard to those occupationally exposed. The findings suggest that surface coatings may determine where these particulates may end up in the body which may include less desirable locations such as the brain (“Nanoscience and nanotechnologies” 41). Since the surface coating of the particle will contribute (as may be the case of transition metals) or detract from the toxic response of the material, investigation of specific nanoparticulates and/or their coatings for their particular effects is warranted prior to worker being exposed to them. In particular, nanoparticles created for biomedical purposes and designed to penetrate the body, organs and cells through the use of surface coatings must be evaluated for their potential to do harm to workers (“Nanoscience and nanotechnologies” 42).

4.11.6 Use of Animal Models

While it is accepted and necessary practice to use laboratory animals as models for the investigation of human disease, it is also important to understand some of the different responses to challenge each species typically displays. In particular the rat is considered to be a very sensitive model when it is subjected to pulmonary challenge. “In the rat, the time course and pattern of (particle) accumulation, chronic inflammation, epithelial hyperplasia and tumourigenesis are essentially the same for all particles [...] The potential for tumors (to develop) is especially marked when particles are in the ultrafine mode” (Klaassen 998). Inflammation is not as great in the mouse and hamster model and thus tumorigenesis is not as marked. Warheit states that the rat model is very sensitive to pulmonary challenge and may develop an “exaggerated lung response” to pulmonary overload of particles (33).

So while the rat and other species are considered to be acceptable models of how the human body will react to a specific challenge, there is no guarantee that the human response will be identical or even similar to the animal model. Instilling high doses of particulate matter into the lung is also a relatively common method of delivering particulates to the lung. “In long term high dose inhalation studies in animals, the chronic effects produced by ultrafine particles include inflammation, increased chemokine expression, epithelial hyperplasia, pulmonary fibrosis and lung tumours. However these effects are a consequence of overload” (Brown et al. 685). The overload model is considered to be an extreme case of exposure and does not reflect typical exposure episodes found in the workplace.

4.12 Risk Assessments

“The purpose of a risk assessment is to provide pertinent information to risk managers, specifically, policy makers and regulators, so that the best possible decisions can be made” (Paustenbach 4). The United States Environmental Protection Agency (EPA) defines a risk assessment as a four step process: hazard identification, exposure assessment, dose-response assessment and risk characterization (“Risk Assessment for Toxic Air Pollutants”).

The first step is hazard identification or what health problems can be caused by an exposure to a material (“Risk Assessment for Toxic Air Pollutants”). According to the National Academy of Sciences, hazard identification involves determining whether human exposures to a particular agent will “cause an increase in the incident of a health condition (cancer, birth defect, etc.)” (Paustenbach 7). The National Research Council states that these hazards are identified through toxicological experiments with laboratory animals, and rarely is there adequate and definitive data from health effects on humans (Paustenbach 7).

The second step is exposure assessment or how much of these materials are people exposed to over a given time period (“Risk Assessment for Toxic Air Pollutants”). “Exposure assessment measures or estimates the intensity, frequency, and duration of human or animal exposure” (Paustenbach 9) to a particular agent.

Step three involves a dose response assessment or what health problems are associated with different exposure concentrations and the various routes of exposure (“Risk Assessment for Toxic Air Pollutants”). “Dose response assessment is the

process of characterizing the relationship between the dose of an agent administered or received and the incidence of an adverse health effect” (Paustenbach 7).

Finally, the risk is characterized several different ways to describe how exposure to a particular contaminant will increase the risk to one’s health (“Risk Assessment for Toxic Air Pollutants”). “Risk characterization is the process of estimating the incidence of a health effect under the various conditions of human or animal exposure” (Paustenbach 9).

Currently there is not enough data available to make a definitive statement about the risks that nanomaterials will pose in the workplace. It is expected, however, that some nanomaterials may be characterized as hazardous while others may not be. Much work has been done on the health hazard side of this issue in laboratory animals and through epidemiology studies of human populations with ultrafine, but work is just beginning with hazard identification and effects on target organs as they relate to particular routes of exposure associated with nanomaterials. Currently the other steps in the risk assessment process have not been addressed to any acceptable degree. “Research into the hazards and exposure pathways of nanoparticles and nanotubes is required to reduce the many uncertainties related to their potential impacts on health, safety and the environment. This research must keep pace with the future development of nanomaterials” (“Nanoscience and nanotechnologies” 5).

4.13 Regulation

While a moratorium on work with nanomaterials will not occur, there appears to be a consensus among stakeholders that some sort of regulatory framework is necessary. In

order for there to be meaningful and effective regulation there must be reliable information on risk and the potential health effects of these materials.

In Europe the NANOSAFE project has been initiated to investigate the risks of occupational exposure to nanoparticles. The United Kingdom's Task Force on Better Regulation warned in 2003 that nanotechnology safety regulations were needed.

The Task Force also outlined five necessary principals for effective regulation. They are:

Proportionate: Regulators should only intervene when necessary. Remedies should be appropriate to the risk posed, and costs identified and minimized.

Accountable: Regulators must be able to justify decisions, and be subject to public scrutiny.

Consistent: Government rules and standards must be unified and implemented fairly.

Transparent: Regulators should be open, and keep regulations simple and user friendly.

Targeted: Regulation should be focused on the problem, and minimize side effects. ("Principles of Good Regulation")

This Task Force was also responsible for initiating the "Nanoscience and nanotechnologies" Report from the Royal Society and the Royal Academy of Engineering. The conclusions within this report state that they do not support a full moratorium on nanotechnology. The Academies recommend that regulators work within their own existing regulatory frameworks to address potential issues and use a precautionary framework to address knowledge gaps ("Nanoscience and nanotechnologies" 78). Indeed, "with real nanotech products already on the marketplace, and a deluge to follow, an urgent set of issues revolve around the adequacy of our

existing regulatory system to provide the necessary safeguards and early warnings”

(Wardak 1). The Academies also recommend that the UK Research Councils

assemble an interdisciplinary centre (perhaps from existing research institutions) to undertake research into the toxicity, epidemiology, persistence and bioaccumulation of manufactured nanoparticles and nanotubes, to work on exposure pathways and to develop measurement methods. The centre should liaise closely with regulators and with other researchers in the UK, Europe and internationally. (“Nanoscience and nanotechnologies” 5)

NIOSH has recently begun to develop the NIOSH Nanotechnology Research Center which will coordinate all agency-wide nanotechnology activities. Additionally, the NIOSH Nanotechnology and Health & Safety Research Program, “which is a five-year multidisciplinary study into the toxicity and health risks associated with occupational nanoparticle exposure” (“NIOSH Safety and Health Topics”) has just recently been initiated.

In October of 2004 the First International Symposium on Nanotechnology and Occupational Health was held. This is a cooperative effort between the United Kingdom and the United States where what is known and what needs to be known about nanotechnology will be discussed to enhance workplace safety (“NIOSH Safety and Health Topics”).

