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Nanotechnologies — Health and safety practices in occupational settings relevant to nanotechnologies

Nanotechnologies — Pratiques de sécurité dans les arrangements professionnels relatifs aux nanotechnologies

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

In exceptional circumstances, when a technical committee has collected data of a different kind from that which is normally published as an International Standard ("state of the art", for example), it may decide by a simple majority vote of its participating members to publish a Technical Report. A Technical Report is entirely informative in nature and does not have to be reviewed until the data it provides are considered to be no longer valid or useful.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

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1. Introduction

The field of nanotechnologies is advancing rapidly and is expected to impact virtually every facet of global industry and society. International standardization on nanotechnologies should contribute to realizing the potential of this technology for the betterment and sustainability of our world through economic development, improving the quality of life, and for improving and protecting public health and the environment. One can expect many new engineered nanomaterials coming to the market place and work place. The introduction of these new materials into the workplace raises questions concerning occupational safety and health that should be addressed, as appropriate, by international standards. While such standards are being developed, it is important, through this Technical Report, to assemble and make available to users, useful knowledge on occupational safety and health practices in the context of nanotechnologies.

Nanotechnology involves materials at the nanoscale. As a working definition,[i] the "nanoscale" means size range from approximately 1 nm to 100 nm. A nanometer is 1×10^{-9} m or one millionth of a millimeter. It is difficult to fully appreciate these remarkably small scales. To give a sense of this scale, a human hair is of the order of 10,000 to 100,000 nm, a single red blood cell has a diameter of around 5,000 nm, viruses typically have a maximum dimension of 10 to 100 nm and a DNA molecule has a diameter of around 2 nm. The term "nanotechnology" can be misleading since it is not a single technology or scientific discipline. Rather it is a multidisciplinary grouping of physical, chemical, biological, engineering, and electronic processes, materials, applications and concepts in which the defining characteristic is one of size.

The distinctive and often unique properties which are observed with nanomaterials offer the promise of broad advances for a wide range of technologies in fields as diverse as computers, biomedicine, and energy. At this early stage the potential applications of nanomaterials seem to be limited only by the imagination. Articles appear daily in the scientific and popular press and on a host of websites dedicated to the field. New companies, often spin outs from university research departments, are being formed and are finding no shortage of investors willing to back their ideas and products. New materials are being discovered or produced and astonishing claims are being made concerning their properties, behaviors and applications. As of June, 2007, over 400 nano-enabled new products are listed in an inventory of products already utilizing nanotechnology compiled by the Woodrow Wilson Center's Project on Emerging Nanotechnologies (www.nanotechproject.org/inventories/consumer/). Another list of products can also be found on U. S. National Nanotechnology Initiative web-site at www.nano.gov/html/facts/appsprod.html. While much of the current "hype" is highly speculative, there is no doubt that worldwide, governments and major industrial companies are committing significant resources for research into the development of nanometer scale processes, materials and products.

Ordinary materials such as carbon or silicon, when reduced to the nanoscale, often exhibit novel and unexpected characteristics such as extraordinary strength, chemical reactivity, electrical conductivity, or other characteristics that the same material does not possess at the micro or macro-scale. A huge range of nanomaterials have already been produced including nanotubes, nanowires, fullerene derivatives (bucky balls).

A few engineered nanomaterials were developed already in the 19th and 20th centuries, at a time when the word "nanotechnology" was unknown. Among such nanomaterials are zeolites, catalyst supports such as $MgCl_2$, pigments and active fillers such as carbon black and synthetic amorphous silica. Market size of these commodity materials is well above the billion US dollars or million tons threshold.

Nanotechnologies are gaining in new commercial application. Nanomaterials are currently being used in electronic, magnetic and optoelectronic, biomedical, pharmaceutical, cosmetic, energy, catalytic and materials applications. Areas producing the greatest revenue for nanomaterials are chemical-mechanical polishing, magnetic recording tapes, sunscreens, automotive catalyst supports, electro-conductive coatings and optical fibers.

[i] Please note, that definitions used throughout this Technical Report are based on draft definitions developed by ISO TC 229 WG1 and might become obsolete if draft definitions change.

The occupational health and safety effects of new nanomaterials are mostly unknown. This can be attributed to the relatively recent development of the nanotechnology sector and, as a result, the lack of available information on human exposures and working conditions. As a consequence our abilities to accurately predict the impact of some nanomaterials exposures on worker health are limited at this time. In particular our abilities to measure nanoparticles in the workplace (or more generally) are limited by current technologies. Nanotechnology presents us with new challenges as the properties of nanomaterials now depend on size and shape as much as the more conventional factors of chemical structure and composition. Measuring these additional attributes will be necessary to accurately assess nanomaterials in the workplace. In addition, the capability of the human body to recognize and appropriately respond to most nanomaterials is essentially unknown at the moment. On the other hand, in the case of some nanostructured materials, such as carbon black and synthetic amorphous silica, toxicologic and epidemiologic data are available.

There are many gaps in current science about identifying, characterizing, and evaluating potential occupational exposures in the nanotechnology context. These gaps in our knowledge will best be addressed at a multidisciplinary level. Occupational health practitioners and scientists and practitioners in the toxicology field including medical scientists and environmental scientists have vital roles to play in safeguarding health in this fast-moving field. Collaborative studies - ideally with international coordination - are essential in order to provide the critical information required within a reasonable time frame.

2. Scope

This Technical Report describes health and safety practices in occupational settings relevant to nanotechnologies. The initial outline was prepared using U. S. NIOSH's Approaches to Safe Nanotechnology: An Information Exchange with NIOSH.[1] This Technical Report focuses on the occupational manufacture and use of engineered nanomaterials. It does not address health and safety issues or practices associated with nanomaterials generated by natural processes, hot processes and other standard operations which unintentionally generate nanomaterials, or potential consumer exposures or uses, though some of the information in this Technical Report might be relevant to those areas. For more general information on the environment, health and safety of nanotechnologies, the reader can refer to other existing well documented reviews.[2-7] Use of the information in this Technical Report could help companies, researchers, workers and other people to prevent adverse health and safety consequences during the production, handling, use and disposal of manufactured nanomaterials. This advice is broadly applicable across a range of nanomaterials and applications.

This Technical Report is based on current information about nanotechnologies, including characterization, health effects, exposure assessments, and control practices. The authors of the Technical Report have attempted to remain current with the use of terms and their definitions. However, definitions in this field are evolving and some terms have not yet undergone ISO consensus review. Therefore, the terms are intended to be used solely for the purpose of this Technical Report and not to be considered formal definitions beyond this Technical Report. It is expected that this Technical Report will be revised and updated and new safety standards will be developed as our knowledge increases and experience is gained in the course of technological advance.

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3. Nanomaterials: description and manufacturing

3.1. Engineered nanomaterials

Engineered nanomaterials are designed with specific properties in mind. Engineered nanomaterials encompass nano-objects and nanostructured materials. The former are defined as materials with one (nanoplate), two (nanorod) or three external dimensions (nanoparticle) in the nanoscale (i.e. between approximately 1 and 100 nm). Examples of nanostructured materials are nanocomposites composed of nano-objects embedded in a solid matrix or nano-objects bonded together in simple random assemblies as in aggregates and agglomerates or ordered as in crystals of fullerenes or carbon nanotubes.[1] Discussion in this Technical Report will focus primarily on nano-objects and their simple assemblies.

Relatively simple nanomaterials presently in use or under active development can be classified in terms of dimensionality and the primary chemical composition. However, even simple nanomaterials are often coated and have complex chemical and physical structure. Any attempt to classify nanomaterials is highly artificial with many materials falling into several classification categories. Thus, the following description is for organizational purposes only.