A search of the Occupational Safety and Health Administration (OSHA) website did not produce any information on nanotechnology and its risk. When the local OSHA area office was contacted by Rice University concerning guidance for safely working with nanomaterials, the area office supplied a copy of the chemical hygiene standard, CFR 1910.1450, “Occupational exposure to hazardous chemicals in laboratories” (Kulinowski). Presumably this regulation and OSHA’s general duty clause will be the

mechanisms of enforcement for research laboratory and manufacturing facilities providing that these nanomaterials are classified as hazardous.

The EPA through its Science to Achieve Results (STAR) grant program has allocated approximately \$6 million to support 16 universities in their efforts to study this emerging technology. While the research concentration is on the use of this technology for environmental remediation, the EPA does recognize that there may be some detrimental environmental issues associated with the use of nanomaterials. “Alongside the vision of nanotechnology that could lead to big advances in environmental protection are questions related to the potential environmental concerns that could be associated with this new technology” (“EPA Research and Development”). Also, through the Toxic Substances Control Act (TSCA) “the EPA has the power to prohibit and or limit the manufacture of particular chemicals based on risk assessments” (Wardak 3). So while OSHA usually regulates chemical exposure in the workplace “the EPA has used TSCA as a means for exercising its own regulatory authority to minimize workplace exposures” (“How the Small World of Nanotechnology” 4).

In the UK the recent “Nanoscience and nanotechnologies” Report states that the present regulatory frameworks in European Union and United Kingdom are “broad and flexible enough” to handle nanotechnology development at this point, but further work is needed to be done to determine if new regulations are required or existing ones need to be modified to accommodate the Precautionary Principle (6). The Academies further state “We recommend that the Health and Safety Executive carry out a review of the adequacy of existing regulation to assess and control workplace exposure to nanoparticles and nanotubes including those relating to accidental release. In the meantime they should

consider setting lower occupational exposure levels for chemicals when produced in this size range” (“Nanoscience and nanotechnologies” 6).

4.14 Application of the Precautionary Principle

According to the NANOSAFE initiative there will be a dramatic increase in the manufacture of nanoparticles. As a result, there is likely to be an increase in significant exposures to the worker populations within affected industries as well as an increase in health effects from those exposures unless work is carried out to address this problem (“Risk Assessment of Airborne Nanoparticles” 1). It is the author’s contention that given the recent information generated from preliminary toxicological and exposure assessment studies and previous work performed with ultrafine particles, there is ample reason to proceed cautiously when working with nanomaterials. It is acknowledged that the evidence is by no means definitive, but it does suggest that there are hazards associated with exposures to nanoparticles and nanotubes. Given the fact that exposures to these materials will be increasing as this technology insinuates itself into various types of industries, it would be prudent to adopt the Precautionary Principle and treat nanomaterials as if they are hazardous to ensure worker safety until research provides information that justifies relaxing these precautions. To paraphrase Paul C. Lin-Easton, the Precautionary Principle states that decision making in extreme uncertainty should not be delayed due to the lack of information in matters that concern environmental threats. Applying this reasoning to occupational health and safety would not only benefit personnel exposed to these potentially hazardous materials but it would also reduce potential liability issues as well as worker compensation and insurance costs in affected industries.

While the hazards associated with the types of conventional chemicals and physical processes used to make nanomaterials have been well characterized and risk assessments could be reasonably completed in an accurate fashion, there is not enough information available to make reasonably accurate risk assessments of nanomaterials themselves. Since characterization of harmful properties is paramount but the necessary information is not available, precautionary measures must be taken and the materials assumed to be toxic until proven otherwise. “Specifically, we [The Royal Society and Royal Engineering Society] recommend as a precautionary measure that factories and research laboratories treat manufactured nanoparticles and nanotubes as if they were hazardous and reduce them from waste streams” (“Nanoscience and nanotechnologies” 5).

The Health and Safety Commission of the United Kingdom states that the defining characteristic of nano-scale materials is that they are very different from their macro scale counter parts due to physical, chemical and biochemical differences in properties. Because of the lack of knowledge concerning the properties of these materials there is considerable uncertainty in any assessment of health and safety risks[...] Similarly there may be a lack of knowledge about the effectiveness of risk control measures [...] All modern health and safety legislation is based upon the principle of suitable and sufficient assessment of the risks leading to the implementation of proportionate preventative and protective measures. Proportionate in this context means erring on the side of safety [...] It allows for uncertainty both in the risk assessment and in the effectiveness of the control measures – the greater the uncertainty the more precautionary the duty holder needs to be. (Davies 2-3)

4.15 Workplace Controls

While production of various nanoscale materials continues and is increasing, there is virtually no information available in the literature on reducing exposure to nanomaterials in the workplace. It is important to note that in nanotechnology research

and development laboratories and manufacturing facilities additional hazards are typically posed by the conventional hazardous materials that must be used to create nanomaterials. The various types of materials include hazardous chemicals in liquid, solid and gaseous form that may be oxidizers or flammable, corrosive, toxic or biological in nature. Presumably these exposures will be addressed through OSHA regulations including Hazard Communication CFR 1910.1200, Chemical Hygiene CFR 1910.1450 and Process Safety CFR1910.119.

At a recent Tradeline Conference held in August 2004, specific chemicals mentioned as being necessary for R& D work with nanomaterials include pyrophoric materials such as the compressed gas, silane. Flammable liquids are also used in open systems including acetone, benzene, butyl acetate and alcohols. Flammable compressed gases, including hydrogen, methane, dichlorosilane, carbon monoxide and ammonia, are used to process these materials. Oxidizing compressed gases such as chlorine, fluorine, nitrogen trifluoride, oxygen and nitrous oxide are also used. Corrosive liquids, including hydrochloric acid, hydrofluoric acid, nitric acid and other photoresistive strippers, are also used in open systems. Corrosive solids such as potassium and sodium hydroxide were also mentioned. Significant amounts of toxic materials including developers are also used (Case and Grant). In addition to these chemical hazards, there will also be physical hazards associated with this work including the previously mentioned high pressure gas, lasers and associated hot plasmas.

The question of what types of equipment will work to protect personnel from nanomaterials has yet to be completely answered, but such controls will most likely be found in the accepted hierarchy of protection. The methods of controls will include

engineering and administrative controls and, as a last resort, personal protective equipment. Interestingly the “Nanoscience and nanotechnologies” Report from the UK does not emphasize the use of engineering controls but states “that workers should seek protection by the usual methods of industrial hygiene, including the provision for respiratory protection and appropriate hazard information, together with appropriate procedures for cleaning up accidental emissions and for making repairs to machinery (“Nanoscience and nanotechnologies” 42). The UK Health and Safety Commission also emphasizes the use of appropriate respiratory protection including the use of self contained breathing apparatus should the situation warrant it (Davies Annex 1).