Quantum dots and fullerenes are confined to the three-dimensional nanoscale domain. Nanotubes, nanowires, nanofibers and nanofibrils have at least two nanoscale dimensions, while nanoscale surface coatings, thin films and layers have at least one nanoscale dimension. In the following subsections, nanomaterials are described according to the primary (or core) chemical composition of nano-objects: carbon containing nanomaterials (e.g. fullerenes, carbon nanotubes); oxides nanomaterials (e.g. TiO_2 and ZnO); metal nanomaterials (e.g. Au); semiconductor nanomaterials (e.g. quantum dots); organic polymeric nanomaterials (e.g. dendrimers); and bio-inspired nanomaterials (e.g. capsid nanoparticles). Within these classes, different nanomaterials are listed in the order of decreasing necessary number of dimensions in nanoscale from 3D particles to fibers to layers.

3.1.1. Carbon containing nanomaterials

3.1.1.1. Fullerenes

Fullerenes are chemical entities which can be envisioned as spherical cages built from carbon atoms chemically bonded to three nearest neighbors. The best known example is a soccer-ball shaped C_{60} fullerene. Fullerene molecules can contain from 28 to more than 100 carbon atoms with some experimental studies reporting molecules containing up to 1 500 atoms with 8.2 nm diameter.[2] Existence of even larger fullerene molecules has been postulated from theoretical considerations.[3] Multi-shell fullerene-like nanoparticles referred to as carbon nano-onions, can range in size between 4 and 36 nm.[4] Fullerenes are actively investigated for a wide range of potential applications including: lithium-ion batteries, solar cells, fuel cells, oxygen and methane storage materials, additives to plastics, oil and rubber, and cancer and AIDS treatments.

3.1.1.2. Carbon black

Carbon black consists of partially amorphous material, organized into spherical or near-spherical particles fused together to give aggregates, weakly interacting to form agglomerates, usually further organized into macroscopic pellets.[5] Furnace black accounts for 98 % of the worldwide production and has an average aggregate diameter of 80-500 nm and an average primary particle size of 11-95 nm. The main industrial uses of carbon black are as a pigment and as reinforcing filler for rubber articles, in particular, tires.

3.1.1.3. Carbon nanofibers

Carbon nanofibers (CNFs) are cylindrical or conical structures that have diameters ranging from a few to one hundred nanometers and lengths ranging from under micrometer to several millimeters. The internal structure is comprised of stacked curved graphite layers (or graphene sheets, see also section 3.1.1.5) that form cones (herringbone structure), cups (bamboo structure), rods (solid structure), or tubes (hollow structure).[6] The main distinguishing characteristic of nanofibers from nanotubes is the stacking of graphene sheets which make a non-zero angle with the fiber axis. When graphene sheets are parallel to the fiber axis, they form carbon nanotubes (see next section). Since there are “in-plane” and “interplane” components of transport and mechanical properties along the fiber axis, as well as presence of unsaturated bonds similar to graphite, carbon nanofiber characteristics differ from those of carbon nanotubes.

Carbon nanofibers are produced during chemical vapor deposition processes from carbon rich gases such as hydrocarbons over metal catalysts.[7] A greater control over carbon nanofiber structure and composition can be achieved with catalytic plasma-enhanced chemical vapor deposition.[8] Carbon nanofibers are produced on an industrial scale and find applications as polymer additives, gas storage materials and catalyst supports.[9]

3.1.1.4. Carbon nanotubes

Carbon nanotubes (CNTs) represent a diverse family of carbon-based materials based on a graphene sheet rolled up in the form of a tube. CNTs can be made up of one sheet (Single-Walled) or several sheets (Multi-Walled). Single-walled CNT can be open- or closed-ended depending on whether they are capped with fullerene halves at each end. Carbon nanotubes can have a diameter as small 0.4 nm and reach several centimeters in length.[10,11] Multi-walled form can reach 100 nm in diameter.[12]

Single-walled carbon nanotubes display metallic or semiconductive properties depending on how the graphene sheet is rolled up, and their electronic response can be tuned using elemental subsitution.[13] Carbon nanotubes have been predicted to be as much as sixty times stronger than steel and six times lighter.[14] They are considered excellent heat conductors, have a great capacity for molecular absorption and are chemically and thermally very stable.[15]

Applications which are currently being investigated include; polymer composites, electromagnetic shielding, electron field emitters, super capacitors, batteries, hydrogen storage and structural composites. Main synthesis methods for carbon nanotubes fall into two classes: those in which elemental carbon is vaporized typically by a laser or an electric arc and those in which the carbon is derived at lower temperature from a carbon source usually assisted by a catalyst or plasma.[16]

Commercial manufacturing and supply of carbon nanotubes at a large-scale production rate appears to be taking place in a number of countries.

3.1.1.5. Graphene nanosheet

Graphene sheet is a single layer of graphite structure which can be described as a hexagonal network of carbon atoms bonded to three nearest neighbors. Microscopic roughening through out-of-plane deformations makes graphene sheet effective thickness of about 1 nm. Graphene was shown to possess unique electronic, magnetic, optical and mechanic properties and might find applications in flat flexible electronic devices and coatings.[17] Micromechanical cleavage is presently the main method used to prepare this material.

3.1.2. Oxides

Metal oxide nanostructured materials in the form of agglomerated and aggregated nanoparticles are used mostly as paint and sunscreen additives and often coated to achieve desired properties. Main production methods are spray pyrolysis, laser ablation and solution phase synthesis.

Metal oxide nano-objects can be grown with a variety of simple shapes such as nanorod, nanotubes,[18] nanoflakes, and more complex structures such as nanobrushes, nanosprings, and nanobelts.[19] These nanostructures exhibit unique electronic properties and can find novel applications in optoelectronics, sensors, transducers, and medicines.

Synthetic amorphous silica can be manufactured as a nanostructured material via gas-phase synthesis or wet chemical processes, such as precipitation or sol-gel process. The nanostructured material consists of primary particles within a range of 5-10 nm forming hard aggregates (1-40 µm). Primary particles do not exist as individual units; aggregation and agglomeration are predominant in particle formation and growth. Synthetic amorphous silica is currently used in a wide variety of industrial applications. Most of them are related to the reinforcement of various elastomers, the thickening of various liquid systems, the free-flow of powders or as a constituent of matting, absorbents and heat insulation material.[20,21]

3.1.3. Metals

Gold nanoparticles are one of the most extensively studied. Gold nanoparticles are characterized by a prominent optical resonance in the visible range, which is sensitive to environmental changes, size, and shape of the particles as well as to local optical interactions in resonant systems. This unique property of gold nanoparticles is utilized in a number of applications such as optical markers and as thermal targeted cancer treatment agent in medicine. Silver nanoparticles are produced in largest volumes among metal nanoparticles and used in numerous applications ranging from wound dressings to washing-machine disinfectant for its anti-microbial activity.[22]

Metal nanoparticles with well-defined size and shape can be synthesized using metal reduction from a solution phase.[23]

Metal nanowires such as cobalt, gold and copper-based can be conductive or semiconductive and could be used as interconnectors for the transport of electrons in nanoelectronic devices.[16] Nanowires are typically manufactured by involving a template followed by the deposition of a vapor to fill the template and grow the nanowire.[16] Deposition processes currently include Electrochemical Deposition and Chemical Vapor Deposition. The template might be formed by various processes including etching, or the use of other nanomaterials such as nanotubes.[16]

3.1.4. Quantum dots

Spherical nanocrystals from 1 to 10 nm in diameter composed of semiconductor materials often possess unique optical properties due to quantum effects, hence they are often called quantum dots. The number of atoms in quantum dots makes them neither an extended solid structure nor a molecular entity. The light emitted can be adjusted to the desired wavelength by changing the overall dimension. [24]

Quantum dots are used, among other purposes, as fluorescent probes in diagnostic medical imaging and in therapeutics; they are used for these purposes due to their optical properties and our ability to coat and modify their surfaces with peptides, antibodies, nucleic acids and other biologically important molecules.[25]

Currently, chemistry, physics and material science have provided methods for the production of quantum dots and are allowing tighter control on factors such as particle growth and size, solubility and emission properties. The most common method to produce quantum dots is by wet chemical colloidal processes. [16]

3.1.5. Organic polymeric nanomaterials

3.1.5.1. Dendrimers

Dendrimers are a new class of controlled-structure multi-branched polymers with nanoscale dimensions. They allow precise, atomic-level control of the synthesis of nanostructures according to the desired dimensions, shape and surface chemistry. They can display both hydrophilic and hydrophobic characteristics and can accommodate a wide variety of functional groups for medical applications. They are expected to be used in the medical and biomedical field.[26] Most syntheses of dendrimers involve the repetitious alternation of a growth reaction and an activation reaction such as the more traditional Michael reaction, or the Williamson ether synthesis, and more modern solid-phase synthesis, organo-metallic chemistry, organo-silicon chemistry, and organo-phosphorus chemistry.[26]

3.1.5.2. Fibers

Nanofibers can be made of a wide variety of polymeric materials. The main manufacturing techniques are electrospinning and gas-blowing. These techniques allow for great flexibility in controlling chemical composition and physical parameters such as fiber diameter and length. Nanofiber scaffolds can be used in a number of applications such as sensors and ultrafiltration devices for liquid and gas phase.[27] Biodegradable polymer nanofibers can find numerous applications in medicine as scaffolds for tissue engineering, in controlled drug release, wound dressings, molecular separation, and bone restoration.[28]

3.1.6. Bio-inspired nanomaterials

Bio-inspired nanomaterials are generally materials in which a biological substance is trapped, encapsulated or adsorbed on the surface. They include a wide range of engineered assemblies of biological building blocks such as lipids, peptides and polysaccharides utilized as carriers for drugs, receptors, nucleic acids and imaging agents. Examples are polymeric micelles, protein cage architectures, viral-derived capsid nanoparticles, polyplexes, and liposomes[29] used in transport and optimal targeting of drugs. A number of formulations are under development for drug delivery via gastrointestinal and inhalation routes and skin applications.

Micelles are formed in solution as aggregates in which amphiphilic molecules are arranged in a spheroidal structure with hydrophobic cores shielded from the water by a mantle of hydrophilic groups. These dynamic systems, which are usually below 50 nm in diameter, are used for the systemic delivery of water-insoluble drugs. Drugs or contrast agents might be trapped physically within the hydrophobic cores or can be linked covalently to component molecules of the micelle.[29]

Liposomes are closed lipid bilayer vesicles that form by hydration of dry phospholipids. Drug molecules can be either entrapped in the aqueous space or intercalated into the lipid bilayer of liposomes, depending on the physicochemical characteristics of the drug. The liposome surface is amenable to modification with targeting ligands and polymers.[29]

Polyplexes are assemblies, which form spontaneously between nucleic acids and polycations or cationic liposomes (or polycations conjugated to targeting ligands or hydrophilic polymers), and are used in transfection protocols. The shape, size distribution, and transfection capability of these complexes depends on their composition and charge ratio of nucleic acid to that of cationic lipid/polymer. Examples of polycations that have been used in gene transfer/therapy protocols include poly-L-lysine, linear- and branched-poly(ethylenimine), poly(amidoamine), poly-ß-amino esters, and cationic cyclodextrin.[29]

Protein cage architectures and viral-derived capsid nanoparticles are formed by self-assembly of certain proteins.[29]

Building blocks of bio-inspired nanomaterials can be obtained from natural materials and using synthetic microbiology techniques,[30] while self-assembly often takes place in a liquid phase.

3.2. Production processes

3.2.1. Typical production processes

Methods typically used for the manufacturing of nanomaterials are:

- Aerosol generation such as flame pyrolysis, high temperature evaporation and plasma synthesis;
- Vapor deposition;
- Liquid phase methods: colloidal, self-assembly, sol-gel;
- Electropolymerization and electrodeposition;
- Electro-spinning for polymer nanofiber synthesis;
- Mechanical processes including grinding, milling and alloying.

3.2.2. Aerosol generation methods

The aerosol generation method is used to produce a wide range of nanomaterials. This method is based on homogeneous nucleation of a supersaturated vapor and subsequent particle growth by condensation, coagulation and capture. The formation of vapor typically occurs within an aerosol reactor at elevated temperatures where often a super saturate of a solid is cooled into a background of gas. The methods used to produce nanomaterials are usually categorized by the heating or evaporation process and include:[16]

- Flame pyrolysis
- Furnace/hot wall reactors
- Laser induced pyrolysis

3.2.3. Vapor deposition methods

These methods are traditionally based on already well known and established methods for the manufacture of semiconductors. Here, vapor is formed in a reaction chamber by pyrolysis, reduction, oxidation and nitridation. The first step is the deposition of a few atoms. These first atoms form islands which spread and coalesce into a continuous film. Later, growth continues until thicker film develops.[16]

These methods have been used to produce nanofilms including TiO_2, ZnO and SiC.[16] Vapour deposition processes mediated by a catalyst are used to produce carbon nanotubes commercially.

3.2.4. Colloidal/self-assembly methods

The colloidal methods are also well established conventional wet chemistry precipitation processes in which solutions of different ions at required concentrations are mixed under controlled conditions of temperature and pressure which form insoluble precipitates.[16]

Recently, a rapidly expanding sub-set of colloidal methods called sonochemistry methods, where acoustic cavitation is used to control the process.[31] Here molecular precursors undergo chemical reactions because of the application of ultrasound radiation. It is the creation, growth and rapid collapse of a bubble that is formed in the liquid which is the main event. In this process, high temperatures and high cooling rates accompany the collapse of the bubble and nucleation centers formed whose growth is limited by the rapid collapse.[16]

Chalcogenides, metals and alloys including gold, cobalt and nickel as well as carbon and titania nanotubes have been produced using this method.[16]

3.2.5. Electrodeposition

Polymer nanofiber and metal nanowire films can be fabricated on an substrate through a controlled electropolymerization (polymers) or electrodeposition (metals) process.[32,33]

3.2.6. Electro-spinning

Electro-spinning method is a major method in the manufacture of polymer nanofibers. It utilizes electrical force to produce polymer fibers from polymer solutions or melts.[34]

3.2.7. Attrition methods

In attrition methods, size reduction is accomplished by grinding and milling and production of materials such as clay, coal and metals have been made.[16] Production rates in the order of tons per hour can be obtained using these methods.

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4. Hazard characterization

4.1. Health effects

The potential health risk of a substance is generally associated with the magnitude and duration of the exposure, the persistence of the material in the body, the inherent toxicity of the material, and the susceptibility or health status of the person. Since nanotechnology is an emerging field, there are uncertainties as to whether the unique properties of engineered nanomaterials also pose unique occupational health risks. These uncertainties arise because of gaps in knowledge about the factors that are essential for evaluating health risks (e.g., routes of exposure, translocation of materials once they enter the body, and interaction of the materials with the body's biological systems). An important issue is whether the nanoscale version of a particular material poses risks that are significantly different in type or intensity than the macroscale forms of the same material.

Results of existing studies in cell cultures (in vitro), animals (in vivo) or humans (epidemiological) on exposure and response to nanoscale or other respirable[1-4] particles, as well as available toxicity information about a given material in macroscopic form, provide a basis for preliminary estimates of the possible health effects from exposures to similar engineered materials on a nano-scale. However, it should be recognized that there are significant uncertainties and variables associated with predicting human health effects based on animal studies. Presently, in vitro cell culture methods are used mostly to delineate mechanisms of toxicity. In general, these in vitro data can not be extrapolated to humans without additional information (e.g. in vivo data). Initial experimental studies in animals have shown that the biological response (whether beneficial or detrimental) to certain incidental or engineered nanoparticles can be greater than that of the same mass of larger particles of similar chemical composition.[5-12] In addition to particle number and combined surface area, other particle characteristics might influence the biological response, including solubility, shape, charge and surface chemistry, catalytic properties, adsorbed pollutants (e.g. heavy metals or endotoxins), as well as degree of agglomeration.[13-15]

Often nanoparticle surfaces are intentionally modified with coatings or functionalized in order to prevent agglomeration of particles and to achieve desired properties, e.g. pharmacological activity. Such modifications, as well as the contamination of particle surfaces with impurities can lead to changes in biological responses. More research is underway to study the influence of particle properties on interactions with living organisms and the potential for adverse effects.