Perhaps the reason for the emphasis on PPE and respiratory protection is because there is no information available on proper containment for these materials. Additional considerations may be the generation of air currents, vibrational forces, electromagnetic radiation (Rossrucker) and any other potentially disruptive forces that may make working with nano-scale materials difficult or impossible. Therefore it may be necessary to invent new and innovative containment equipment to address these issues.

Additionally, standardized and validated methods for monitoring occupational exposure must be developed to monitor levels of these materials in the workplace and academic institutions. Efficacy testing of filtering materials for engineering controls and respirators is needed as well (“Nanoscience and nanotechnologies” 42).

On December 18, 2003 a panel of grantees from the National Science Foundation met to discuss issues related to environmental safety and health best practices. The panel essentially made use of existing regulation and guidance to compile a list of

general precautions designed to reduce or eliminate occupational exposure to nanoparticulates. This document is in draft form.

The panel recommends a strong chemical hygiene plan to handle conventional chemicals, an effective biosafety program and a strong training program. General statements are also made concerning proper engineering controls to minimize exposure as well as personal protective equipment to minimize inhalation and dermal exposures. At the organizational level, the program should be overseen by the EHS Department and actively monitored by the Safety Committee through audits. The EHS program must also be backed up by top management.

The National Science Foundation document follows the OSHA recommendations for a model safety program (“Draft Proposed Safety and Health Program Rule”). However, what is lacking in this document is specific information on what will actually work to prevent exposure to these materials in the workplace.

Research on high efficiency particulate air (HEPA) filtration addresses some specific questions relating to the size of particles that are efficiently removed by this process. The size range of the particles tested were from 0.0032 μm (3.2 nm) to 1.0 μm . The particle size found to be most penetrating with an Oshitari SO HEPA filter was in the range of 0.1 to 0.18 μm (100 to 180 nm) at the manufacturer recommended air flow rate of 2.4 centimeter/second (Yamada et al. 547). Removal efficiencies were greater in the ranges above and also below this particle size range. The results infer that a least some size ranges of nano-scale materials may be captured but no statements on collection efficiencies of nanomaterials were made as this was not the researcher’s primary focus.

On August 23, 2004 Vincent Castranova, Ph.D., Nanotechnology Safety and Health Research Coordinator for NIOSH was interviewed concerning the viability of using HEPA filtration for work with nanomaterials. Dr. Castranova stated that HEPA filters in theory should work for containment of nanomaterials but that more research needs to be done to verify this. When you get down to the size scale of nanoparticulates the mass of the particles is so low that particle inertia for impaction and mechanical capture is not significant. Nanoparticles are so small that they move by diffusion and Brownian motion rather than through inertial forces as do larger particles which have more mass. For diffusion to work and trap particles in the filter, the particles must have sufficient dwell time in the filter medium. Thus, if the flow rate of contaminated air through the filter is too high the removal efficiency of nanoparticles should decrease.

While not being able to definitively state what would work for the capture of nanoparticulates, Dr. Castranova did relate what doesn't work. Misuse of impaction filters can actually increase the release of ultrafine particles from a contaminated air stream such as diesel exhaust, and this may also apply to the misuse of HEPA filters. Researchers found that using a paper filter to trap particulates at the exhaust outlet of a diesel engine actually increased the availability of free ultrafine particles because the fine particles in the exhaust stream were filtered out by the paper and were not available to agglomerate and capture the ultrafine particles.

Since the size of nano-scale materials approach those of gas molecules, the question was posed if other types of media for trapping these materials, such as activated carbon which works by adsorbing contaminants on its surface, or if electrostatic precipitation would work. Dr. Castranova did state that many of the types of nanoscale particles have

significant surface charges but that it is too premature to make any blanket statements about what works and what doesn't. A more recent e-mail correspondence with Dr. Andrew Maynard, an ultrafine particle expert with NIOSH, also verifies that controls knowledge is still theoretical and further investigation is required ("RE: Nanotechnology Thesis"). NIOSH is currently working on many of these issues.

4.16 Explosive Dusts

The generation of combustible dusts is also a potential problem with these materials. "Any dry, fine and combustible powder poses an explosion risk, either through spontaneous combustion or ignition. The increased surface area of nanoparticles might mean that they would more likely become self-charged, and be more easily ignited" ("Nanoscience and nanotechnologies" 47). Given their vanishingly small size, these particulates will not be readily visible even in dense concentrations and therefore may not be easily detected as potential explosion hazards. According to the "Nanoscience and nanotechnologies" Report there is no information available concerning this potential hazard which could be significant in manufacturing facilities. The Academies recommend that the dusts be handled in liquid. "The risk of explosion can be avoided if combustible powders are manufactured, handled and stored in liquid. By contrast, the drying of nanopowders in rotary driers is of particular concern" ("Nanoscience and nanotechnologies" 47). The bottom line is that there may be an increased risk of explosion because of the increased surface area available from nanomaterials and potential for enhanced reaction. "Until this hazard has been properly evaluated this risk should be managed by taking steps to avoid large quantities of these nanoparticles becoming airborne" ("Nanoscience and nanotechnologies" 5)

5.0 Results and Discussion

5.1 Thesis Questions

The following research questions were asked

- 1.) What is the current state of knowledge concerning occupational exposure risk associated with nanotechnology?
- 2.) What are the areas of agreement and disagreement concerning nanotechnology in the literature and among the experts, and what additional research is required to generate a more complete picture of the health and safety problems surrounding the issue?
- 3.) What occupational safety precautionary recommendations can be made for research laboratory staff based on the current state of knowledge concerning the occupational risks of nanotechnology?

The primary research question asked by the author concerning the health effects of exposures to nanomaterials is important for several reasons. There are good indications that several types of nano-scale materials are significantly more toxic than their larger particle counterparts made of identical elements, meaning that by virtue of their size they present significant health and safety hazards. In fact, relatively inert materials have significantly increased toxicity as particle size decreases and relative surface area per unit of mass increases. Nanoscale materials have a larger and more reactive surface area by virtue of the significantly greater number of particles necessary to equal the same mass of larger diameter particles. Additionally, because of their size, they can readily penetrate various organs and circumvent body defense systems potentially causing disease.

Currently the workers primarily exposed to nano-scale materials are in the research and development field as well as those in manufacturing facilities.

The amount of individuals exposed is expected to increase, perhaps exponentially, as the technology takes off as anticipated. It is extremely important that the risks involved with these materials be thoroughly understood so appropriate controls can be put in place to prevent injury to workers. Based on the merit of information found in the literature review, a set of hypothetical precautionary recommendations are included as well as two standard operating procedures for working with free nanomaterials in the research and development arena. The control technologies include the use of engineering controls such as local exhaust ventilation and personal protective equipment to ensure worker safety.

Due to the lack of information on the safety and health risks of nanomaterials, it was anticipated that there would be a significant amount of disagreement on the safety of nanotechnology among the experts in the field. Only minor disagreements were found within the scientific community related to specific details of study results such as the role transition metals play in lung inflammation. While the question of the occupational risks of nanomaterials is being definitively answered, precautionary measures are recommended for work with all nanoscale constructs in the interim.