4.1.1. Basic principles and uncertainties

The existing literature on particles and fibers provides a scientific basis from which to evaluate the potential hazards of engineered nanoparticles. While the properties of engineered nanoparticles can vary widely, the basic physicochemical and toxicokinetic principles learned from the existing studies are relevant to understanding the potential toxicity of nanoparticles. For example, it is known from studies in humans that a greater proportion of inhaled nanoparticles will deposit in the alveolar region of the respiratory tract (both at rest and with exercise) compared to larger particles.[16,17] However, it has to be realized that nanoparticles might agglomerate and that these agglomerates can deposit in other areas of the respiratory tract or possibly cannot be inhaled at all. Further, animal studies indicate that nanoparticles after initial exposure can be translocated to other organs in the body, although it is not well known how this might be influenced by the chemical and physical properties of the nanoparticles.[18-22] Additional uncertainties are introduced by the difficulties in predicting human health effects based on animal studies. There might also be the potential for greater dermal and gastro-intestinal uptake of nanoparticles when compared to larger particles. Evidence from nanotoxicological studies (in vitro and animal studies) suggests that exposure to some nanoparticles might have the potential to cause cell/ tissue/ systemic toxicity. Due to their small size, nanoparticles have the potential to cross cell membranes and interact with subcellular structures, such as mitochondria and the nucleus (and some nanoparticles have been shown to cause oxidative damage and impair some function of cells in culture).[23,24] Animal studies have indicated that some nanoparticles are more biologically active due to their greater surface area per mass compared with larger-sized particles of the same chemistry when dose response relationships are expressed as mass.[5-12] The greater surface area per mass of nanoparticles compared to larger particles is a fundamental contributor to the greater chemical reactivity and utility of nanoparticles for industrial, commercial, and medical applications, but it also raises concern about the potential for adverse health effects in workers exposed to nanoparticles.

4.1.2. Potential relevance of health effects information about incidental or naturally-occurring nanoparticles and nanofibers

While there is limited information on the health effects of engineered nanoparticles, there is a larger body of research on the health effects of incidental nanoparticles (e.g. diesel exhaust particulate[25,26] and welding fumes[27]). The biological mechanisms of particle-related lung responses (e.g., oxidative stress, inflammation, and production of cytokines, chemokines, and cell growth factors) appear to be a consistent lung response to incidental respirable, including nanoscale, particles[13,28,29] (contaminants such as transition metals[30] might also contribute to the lung response[31]). Although the composition and thus the physicochemical characteristics of incidental and engineered nanoparticles can differ substantially, the toxicological and dosimetric principles derived from studies of incidental nanoparticles might be relevant to assessing the health effects of engineered particles.

There is a very large body of research on the health effects of certain respirable fibers. For example, it is well established that particular forms of asbestos are causative factors in otherwise rare, occupationally-derived, malignant mesotheliomas[32] and other lung disorders (including pulmonary interstitial fibrosis, pleural plaques, calcification and thickening).[33] The harmful effects of fibers are driven by three important factors: length, diameter and persistence.[34-37] It is difficult to draw conclusions regarding the health effects of engineered nanoscale fibers based on asbestos studies, but they suggest that particle properties of size, shape and composition are important factors influencing the toxicity of nanoparticles. There have been shorter-term studies of the effects of single-walled carbon nanotubes[38,39] and multi-walled carbon nanotubes[40] in the lungs of rats and mice (administered by intratracheal instillation or pharyngeal aspiration). These studies have shown unusual inflammatory and fibrogenic reactions in the lungs, including transient inflammation followed by early onset of fibrosis at mass doses lower than those causing fibrosis from quartz or carbon black.[38,39]

4.1.3. Relationship between toxicity and surface area, surface chemistry, and particle number

To the extent that nanoparticles might pose increased hazards, the most significant factors might relate to the greater number or surface area of nanoparticles compared with that for the same mass concentration of larger particles. This hypothesis is based primarily on the pulmonary effects observed in studies of rodents exposed to various types of poorly soluble nanostructured materials in the form of agglomerated and aggregated nanoparticles or larger respirable particles (e.g., titanium dioxide, carbon black, barium sulfate, carbon black, diesel soot, coal fly ash, and toner). These studies found that for a given mass of particles, poorly soluble nanostructured materials in the form of agglomerated and aggregated nanoparticles produced greater observable effect than larger particles of similar chemical composition and surface properties. Dose-response relationships obtained in animal studies for poorly-soluble and low toxicity particles appear consistent across particle sizes when dose is expressed as particle surface area.[5-12,41-45] The mechanisms by which these materials exhibit higher levels of toxicity at smaller particle sizes (on a mass basis) appear to involve pulmonary inflammation, oxidative stress, and tissue injury.[13,28,29] The biological activity of particles is affected by their number and their physical and chemical properties, including size, surface area, solubility, shape, crystal structure, charge, catalytic activity and chemistry.[5-9,13,14,46-49]

Through engineering, the properties of nanomaterials can be modified. For example, recent in vitro studies have shown that the in vitro cytotoxicity of fullerenes (measured as cell death) and carbon nanotubes can be reduced by several orders of magnitude by modifying the surface chemistry of the fullerene molecules and carbon nanotubes (e.g., by hydroxylation).[50,51] Cytotoxicity studies in vitro with quantum dots have shown that the type of surface coating can have a significant effect on cell motility and viability.[52-54]

4.1.4. Inflammatory response to nanoparticles

A variety of nanoparticles ranging from carbon-based combustion products to transition metals, having entered tissues and cells, can elicit generalized inflammatory and acute phase responses which incorporate the release of signaling molecules such as chemokines, cytokines, C-reactive protein and fibrinogen (a coagulant).[55-61] In addition, macrophage and neutrophil activation is also associated with the production of reactive oxygen species. Macrophages are the well-known surveillance cells in the tissues which react with particulate matters, including nanoparticles to produce these biological responses. Exposure to different nanoparticles has been found to modulate, in different ways, the defence/inflammatory capacities of macrophages.[62] In response to cytokines and chemokines, plasma proteins and neutrophils migrate from the blood to start inflammation. One of the roles of neutrophils in the inflammation is to destroy foreign bodies by proteolysis as well as reactive oxygen species. However, the excess or prolonged defence reactions against foreign bodies by these cells damage the tissues, too. When the process of macrophage ingestion and (attempted) proteolytic breakdown go awry or when nanoscale particles become internalised in non-immune-related cell types (e.g. parenchymal cells), intracellular molecular defenses are initiated which result in the new expression of protective genes. When these protective mechanisms (e.g., antioxidants) are depleted, tissue injury and disease might occur.[29,63] Several broad intracellular protective responses are known, from cell culture and animal studies, to be induced by the exposure to particulate/fibrous materials (carbon black, carbon nanotubes, ambient air particles, and nanostructured titania): the pro-inflammatory cytokines and relevant genes; the antioxidant-response element-inducible genes and proteins; and the stress (or “heat shock”) response proteins.[55-61] Consequently, effects such as persistent inflammatory responses and gene inductions are likely to represent precursors of downstream pathological conditions. It is important to note that contaminants, such as metal catalysts or bacterial endotoxins (lipopolysaccharides), contributed to the

induction of inflammatory responses observed in experimental toxicological studies of nanoparticles. Specifically, the unpurified single-walled carbon nanotubes which contained more than 20 % by weight of iron induced stronger pulmonary inflammation than purified counterparts;[30] and the conventional formulations of gold nanoparticles which contained significant amounts of endotoxins stimulated immune cells *in vitro,* and the improvement of formulation process, which diminished the endotoxin contamination, also effectively reduced the bilogical responses.[64]

4.1.5. Animal and cell-culture studies

4.1.5.1. Carbon containing nanomaterials

Major manufactured nanoscale carbon containing materials are carbon nanotubes (CNTs), carbon nanofibers, fullerenes and carbon black. Single-walled CNT can be described as a single sheet of graphite rolled to form a seamless cylinder (see also Chapter 3.1.1). This new class of material offers excellent electrical, mechanical and thermal properties. Due to such unique advantageous material properties an increased production and use of CNTs makes it likely that human exposure will occur.