While no complete risk assessment information was found for nanomaterials, there appears to be a general agreement within the academic, industrial and regulatory communities that there is a need for meaningful regulation which will provide a safe and healthful work environment balanced with the need for rapid innovation. The question is

what degree of regulation is necessary. A review of published opinions from experts representing these stakeholders has confirmed this.

The original intent of this thesis was to review the literature and contact experts concerning the risks of working with nanoparticulates and nanotubes in the occupational setting and use this information to form a set of precautionary practices to work safely with these materials. However, the information on the risks associated with working with these materials is either extremely preliminary or non-existent and, as a result, a full risk assessment is not possible at this point in time. Also due to this lack of data, safe work practice information recommendations can only be made on the basis of the Precautionary Principle, which in this case means to treat all uncharacterized nanomaterials as hazardous substances until proven otherwise. A precautionary approach using the attributes of existing exposure control systems has also been included in this document.

5.2 Background

Nanotechnology is a relatively new field that is expected to have huge potential to impact many different fields of technology. The field has evolved very rapidly due primarily to the development of other tools that have permitted the visualization and manipulation of materials on the scale of molecules and atoms. While the impacts are expected to be positive in virtually all cases, there has been growing concern from a safety and health standpoint that exposures to free or unfixed nanoparticles may pose a risk to those working in research laboratories and manufacturing. Many nanotechnologies pose no new risks to health, and almost all the concerns relate to the potential impacts of deliberately manufactured nanoparticles and nanotubes that are free

rather than fixed to or within an embedding material (“Nanoscience and nanotechnologies” 4).

It is the properties of the nanomaterials which are primarily a function of their size that set them apart from other materials. At the macromolecular level in which these constructs exist “quantum effects can begin to dominate the behaviour of matter at the nanoscale - particularly at the lower end - affecting the optical, electrical and magnetic behaviour of materials” (“Nanoscience and nanotechnologies” 2). For instance, carbon nanotubes exhibit unusual quantum properties which can serve as wiring for molecular computers at scales of size so small that ordinary electrical current flow is not possible (Akin 3). Concerns have been expressed that the very properties of nanoscale particles being exploited in certain applications (such as high surface reactivity and the ability to cross cell membranes) might also have negative health and environmental impacts.

5.3 Health Effects

Exposure to nanoscale materials is not something new; humans have been exposed to nanoscale particulates from the products of combustion since fire was harnessed. While past studies have focused on workplace exposures to ultrafine particles, recently it has become apparent that ambient exposure to ultrafine particles in the atmosphere has resulted in significant increases in mortality in susceptible portions of the population (G. Oberdorster 1).

The results from studies of nanomaterials are preliminary. The ultrafine particle studies are more numerous but require a more thorough characterization of the toxicological, dose response and potential exposure issues posed by these materials. However, while the routes of exposure have not been adequately identified and

definitively defined for nanotubes, fullerenes and nanoparticulates in general, several general statements can be made about potential exposures to these materials through analogy to ultrafine particles for which there exists much more information on their effects on laboratory animals and also on humans through epidemiological studies. While technically they are not manufactured as nanomaterials are, in many cases they ultrafine particles similar morphology, behave similarly aerodynamically and may undergo similar processes within the body. These particles are thought to enter and reside in the body in the same way as nanoparticles and may be metabolized in a similar fashion to nanoparticles.

Ultrafine particles were found to be more reactive than comparable amounts of larger particles for several reasons: the greater surface area of the materials, the surface characteristics of the particles themselves and the ability of these materials to move relatively freely into and within the body or penetrate deep enough into it, as in the case of alveolar deposition, to cause disease (“Nanoscience and nanotechnologies” 41). Since nanoparticles can also penetrate cells, they may also interfere with phage motility and the ability of these cells to clear the alveoli of deposited particulates and bacteria. (Renwick, Donaldson and Clouter 125).

If these particles are not cleared by phagocytosis when deposited deep in the lung, they can penetrate the interstitium and be actively transported throughout the body by the circulatory system or lymph system (Ferin et al. 383; G. Oberdorster 7). In the short term, these exposures can cause decreased pulmonary function, increased incidents of cardiac events and inflammation (Brook et al. 2666, Donaldson and Stone 409). Chronic inflammation has been shown to promote other diseases such as cancer (Lock 117).

The hazards of these materials to specific segments of the population involving those with impaired pulmonary functions has also been documented and can be further exacerbated by exposure to endotoxin and/or ozone which were found to have a synergistic inflammatory response when coupled with ultrafine particle exposure to affected tissues (G. Oberdorster 6). Additionally, ultrafine particles, particularly those at the lower end of the nanoscale, were found to circumvent the blood brain barrier via the olfactory bulb, potentially causing neurotoxic effects by inducing inflammation which may result in neurodegenerative diseases such as Alzheimer's or promote cancer (G. Oberdorster et al. 444; Calderon-Garciduenas et al. 386). Thus, it can be extrapolated using the preliminary nanomaterials exposures in lab animals and ultrafine particle research that nanomaterials may pose a significant and possibly much different occupational risk to workers in research and manufacturing than what has been seen before.

Inhalation was found not to be a significant route of exposure for unrefined single walled carbon nanotubes (SWCNTs). However, should they be significantly disturbed, they may become airborne and present an inhalation and surface contaminant risk. It was found that there may be a significant dermal risk of exposure to nanotubes that may deposit on surfaces significant distances away from the point of generation which may "lead to dermal exposures in less well protected areas" (Maynard et al. 106). The unrefined SWCNTs with significant amounts of transition metals present were also found to be toxic to human dermal cells (Shvedova et al. "Keratinocytes" 1924). The mechanism of toxicity involved the creation of free radicals which oxidized the exposed cells leading to inflammation, a promoter of some forms of cancer (Lock 117).

SWCNT do pose a potential hazard causing respiratory tract inflammation if made airborne and inhaled. Using SWCNTs containing up to 30% iron and “neutralized” or reduced unrefined SWCNTs with human bronchial epithelial cells, researchers found diminished cytotoxicity from the reduced SWCNTs indicating that the transition metal catalyst may be primarily responsible for the observed cytotoxicity in direct contradiction to an earlier study by Brown, et al. (Shvedova et al. “Bronchial” 100). In the study performed by Brown et al. ultrafine carbon black particulates (UFCB) were found to be more proinflammatory than fine carbon black particles (CB). However, there was no statistically significant difference found between the UFCB coated with the reactive transition metal Fe(III) and uncoated UFCB (690). Future studies are required to separate the cytotoxic effects of the transition metals from those of the carbon nanotubes.

The health effects of water-soluble, polyalkylsulfonated C60 fullerenes (FC4S) in rats were also investigated. It was established that for rats ingestion of these materials is not harmful; however, injection, intravenously or intraperitoneal, eventually will cause damage to the kidneys as the fullerenes are metabolized (Chen et al. 150).