A number of toxicological studies of CNTs have been performed in recent years (see references cited in [15], [65], [66]). These studies have suggested that the biological response to CNTs in cell-culture and animal studies can vary widely depending on the test material and the test method applied. The nature of the test material depends on the method of production and post-production treatment resulting in different levels of impurities (metals, organic molecules, other forms of carbon, support material etc.) and different structures (atomic structure, number of walls, agglomeration state, etc.) and geometries (diameter, length, deformations) of carbon nanotubes. Therefore it is essential that certain physical characteristics of a test material are determined and reported in conjunction with any investigation of their hazards.[67]

Biomarkers of oxidative stress were elevated in an *in vitro* assay after incubation with single-walled carbon nanotubes.[30] Single-walled CNTs purified by acid treatment have been shown to produce adverse effects, including acute inflammation with early onset, yet progressive, fibrosis and granulomas in the lungs of mice after a single pharyngeal aspiration. Application of carbon black at identical mass doses did not induce granulomas or alveolar wall thickening and pulmonary inflammation, and damage was less pronounced.[38] Although these results, obtained by pharyngeal aspiration, suggest some hazardous potential of single-walled CNTs by inhalation, the actual human inhalation toxicity of single-walled CNTs has not been determined yet.

Purified[ii] ground and intact multi-walled carbon nanotubes administered intratracheally to rats were found to be biopersistent (still present in the lung after 60 days) and induced inflammatory and fibrotic reactions.[40] Pulmonary lesions induced by CNTs characterized by the formation of collagen-rich granulomas were caused by the accumulation of large CNT agglomerates in the airways. Ground CNTs were better dispersed in the lung parenchyma and also induced inflammatory and fibrotic responses. Chrysotile asbestos and carbon black were included as reference materials. As expected, asbestos induced inflammatory and fibrotic reactions while carbon black only showed inflammatory reaction. [40]

There have also been studies on the effects of exposure to carbon nanotubes on the skin and eyes. An *in vitro* study reported that unpurified single-walled carbon nanotubes caused a significant decrease in cellular viability and biomarkers of oxidative stress with a dose-response relationship, as well as a significant increase in lipid peroxides on human epidermal keratinocytes.[68] This study concluded that dermal exposure to unrefined single-walled carbon nanotubes might lead to dermal toxicity in exposed workers. Another *in vitro* study using human fibroblasts and keratinocytes indicates that single-walled CNTs, functionalized with peptides, are capable of penetrating the cell membrane.[69] However, the application of a filter saturated with a solution containing fullerene soot with a high content of single-walled CNTs during a patch test did not cause irritation or allergies in volunteers.[70] Ocular instillation of an aqueous suspension of nanotubes in a modified Draize test with rabbits did not cause irritation.[70]

There have been a few toxicity studies of functionalized carbon nanotubes. Numerous effects have been reported and the toxicity seems to vary greatly with the nature of the functional groups. An *in vitro* study with

[ii] "Purified" in this context means treated with acid to remove metal contaminants.

lung tumor cells showed that the toxicity of unpurified multi-walled carbon nanotubes and nanostructured carbon black obtained by grinding of graphite increases after their surfaces are chemically functionalized with carbonyl, carboxyl and hydroxyl groups.[71] On the other hand, another *in vitro* study using cultured human dermal fibroblasts showed that cytotoxicity of purified single-walled carbon nanotubes functionalized with phenyl-SO_3H and phenyl-$(COOH)_2$, decreases as the degree of functionalization increases.[51] In vivo mice studies showed that water-soluble, single-walled CNTs functionalized with diethylenetriaminepentaacetate and labeled with indium (^{111}In) for imaging purposes, were not retained in either liver or spleen and were rapidly cleared from systemic blood circulation through the renal excretion route after intravenous administration.[72]

4.1.5.2. Oxides

Experimental studies in animals have shown that at equivalent mass doses, poorly soluble nanostructured metal oxides in the form of agglomerated or aggregated nanoparticles (e.g., titanium dioxide, aluminum oxide, and manganese dioxide) are more potent than larger particles of similar composition, in causing pulmonary inflammation, tissue damage, and lung tumors in animals.[5-9,41,43,44] For these and other poorly soluble particles, a consistent dose-response relationship is observed when dose is expressed as particle surface area.[6,7,13,42,45] These animal studies suggest that for nanostructured materials and larger particles with similar chemical properties, the toxicity of a given mass dose will increase with decreasing particle size due to the increasing surface area. In addition to particle size and surface area, other physical and chemical properties of particles are known to influence toxicity, including solubility, shape, surface reactive sites, charge, and crystal structure.[13,14,47,48,73] For poorly soluble particles of relatively low toxicity, some animal studies have identified doses that were not associated with observed adverse responses. For example, a recent animal study reported mass doses of either fine or nanostructured TiO_2 in rats at which the lung responses did not significantly differ from controls, while crystalline silica caused more severe lung responses at the same mass dose.[74,75]

4.1.5.3. Metals

In vitro studies indicate that some metal nanoparticles can exhibit acute inflammatory effects in animals related to the ability of metal ions to generate reactive oxygen species. The dose-response relationships differ for different metals, which might relate to the physico-chemical properties and mechanisms of toxicity. For example, recent studies using rat liver derived cell lines *in vitro* indicate that silver nanoparticles (15 and 100 nm) at 5 - 50 µg/ml showed a significant cytotoxicity to the cells, whereas other particles such as aluminum nanoparticles (30 and 103 nm) and micrometer scale tungsten particles (27 µm), had no measurable effects at the same mass doses.[76] *In vitro* studies of mouse spermatogonia cell lines reported cytotoxic effects of silver nanoparticles (15 nm).[77] Peters *et al.* studying the behaviour and viability of human endothelial cells *in vitro*, observed that cobalt and nickel nanoparticles were incorporated into the vacuoles of the cells.[78] Cobalt nanoparticles were found to cause inflammation and to be cytotoxic, while nickel nanoparticles did not produce these effects. In contrast, an *in vivo* study found nickel nanoparticles was more toxic than cobalt nanoparticles, and that the toxicity correlated with the free radical activity.[79] In other *in vivo* studies, nickel nanoparticles was found to be more toxic to the lungs than the same mass dose of micrometer scale nickel particles,[80] and cobalt nanoparticles were more toxic than micrometer scale cobalt particles.[81] In an oral gavage study, copper nanoparticles caused severe toxicity and injury to the kidney, liver, and spleen, while microscale copper particles did not.[82] Colloidal gold nanoparticles, which have been developed for therapeutic and diagnostic uses, did not generate any toxicity in mice by an intravenous injection at a therapeutic dose level.[83]