Quantum dots made from cadmium were found to be toxic when surface coatings break down and a portion of the metal is released (Kalaugher 1). Based on the limited evidence gathered, some nanomaterials may pose a significant health and safety risk to humans through exposures to free nano-scale materials in the occupational setting.

5.4 Manufacturing

It has been determined that there is potential for exposure to agglomerated nanomaterials in all four of the manufacturing processes identified: the gas-phase, vapour deposition, colloidal and attrition processes “which may potentially result in exposure by

inhalation, dermal or ingestion routes... during recovery, powder handling and product processing” (Aitken, Creely and Tran 57). Of the four manufacturing processes “only the gas-phase processes have the potential to cause exposure to primary nanoparticles by inhalation during the synthesis phase” (Aitken, Creely and Tran 57).

The full potential of nanotechnology has not been fully realized yet because of difficulties in manufacturing a standardized product whether of a particular particle size or a discrete uniform unit (“Nanoscience and nanotechnologies” 3). In most applications nanomaterials are usually embedded in a matrix, for example titanium dioxide added to glass to make it more dirt resistant or nanotubes embedded in car bumpers to add strength. It is expected that the likelihood of nanoparticles or nanotubes being released from products in which they have been fixed or embedded (such as composites) is low (“Nanoscience and nanotechnologies” 4), “but in some, such as those used in cosmetics and in some pilot environmental remediation applications, free nanoparticles are used” (“Nanoscience and nanotechnologies” 3). It is these free nanomaterials that pose the greatest risk of adverse exposure not only as consumer products but also further up the pipeline during manufacture and processing of these materials and initially as exposure issues in the research and development laboratory.

Presently there is relatively limited manufacturing capacity available for the production of nanomaterials. It is imperative at this point in time that regulators address this issue so that there is a uniform method for identifying hazardous properties of these materials and communicating this information to the end user and the public. They must also develop effective controls to limit exposures and a means to effectively promote

compliance in a flexible manner to allow for the innovation and growth necessary for the state of the technology and its control to stay current.

5.5 Regulation

Currently there are no regulations in place in the United States or any portion of the world that specifically address the unique issues nanomaterials present. Additionally, they have not been characterized as hazardous materials at this point in time. Within the United States there is not even a regulatory requirement to test nanomaterials for health, safety and environmental impacts (“Nanotechnology Safety Assessment”).

The United States Environmental Protection Agency (EPA) defines risk assessments as a four step process: hazard identification, exposure assessment, dose-response assessment and risk characterization. Unfortunately, the only portion of this process currently being addressed is step one, the identification of potential health problems associated with exposure to these materials. A preliminary portion of the dose response assessments has also been done concerning the effects these materials have on target organs. This work will eventually lead to characterization of the routes of exposure for nanotubes, fullerenes, quantum dots and other nanoparticulates. The majority of the studies completed are associated with exposures of laboratory animals to nanomaterials either in simulated exposure scenarios or through direct instillation of these materials to the animals. The more extensive body of literature on ultrafine particles primarily includes lab animal exposures and also epidemiological surveys of ambient exposures to pollutants.

It will be years before scientifically meaningful information will be available to perform a rigorous risk assessment. Only recently have safety and health initiatives such

as NANOSAFE from the European Union been launched, and it will be several years before such initiatives bear fruit. Additionally, in the United States, the National Institute of Occupational Safety and Health (NIOSH) is currently embarking on a 5 year initiative to research the potential hazards associated with nanomaterial exposures in the workplace.

5.5.1 A Regulatory Scenario

In the United States, the EPA is given broad discretion through the Toxic Substances Controls Act (TSCA) of 1976 (40 CFR 720.36) “to gather health/safety and exposure data on, require testing of, and control exposures and/or use of, new and existing industrial chemical substances and mixtures” (“Environmental Management Guide for Small Laboratories” 37). TSCA, however, contains loopholes and exemptions allowing producers of these materials to circumvent this regulation (Wardak).

The first step in the regulatory process should be the assignment of a unique Chemical Abstracts Systems (CAS) number to each new or existing nano-scale construct. This system provides the first early warning mechanism to the EPA that a new chemical material exists (Wardak). However, as the system is currently set up, it may not catch all nano-scale substances. Use of this system is currently not mandatory for proprietary substances, also and there are exemptions for research and development. Parent compounds may already be registered or comprised of inert materials on the macro-scale allowing the more toxic nanomaterials made of the same elements escape surveillance. It is recommended that the regulation be modified to capture all constructs below a certain size in one dimension, for instance. Once a compound has the CAS number and is manufactured or imported into the United States TSCA will most likely apply.

Slightly modifying the language of the Toxic Substances Control Act (TSCA) provides a reasonable starting point [...]using TSCA as a model, anyone wishing to manufacture a new chemical must give prior notice to the EPA for review under the pre-manufacturing notice requirement. In the face of civil and criminal penalties (as in TSCA) most firms and researchers would comply with the notification requirements. (Forrest 7)

Once a pre-manufacturing notification (PMN) is received, within 90 days risk managers within the EPA draw upon existing information submitted with the PMN form, research for other information and look at exposure and release models to form a conclusion about the risk this material may present. When sufficient toxicity information is not available to properly characterize a substance, more data will be requested by the EPA through its New Chemicals Program (“Assessing Risk”).

Section 5(e) of TSCA provides authority to the EPA to regulate chemicals that are lacking safety and environmental risk data based on the potential risk, on the basis of substantial production volume, significant/substantial exposure to humans or significant/substantial releases to the environment (“TSCA” 5(e) 1). Such regulation could lead up to an outright ban of a substance but generally if a PMN substance may present an unreasonable risk to human health via and typically through inhalation, a TSCA section (e) consent order may be issued in which a New Chemical Exposure Limit (NCEL) modeled after OSHA Permissible Exposure Limits is established (“New Chemicals Exposure Limits”).

Once it has been established that a chemical is hazardous, it is then the manufacturer’s responsibility to communicate this information to the end user. In academic research and development labs the EPA has been more effective in enforcement due to the fact that they are not as limited as OSHA is to protecting only paid employees; thus, the EPA can

more effectively address potential exposure issues with students. In the workplace, in addition to the claim that the EPA has to limiting worker exposure to hazardous materials, OSHA bears a good portion of the enforcement burden through its Hazard Communications Standard, CFR 1910.1200, which includes training, labeling and material safety data sheet requirements. OSHA would then cover any workplace exposure issues using the Chemical Hygiene Standard, 40 CFR 1910.1450 and by using the general duty clause, 29 USC 654 (ATL International).

OSHA can also promulgate safety and health regulations by means of consensus standards.

Voluntary consensus standards are developed by organizations with the participation of interested parties—producers, users, and general interest groups [...] The advantage of utilizing the private sector's technical expertise in formulating health, safety, and environmental regulatory standards cannot be overemphasized. It is a fact that this expertise cannot be matched, in the vast majority of instances, by the technical staffs of federal, state, and local regulatory authorities. In addition, the utilization of active technical standards-writing committees from the private sector is an efficient and dependable means of ensuring that standards are kept up to date with developing technology. (Forrest 10)

Coincidentally, one such consensus standard organization, the American National Standards Institute (ANSI) announced the “formation of the Nanotechnology Standards Panel (ANSI-NSP), a new coordinating body for the development of standards in the area of nanotechnology” (ANSI) on August 5, 2004.

A barrier to attaining a meaningful consensus standard may be the proprietary nature of the work performed to make nanoparticles. Therefore, a requirement or an incentive to keep such information sequestered while allowing its use to develop and maintain

standards is imperative. The Royal Academies have gone a step further in their recommendations and recommended that all safety related data pertaining to nanoscale materials be released to the public domain (“Nanoscience and nanotechnologies” 83).

Millions of people will be working with these materials which, if handled improperly, could pose a significant health risk to exposed individuals. Granted, not all constructs will be found to be hazardous; however, as the industry grows there will be more and more types of compounds created that will provide a wide range of benefits but also present new risks. As a result, a regulatory framework must be set up that is both effective and flexible enough to allow for innovation not only in the creation of new nanomaterials but also in the control of their exposures.

5.6 Proposal of a Specific Control Methodology

It may be useful to use as a model the National Institute of Health (NIH) biosafety levels and the European Union’s chemical control banding methodology to formulate an effective and adaptable set of containment standards to address hazards associated with discreet classes of nanomaterials. For instance, physical characteristics of particles could be taken into account in which particle size, the presence of transition metals in and on the construct, the ability of the material to be made airborne and/or penetrate the skin and other parameters could be taken into account and applied to a set of “Nanosafety” guidelines which are based on engineering controls, personal protective equipment and administrative practices.

The biosafety precautions employed to protect workers are based on the risk group designation assigned to the pathogen of interest. Each risk group category is based on the ability of a pathogen to cause disease and death. Risk group 1 is composed of

microorganisms that rarely cause harm while pathogens in Risk group 4 can cause disease and death. Although there are exceptions to the rule, generally a microorganism in risk group 1 is handled at a biosafety level 1 and so on up through risk group and biosafety level 4 which addresses pathogens presenting the highest hazard (“Appendix B”). But there is some flexibility built into the system in that a pathogen such as monkey virus B, which can be deadly if contracted, is categorized as risk group 3 and is generally handled at a biosafety level 2. This exception applies because the virus is not easily transmitted. This type of flexibility would be necessary to deal with the unique issues presented by nanomaterials while providing a framework of risk classification and control.

To demonstrate this approach, a hypothetical ‘Nanosafety’ Guide for work in research and development laboratories has been developed (see Table 1). For the purposes of this demonstration the following nanoscale constructs are used:

- Embedded nanomaterials are presumed to be low risk or risk group 1.
- Single walled carbon nanotubes would fall into the risk group 2 category since they are presumed not to be made readily airborne and as such present an inhalation hazard only if significantly disturbed.
- Free quantum dots are thought to fall into the risk group 3 category. It is presumed that they can be made readily airborne without the benefit of containment in liquid and are toxic by inhalation.

The control measures noted in this table are for demonstration purposes only and should not be construed as effective precautionary measures endorsed by the author.

Table 1. Nanosafety Levels

Nanosafety Level	Agents	Practices	Safety Equipment (Primary Barriers)	Facilities (Secondary Barriers)
1	Embedded nanomaterials (embedding matrix will not be disturbed)	Training None	None required	Open bench top
2	Single walled carbon nanotube	Training Limited access Hazard warning signs Nanosafety manual defining handling procedures	Class I or II Biosafety cabinets (BSCs) or other physical containment devices. Respiratory protection recommended for all manipulations of nanomaterials that cause splashes or aerosols (if in liquid) or release of particulate materials Double nitrile gloves, impervious clean room gown, safety glasses	Room with door Room should be negatively pressurized with no recirculation
3	Quantum Dots (containing cadmium)	Training Controlled access Hazard warning signs Nanosafety manual defining handling procedures	Class I or II BSCs , glove boxes or other physical containment devices Respiratory protection used for all open manipulations of agents Double nitrile gloves, impervious clean room gown, safety glasses	Room must be negatively pressurized with no recirculation Physical separation from access corridors Self-closing, double-door access

(BMBL)

The chemical control banding procedure is also of interest because it provides a standardized means of communicating hazard and risk information to the end-user. Control banding is a risk based exposure control system set up by the European Union (EU) for small to medium businesses and emerging economies where chemical safety expertise may not be readily available. It involves the use of R phrases that in the EU must be assigned to hazardous chemicals. These R phrases have been standardized and

organized by industry toxicologists into hazard groups. By reading the R phrases on the container label or material safety data sheet, the consumer is informed of the product hazards and then is responsible to perform an exposure assessment of the work place. Several exposure assessment parameters are defined and questions based on these parameters must be answered. The questions relate to the amount of material used, its volatility based on boiling point and the temperature at which it will be handled. The consumer then applies the results of the assessment to a simple table which is keyed to specific information on one of three control approaches. Three broad control approaches are then applied to the situation to control exposure and reduce or eliminate risk. The control technologies used are: general ventilation; engineering control; containment (Jackson 1).

A similar communication and control approach could be applied to nanomaterials. Each unique nanomaterial construct would be assigned to one of various risk groups based primarily on the physical and chemical hazards presented by each construct. Once the construct was characterized by hazard, a set of containment strategies and other protective measures would be cross-referenced and applied to handling this material in the workplace.

Currently, there is no information available on specific containment methods for working with nano-scale materials. As mentioned earlier, HEPA filtration should work theoretically but its use has not been approved by NIOSH for that purpose. Also the use of apparatus such as biosafety cabinets or fume hoods may not be viable due to the air currents necessary for containment and vibrations generated by the operation of these units. Vibration and its avoidance is an important consideration in the siting of

nanotechnology research facilities (Rossrucker). Presumably, sealed glove boxes and other containment engineering controls which protect the worker and do not rely on the continual operation of fans and motors to control these units may be of practical use. It has also been suggested that production processes where dusts are generated be carried out in liquid to reduce the generation of airborne particulates (“Nanoscience and nanotechnologies” 47).

6.0 Conclusion

While there is adequate information available to raise questions concerning the safety of exposures to free nanoparticles, the current state of knowledge concerning the occupational exposure risks associated with nanotechnology is poor. There have been several preliminary toxicological studies performed using actual nanomaterials, but none have been associated with actual human exposures. The majority of potential evidence concerning potential health effects comes from the work performed with ultrafine particle exposures. The results from these studies suggest that there are significant pulmonary and cardiovascular effects as well as extra-cardiopulmonary impacts on organs, such as the liver, occurring as a result of exposure to UFPs entering the bloodstream from inhalation exposures (Donaldson and Stone 409; Borm 316; Ferin et al. 383). Additionally, ultrafine particles are able to cross the blood brain-barrier and potentially affect the central nervous system (G. Oberdorster 444). Thus, there is significant evidence that ultrafine particles and, by association, nanoparticles may present significant health risks.