4.1.5.4. Semiconductors

The main application of semiconductor nanoparticles is as quantum dots. Health hazard properties of quantum dots depend on a host of factors arising from their chemical structure and environmental conditions. Size, charge, concentration, bioactivity of the surface coating, and oxidative, photolytic, and mechanical stability contribute to their toxicity.[84] The long-term stability of the complexes and their complete degradation before elimination needs to be further evaluated given that some of their constituents, such as Pb, As, Cd, and Tl, are potentially highly toxic.[85] Coatings can inhibit quantum dot degradation which might result in the release of toxic constituents, as well as loss of quantum dot fluorescence in vivo.[86]
In vitro studies suggest that some quantum dots can be cytotoxic, with dose-response relationship. For example, CdTe quantum dots caused rat pheochromocytoma cell death *in vitro* indicated by chromatin

condensation and membrane blebbing.[87] Smaller positively charged quantum dots were more toxic than larger, equally charged, quantum dots with the former localized in the nuclear compartment and the latter in the cytosol. Authors explained this by the presence of Cd^{2+} ions, free radical formation, or interaction with intracellular components leading to loss of function. Other, *in vitro* studies, reported that CdSe quantum dots were cytotoxic to liver cells and that surface oxidation of the quantum dots produced Cd^{2+} ions, recognized as carcinogenic.[52,88] Encapsulation of the quantum dots with ZnS tended to reduce this effect and it declined to almost zero with encapsulation by bovine serum albumin. The *in vitro* cytotoxicities of realgar (As_2S_2, a semiconducting material which is also used in some traditional medical formulations) with small sizes (100 - 150 nm) to human umbilical vein endothelial cells were stronger than those of larger particles (200 - 500 nm).[89] The surface area-dependent cytotoxicity of realgar particles can be explained by the amount of released active ingredients in the incubation medium from the particles, which might be highly dependent on the amount of surface area.

Some in vivo studies showed no observed ill effects: mice injected with amphiphilic polyacrylic acid polymer-coated quantum dots and with polyethyleneglycol amine conjugated quantum dots;[90] mice injected with CdSe/ZnS quantum dots.[91]

4.1.5.5. Organic polymeric nanomaterials

Certain incidental organic nanoparticles have been shown to pose acute toxic hazard upon human inhalation exposure. Among nanoscale particles, freshly-generated polytetrafluoroethylene (PTFE) fume (generated at temperatures of more than 425 ^{o}C) is known to be highly toxic to the lungs. Freshly-generated PTFE fume (15 nm) caused hemorrhagic pulmonary edema and death in rats exposed to less than 60 $\mu g/m^3$.[46] In contrast, aged PTFE fume was much less toxic and did not result in mortality, which was attributed to changes in surface chemistry as well as increase in particle size from accumulation (>100 nm).[13,92] While PTFE fume differs from engineered nanoparticles, these studies illustrate properties of incidental nanoparticles that have been associated with an acute toxic hazard.

Toxicity of nanoscale dendrimers is related to the nature of monomers and dendrimer synthesis.[93] Specifically, *in vitro* and *in vivo* animal studies showed that nanoscale dendrimers with positively charged surface groups similar to other biological macromolecules can destabilize cell membranes and cause cell lysis.[94] Thus, biological response to nanoscale dendrimers can be tailored through functionalization of the surface dendrimer sites. Nature of the dendrimer core also is also thought to affect its biological activity. For example, it has been suggested that dendrimers with aromatic interior can cause hemolysis through hydrophobic membrane contact.[95] Higher generation dendrimers (larger in size) have been found to be more cytotoxic.[96]

4.1.5.6. Bio-inspired nanomaterials

Engineered bio-inspired nanomaterials can potentially produce the full range of health responses observed with naturally occurring nanomaterials, from the benign and beneficial (such as insulin and growth hormone) to adverse and even lethal (such as protein biotoxins “designed” by nature to be toxic).

It was shown that delivery of biologically active bio-inspired nanoparticles into the blood circulation through oral administration can be facilitated by bile acids and proteinase inhibitors.[97] Recently, transdermal delivery of intact, biologically active protein medications, such as insulin, has been shown to be possible in the presence of phage peptide chaperones.[98] It appears that the mechanism of penetration is not specific to insulin and involves interactions between the phage peptide and the skin, facilitating a transfollicular route of insulin transport through the skin. These drug applications could potentially result in accidental exposures of workers during drug production and administration in health care settings.

4.1.6. Observations from epidemiological studies involving fine and nanoscale particles

Initial epidemiological studies in workers exposed to aerosols, including incidental fine and nanoscale particles, have reported lung function decrements, adverse respiratory symptoms, chronic obstructive pulmonary disease, and fibrosis.[2-4,27,99,100] In addition, some studies have found elevated lung cancer among workers exposed to certain incidental nanoscale particles, e.g., diesel exhaust particulate[25,26] and welding fumes.[27] Human case studies have reported pulmonary edema in workers exposed to PTFE fume and an accidental death in a worker when an equipment malfunction caused overheating of the PTFE resin and release of the PTFE pyrolysis products in the workplace.[101,102] The implications of these studies for engineered nanoparticles, which might have different particle properties, are uncertain.

Epidemiological studies in the general population have shown associations between particulate air pollution and increased morbidity and mortality from respiratory and cardiovascular diseases.[103-106] Some epidemiological studies have shown adverse health effects associated with exposure to the incidental nanoscale particulate fraction of air pollution,[107-111] although uncertainty exists about the role of incidental nanoscale particles relative to the other air pollutants in causing the observed adverse health effects. The associations in these studies have been based on measurements of the particle number or mass concentrations of particles within certain size fractions (e.g., PM2.5). In an experimental study of healthy and asthmatic subjects inhaling nanoscale carbon particles, changes were observed in the expression of adhesion molecules by blood leukocytes, which might relate to possible cardiovascular effects of incidental nanoscale particle exposure.[112] Controlled clinical studies in the laboratory have shown deposition of incidental nanoscale dusts throughout the pulmonary tree, accompanied by cardiovascular problems.[13,113-115]

Human studies of nanoparticles are primarily based on people exposed to fumes (e.g., welding), diesel exhaust or particulate ambient air pollution. Epidemiological studies aimed specifically at engineered nanoscale particles have not yet been performed, with the exception of TiO_2[12] and carbon black.[2-4] Therefore, the extrapolation of the findings associated with air pollution and particulates generally (which might include incidental nanoscale particles) to engineered nanoparticles is uncertain. However, the potential risks from exposure to nanomaterials, including occupational exposure, should be considered.

4.2. Physical hazards

4.2.1. Fire (exothermic events)

Although insufficient information exists to predict the potential fire and explosion risk associated with nanoscale powders, nanoscale combustible material might present a higher risk than coarser material of similar quantity due to exothermic events arising from catalytic reactions or due to a lowering of minimum ignition temperatures.[116] Decreasing the particle size of combustible materials can reduce minimum ignition energy and increase combustion rate, leading to the possibility of relatively inert materials becoming combustible. Dispersions of combustible nanomaterials in air might present a greater safety risk than dispersions of micro- and macro-materials with similar compositions. Dust explosiveness, minimum ignition energy and ignition temperature are typical means of characterizing safety relevant aspects of dusts.

Nanoparticles and nanostructured porous materials have been used for many years as effective catalysts for increasing the rate of reactions or decreasing the necessary temperature for reactions to occur in liquids and gases. Depending on their composition and structure, some nanomaterials might initiate catalytic reactions and increase their fire and explosion potential that would not otherwise be anticipated from their chemical composition alone.[117]

Additionally, some nanomaterials are designed to generate heat through the progression of reactions at the nanoscale. Such materials might present a fire hazard that is unique to engineered nanomaterials. The greater activity of nanoscale materials forms a basis for research into nanoenergetics. For instance, nanoscale Al/MoO_3 thermites ignite more than 300 times faster than corresponding micrometer-scale material.[118]

4.2.2. Safety considerations in manufacturing nanomaterials

The manufacture of nanomaterials, as with any other novel materials, can be either on a small pilot scale, including research and development activities, or full scale. Presently, nanomaterial manufacturing can include several high-energy processes, such as flame pyrolysis, laser induced pyrolysis, laser vaporization, thermal plasma, microwave plasma, sputtering, and laser ablation, which present specific safety issues. Typical safety hazards in these processes include handling of high pressure cylinders, low pressure apparatus, inert and toxic gases, high temperature objects, operation of high electrical currents, electro-magnetic radiation emitting devices, and high intensity light sources (including ultra-violet, infra-red, and visible light) and lasers. Working under such hazardous conditions requires implementing appropriate work practices or following respective laboratory safety guidelines.