In “Nanoparticles: An occupational hygiene review,” Aitken, Creely and Tran state that there is inadequate knowledge concerning nanoparticle risks to perform proper and effective risk assessments; the components of which include hazard identification, dose-response assessments, exposure risk and risk characterization (“Risk Assessment for Toxic Air Pollutants”). Areas requiring further study include providing sufficient understanding of the toxicological risks (including potential routes of exposure) posed by each specific nanoscale construct. Also additional work must be done to establish proper risk assessment protocols, a metric by which surface area (for inhalation exposures) can

be measured and an effective, validated means of monitoring exposure. Additional information must also be gathered on an effective means of better controlling presumed exposures (Aitken, Creely and Tran 55-56) not only through personal protective equipment but through engineering and administrative controls. Regulatory bodies must also assess nanotechnology and determine if the existing regulations adequately control the hazards posed by these materials. In areas where regulation is lacking but thought necessary, appropriate action must be taken in relation to the risk posed.

Overall there were no significant disagreements concerning nanotechnology found by this author other than the call for a moratorium for use of nanomaterials from ETC Executive Director; no other stakeholders have expressed concerns with such urgency. Another area of disagreement is the role of transition metals on the surface chemistry and toxicity of carbon nanotubes. Shvedova et al. states that these metals cause higher toxicity than nanotubes without such transition metals being present (“Bronchial”100). Conversely, Brown et al. states that the metals do not contribute to the toxic effects of nanotubes (690). No other areas of significant disagreement were found.

It is premature to assume, based on the available information, that one can develop an effective and definitive set of precautionary recommendations to work safely with nanomaterials. “For exposure by inhalation, control approaches and methods are available which should be effective in nanoparticle processes”(Aitken, Creely Tran 57). Presently though, no definitive and specific control recommendations or rules are available from any public agency. However, included in Appendix A are two standard operating procedures for working with nanomaterials in the research and development setting which may be useful as a tool to complement an existing nanosafety program.

Several assumptions were made including, but not limited to, the efficacy of HEPA filters to adequately capture nanoparticulates and the ability of nitrile gloves to protect the skin from nanoparticle infiltration.

As mentioned previously, an important method of reducing inhalation exposure is the use of liquids to contain nanomaterials. It has been assumed theoretically that HEPA filtration will be an effective means of preventing inhalation exposures. HEPA filtration via respiratory protection rather than through the use of engineering controls is currently emphasized in the literature. However, “for dermal or ingestion exposure, control methods based on personal protective equipment may not be as effective as they are in existing process” (Aitken, Creely Tran 57). Thus the control of significant potential exposures and their control have not been adequately addressed at this time.

It is presumed that once the identified government initiatives complete their missions there will be a frame work implemented to address the hazards posed by existing and new constructs as they are introduced in the workplace. The risk assessment process must be efficient and as effective as possible to meet the demands of this growing field.

Regulation will also necessary. There appears to be an adequate basis to handle some of the preliminary problems associated with this materials within the existing regulatory framework. However, specific sets of standards should be developed to classify nanoparticulates by hazard and address potential exposure issues in the work place through the use of appropriate engineering controls and personal protective equipment. Conversely, these standards must be flexible enough to allow for innovation both within the industry itself and in the development of protective measures.

There are many questions that must be answered in order to work safely with nanomaterials and also to reduce or eliminate any potential environmental effects this material may have. Until these questions are answered, it is imperative that a precautionary approach be adopted that will allow work to continue but ensure that nanomaterials will be responsibly used and no harm comes to those potentially exposed to them.

Appendix A

Nanosafety

Standard Operating Procedures

For

Research and Development Laboratories

Note: These SOPs are for demonstration purposes only and do not constitute recommendations to work safely with nanomaterials.

SOP – 1

Standard Operating Procedures for Nanomaterials

1.) INFORMATION AND TRAINING

Prior to the initiation of work with nanomaterials, each staff member must review the material safety data sheet and any additional manufacturer's information on the safe handling of and health risks associated with the particular construct.

Personnel must also have Nanosafety, Personal Protective Equipment, Hazard Communication and Chemical Hygiene Training and as well as training on the specific hazards posed by this material. Additionally, a Nanosafety Plan must be written (and reviewed by all affected personnel) which documents in detail all procedures and specifies engineering controls, personal protective equipment and any administrative controls use to work safely with these materials.

1.) PERSONAL PROTECTIVE EQUIPMENT (PPE)

Personnel working with nanoparticulates will wear two pairs of nitrile gloves*, disposable forearm guards, lab coats or gowns and safety eyewear. Respiratory protection (N-99 respirators) must be used if a glove box, Class II biological safety cabinet (BSC) or fume hood is not used or the plane of the open hood or cabinet is breached by personnel. For work with sharps remember to set up the area with a sharps container prior to initiation of work. Always dispose of the sharps immediately after use. (*The proper type of glove to wear varies by the hazardous material handled. Consult the MSDS for the proper glove type to wear when working with this compound.)

2.) CONTAINMENT

All work will take place in a posted room or cubicle where access can be restricted. Prior to the start of the project and where needles are used, the work area must be staged with a sharps container within easy reach. All used needles must be disposed of IN the sharps container immediately after use. Re-capping is not recommended but if it must be done a one-handed technique must be used. All nanomaterials will be prepared and handled in a glove box, fume hood or Class II BSC. Use of a negative pressure enclosure, such as a cubicle room is permitted only when the configuration of the glove box, BSC or hood will interfere with proper handling technique. All personnel inside the negative pressure enclosure must use PPE as required above including adequate respiratory protection.

3.) EMERGENCY PROCEDURES

In the event of skin contact, immediately remove contaminated clothing. For small area exposures wash with soap and water continuously for 15 minutes. For large area exposures use the nearest available emergency shower immediately and wash for 15 minutes. In case of eye contact, promptly flush the eye(s) in an eyewash station with copious amounts of water for 15 minutes with lifting both eyelids occasionally and obtain medical attention. If the nanomaterials are ingested or injected, obtain medical attention immediately. If large amounts of nanomaterials are inhaled, move to fresh air and seek medical attention at once. All spills in a glove box, BSC or fume hood will be cleaned up immediately by personnel using proper PPE. The spill will be cleaned up using absorbent

material and placed in a sealed container. For dry spills, wet methods must be used to reduce the risk of generating airborne contaminants. The area will then be decontaminated using a strong alkaline detergent or other appropriate solution (see Section 4). If a spill occurs outside a BSC or hood, the room will be evacuated. Reentry will not occur until the room is clear of airborne contaminants, usually one hour. Spill response personnel will don N-99 respirators or SCBAs, goggles, chemical resistant gloves, a disposable smock or lab coat and shoe covers. The spill will be contained and cleaned up the spill as outlined above. All spills must be reported immediately to the EHS Department.

4.) DECONTAMINATION

Generally, methods of decontamination will vary with the compound used.

Contact the EHS Department for information concerning the proper decontamination procedure.

5.) DISPOSAL OF WASTE

Waste is to be placed in special closable and sealed containers and disposed of as hazardous chemical waste. Spill clean-up waste will be disposed of as hazardous chemical waste.

EHS Officer: _____ Date: _____

SOP- 2

Standard Operating Procedures for Nanomaterials and Research Animals

1.) INFORMATION AND TRAINING

Prior to the initiation of work with nanomaterials each staff member must review the material safety data sheet and any additional manufacturer's information on the safe handling of and health risks associated with the particular construct. Personnel must also have Nanosafety, Personal Protective Equipment, Hazard Communication and Chemical Hygiene Training and training on the specific hazards posed by this material. Personnel caring for the contaminated animals must have Nanosafety, Personal Protective Equipment, Animal Facility Safety and Hazard Communication Training as well as specific instruction on the hazards of the material used and methods for reducing one's exposure during the care of shedding animals. Additionally, a Nanosafety Plan must be written (and reviewed by all affected personnel) which documents in detail all procedures and specifies engineering controls, personal protective equipment and any administrative controls used to work safely with these materials.

1.) PERSONAL PROTECTIVE EQUIPMENT (PPE)

Preparation and Administration of the Hazardous Agent: Personnel working with nanoparticulates will wear two pairs of nitrile gloves*, disposable forearm guards, lab coats or gowns and safety eyewear. Respiratory protection (N-99 respirators) must be used if a glove box, Class II biological safety cabinet (BSC) or fume hood is not used or the plane of the open hood or cabinet is breached by personnel. For work with sharps, remember to set up the area with a sharps

container prior to initiation of work. Always dispose of the sharps immediately after use. (*The proper type of glove to wear varies by the hazardous material handled, consult the MSDS for the proper glove type to wear when working with this compound).

Maintenance of the animals: Personnel will wear two pairs of nitrile gloves*, N-99 respirators, gowns or lab coats, shoe covers and safety eyewear when maintaining the animals. Cages must be changed in a glove box, fume hood, Class II BSC or equivalent cage dump station. (*The proper type of glove to wear varies by hazardous material handled, consult the MSDS for the proper glove type to wear when working with this compound).

2.) CONTAINMENT

Administration: All work will take place in a posted room or cubicle where access can be restricted. Prior to the start of the project and where needles are used, the work area must be staged with a sharps container within easy reach. All used needles must be disposed of to the sharps container immediately after use. Re-capping is not recommended but if it must be done a one-handed technique must be used. All nanomaterials will be mixed, aliquoted for administration and administered in a glove box, fume hood or Class II BSC. Use of a negative pressure enclosure, such as a cubicle room, to perform administration is permitted only when the configuration of the glove box, BSC or hood will interfere with proper administration technique. All personnel inside the negative pressure enclosure must use PPE as required above including adequate respiratory

protection. Only experienced personnel and those adequately trained in the specific technique will administer the compound to the animals.

Housing: Access will be restricted to authorized personnel. All contaminated animals will be housed in micro-isolator cages with properly fitted tops or HEPA filtered Thoren racks. All cages will be labeled with hazard warnings. Unless the investigator can provide written evidence of the animals not excreting the nanomaterials, the EHS Officer will determine the proper amount of time the animals will be housed and handled as potentially contaminated (shedding).

Maintenance: During the period of shedding, Animal Facility personnel will change the cages only in a glovebox, chemical fume hood, Class II BSC or equivalent cage dump station in a posted room where access can be restricted. Waste is to be placed in red bags and leak proof containers for disposal as infectious chemo waste over this time period.

3.) EMERGENCY PROCEDURES

In the event of skin contact, immediately remove contaminated clothing, for small area exposures wash with soap and water continuously for 15 minutes. For large area exposures use the nearest available emergency shower immediately and wash for 15 minutes. In case of eye contact, promptly flush the eye(s) in an eyewash station with copious amounts of water for 15 minutes with lifting both eyelids occasionally and obtain medical attention. If the nanomaterials are ingested or injected, obtain medical attention immediately. If large amounts of nanomaterials are inhaled, move the person to fresh air and seek medical attention at once.

All spills in a glove box, BSC or fume hood will be cleaned up immediately by personnel using proper PPE. The spill will be cleaned up using absorbent material and placed in a sealed container. For dry spills, wet methods must be used to reduce the risk of generating airborne contaminants. The area will then be decontaminated using a strong alkaline detergent or other appropriate solution (see Section 4). If a spill occurs outside a BSC or hood, the room will be evacuated. Reentry will not occur until the room is clear of airborne contaminants, usually one hour. Spill response personnel will don N-99 respirators or SCBAs, goggles, chemical resistant gloves, a disposable smock or lab coat and shoe covers. The spill will be contained and cleaned up the spill as outlined above. All spills must be reported immediately to the EHS Department.

4.) DECONTAMINATION

Generally, methods of decontamination will vary with the compound used.

Contact the EHS Office for information concerning the proper decontamination procedure.

5.) DISPOSAL OF WASTE

Waste is to be placed in special closable containers during the time period the animals are presumed to be shedding and disposed of as infectious chemo waste. Carcasses will be disposed of as infectious waste and nanomaterial waste will be disposed of as hazardous chemical waste. Spill clean-up waste will be disposed of as hazardous chemical waste.

EHS Officer: _____ DATE: _____

Appendix B

Interview Questions

- 1.) Can you direct me to any information concerning nanotechnology and risk, toxicology or any other health and safety study that has been done on any aspect of this technology?
- 2.) Can you recommend engineering controls to prevent potential inhalation of nanoparticles?
- 3.) Are you aware of any papers that cover the use of engineering controls with nanomaterials?
- 4.) Do you have a contact at NIOSH or anywhere else that is looking at engineering controls for nanoparticulates?
- 5.) I was hoping to get information on best safety practices when working with nanomaterials, primarily engineering controls and personal protective equipment. Do you have any information?
- 6.) Do HEPA filters work for nanomaterials?
- 7.) Since nanomaterials behave in ways similar to gases, will adsorption media such as charcoal work for filtering out airborne nanoparticulates?
- 8.) Can you use an electrostatic precipitator to capture nanoparticles?
- 9.) Can I get information on the regulatory procedures involved with getting a new chemical regulated under TSCA? In particular, when is a risk assessment done and how is that information translated to the regulation of that substance in the workplace, through OSHA for instance?
- 10.) What regulation, if any, is necessary for nanomaterials?

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