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5. Exposure assessment to nanomaterials

5.1. Introduction

This section concerns the assessment of the exposure of workers as a result of the manufacture, handling and use of nanomaterials. The scientific framework for exposure assessment is discussed with a consideration of the routes of exposure and the most appropriate measurement metric to be used. This is followed by a summary of the instrumentation currently available and a discussion of possible sampling strategies.

5.2. Scientific framework for assessing exposure to nanomaterials

5.2.1. Routes of exposure

There are three main routes by which workers can be exposed to nanomaterials: a) inhalation, b) ingestion and c) skin contact:[1]

Inhalation. As with most particles in the workplace, inhalation is considered to be the primary route by which nanomaterials in the form of free, unbound, airborne particles will enter the bodies of workers. Once inhaled, nanomaterials will deposit in the respiratory tract regions, depending upon their particle size. Specifically, nanoparticles will deposit in all regions of the respiratory tract. Figure 1 shows the fractional deposition of inhaled nanoparticles in the nasopharyngeal, tracheobronchial and alveolar regions of the human respiratory tract for nasal breathing, using the predictive mathematical model of the ICRP.[2] According to the ICRP model, 80 % of the 1 nm particles are deposited in the nasopharyngeal region, with 20 % in the tracheobronchial region and less than 1 % in the alveolar region. For 20 nm particles, however, 50 % deposit in the alveolar region and 25 % in the nasopharyngeal and tracheobronchial regions.

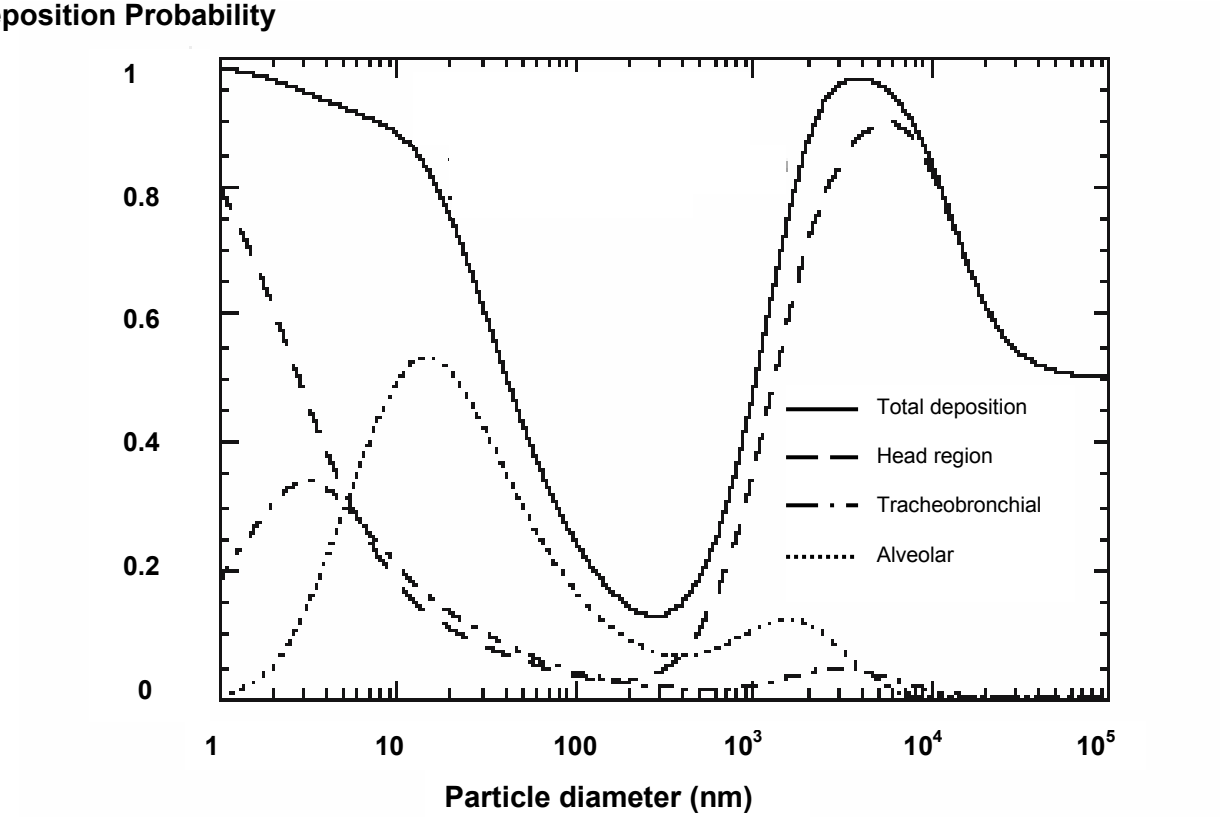

Figure 1 — Predicted total and regional deposition of particles in the human respiratory tract related to particle size using ICRP 66 model.[2] Deposition Fraction includes the probability of particles being inhaled (inhalability). The subject is considered to be a nose breather, performing standard work.

Nanoparticles have been reported to translocate to different organs in the body after penetrating the cell epithelium and entering the blood or lymph systems (see Chapter 4.1.1).

Ingestion. In the workplace, nanomaterials in particulate form could be ingested by swallowing the mucous that traps and clears particles deposited in the airways; by ingestion of contaminated food or water; or by oral contact with contaminated surfaces or hand. Only a few studies have been carried out to investigate the uptake and deposition of nanoparticles to the GI tract.[1]

Skin contact. In the workplace, skin might be exposed to nanomaterials during their manufacture or use or by contact with contaminated surfaces. It is still under discussion if and to what extent nanoparticles in general are able to penetrate the intact skin and cause adverse effects. Most of the reported work has been carried out with individual materials, such as TiO_2 and ZnO, on intact skin. The effect of flexing the skin has yet to be fully explored as has penetration through damaged skin.[3,4] The role of solvents in skin uptake of nanoparticles in the occupational setting is also yet to be fully explored.

Exposure through parenteral route can occur in the workplace primarily due to accidents.

5.2.2. Metric for assessing exposure to airborne nanomaterials

The current method of assessing worker exposure to airborne particles in workplaces involves the measurement of the mass concentration of health-related fractions of particles in the worker's breathing zone[5] and their chemical composition. The health-related aerosol fractions relate to the probability of penetration of airborne particles to the various anatomical regions of the respiratory system and provide a specification for the performance of sampling instruments (see Figure 2). The inhalable convention is the mass fraction of total airborne particles that enters the nose or mouth during breathing, The thoracic convention is the mass fraction of inhaled particles that penetrate the respiratory tract beyond the larynx, with 50 % penetration at an

aerodynamic equivalent diameter (Da) of 11.64 µm (equivalent to 10 µm when expressed as a fraction of total aerosol) and the respirable convention is the fraction of inhaled particles that penetrate to the alveolar region of the lung, with 50 % penetration at Da 4.25 µm (equivalent to 4 µm when expressed as a fraction of total aerosol).

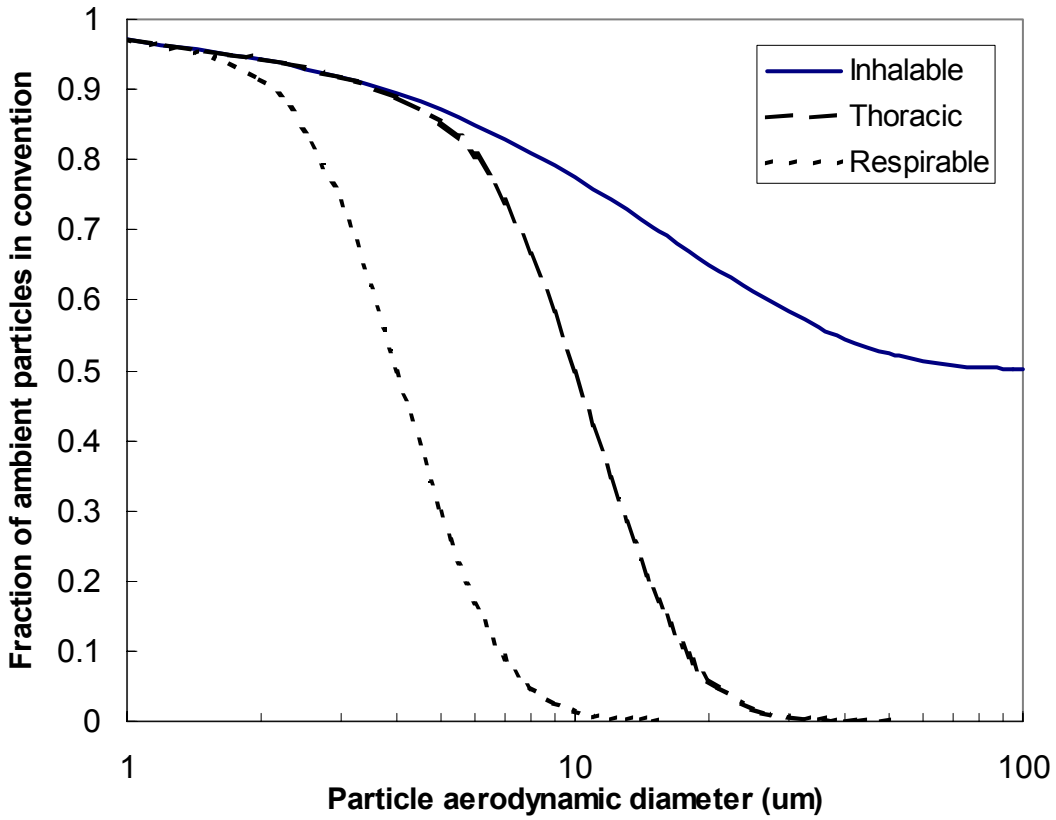

Figure 2 — Health-related sampling conventions for workplace aerosols from ISO 7708.[5]

The main exceptions to this methodology are particle-number-based metrics of exposure used a) for fibers such as asbestos for which airborne particles (defined as of length > 5 µm, width < 3 µm and length: width aspect ratio ≥ 3:1[iii]) are collected on a membrane filter sampler and are counted using optical or electron microscopy,[7] and b) for microorganisms, for which the standard method is to collect them on a growth medium and to count the number of colony-forming units.[8,9]

However, recent toxicological evidence indicates that the potential health effects associated with inhaling nanoaerosols (defined as airborne nanoparticles and particles of nanostructured materials) might not be closely associated with particle mass. A number of studies have indicated that the toxicity of insoluble materials increases with decreasing particle size, on a mass for mass basis.[1,10,11] The mechanisms by which these materials exhibit higher levels of toxicity at smaller particle sizes have yet to be explained, although there are many hypotheses. A number of studies indicate that biological response depends on the surface-area of particles deposited in the lungs.[1,12,13] It has also been suggested that due to their small diameter, nanoparticles are capable of penetrating epithelial cells, entering the bloodstream from the lungs,[14] and even entering the brain via the olfactory nerves.[15] As particles in the nanometer size range have a high percentage of surface-atoms, and are known to show unique physico-chemical properties, it would be expected that nanoparticles would demonstrate biological behavior closely associated with particle diameter, surface-area and surface activity.

[iii] Please note that the definition and sampling methodology of asbestos fibers can vary for different jurisdictions. This definition of fiber is based on WHO definition[6]

It is apparent from the above discussion that measuring exposures to nanoaerosols in terms of mass concentration alone is not sufficient to assess potential health risk. In addition, there is strong evidence to suggest that occupational nanoaerosols should be monitored with respect to surface-area. However, in this context, aerosol surface-area is not well defined and it is dependent on the measurement method used. Geometric surface-area refers to the physical surface of an object, and is dependent on the length-scale used in the measurement. Measurement length-scale determines the upper size of features that are not detected by the measurement method. For example, methods utilizing molecular surface-adsorption have a length-scale that approximates to the diameter of the adsorbed molecules.[16] Similarly, biologically relevant surface-area will most likely be determined by the smallest biological molecule that interacts with particles within the body.

While a strong case might be made for using aerosol surface-area as an exposure metric, it is also necessary to consider characterizing exposures against aerosol mass and number concentration until further information is available. In the case of a nanomaterial with consistent composition, size and shape, one can measure the specific surface area and correlate it to mass concentration. However, the correlation coefficient will not be transferable to other nanomaterials with different distributions in composition, size and shape. For each of these exposure metrics, but particularly in the case of mass concentration, particle size selective inlets will need to be employed to ensure only particles within the relevant size range are sampled.[17]

The actual cut size that particle selection should be made for assessing potential human health impact is still open to debate and depends upon particle behavior and subsequent biological interactions. The currently proposed cut size for nanoparticles is 100 nm, although this is not derived from particle behavior in the respiratory tract following deposition and it excludes larger particles of nanomaterials. However, at this scale it is thought that the properties of materials can be different from those at a larger scale. For instance, it could be possible to develop a health-related description of a nanoparticle based on the deposition probability in the lungs (see the curves in Figure 1). Particle deposition efficiency in the respiratory tract reaches a minimum at about 200-300 nm in diameter, and increases for particles of lesser diameter. In addition, as particles become smaller, surface curvature, the arrangement (and percentage) of atoms on the particle surface and size-dependent quantum effects play an increasingly significant role in determining physico-chemical behavior.

It is currently unclear whether the biological impact of discrete nanoparticles depositing within the respiratory system, is distinct from or similar to the impact of large agglomerates or aggregates of nanoparticles containing the same mass of material. Several factors can affect biological response. First, the location of deposition depends on aerodynamic particle size which will change with degree of agglomeration/aggregation. Next, if agglomerates or aggregates of nanoparticles either de-agglomerate or disaggregate completely following deposition, it is conceivable that the resulting biological impact will be similar to an equivalent exposure of discrete nanoparticles. In addition, if biological response is associated with the surface-area of the deposited aerosol, then for a given volume of material, the response to deposited agglomerates/aggregates with an open fractal-like structure will conceivably be similar to that from an equivalent dose of discrete particles. However if the nanostuctured particles do not de-agglomerate then it is likely that they will not translocate to other organs in the body as readily as the discrete nanoparticles and so the biological impacts will be different. So, knowledge of the ease with which the specific particles will de-agglomerate will be required before deciding at which particle size to exclude unwanted particles (bulk particles which are not nanostructured materials) and might vary with the particle properties.

5.3. Review of methods for characterizing exposure to nanoparticles

5.3.1. General

The principal purpose for most particle sampling is for the protection of workers, some of the aspects of which include:

1) assessment of personal exposure for compliance with regulations,
2) assessment of personal exposure for linking with potential adverse health effects in epidemiological studies,
3) identification of major emission sources for establishing targeted control plan
4) assessment of efficiency of control systems deployed

Each of these tasks requires specific and often different types of instrumentation. For example, for personal exposure measurements the best solution is to use small, battery-powered samplers, mounted on the worker's body, that move with him/her during the working shift. While for source identification, portable

monitors can be used, generally giving continuous measurements of concentration that can be correlated with details of the location, ventilation and the specific work processes being undertaken. In order to assess the efficiency of control measures in the workplace, many different types of instruments can be used, including static, mains-driven instruments, depending upon the information required.

However, for assessing exposure to engineered nanoparticles a major confounding factor in most workplaces is that of incidental nanoscale particles derived from ambient aerosols that penetrate workplaces to differing degrees,[18,19] and incidental nanoparticles generated within the workplace itself.[20] These confounding particles can both directly impact measurements of particle count, but also rapidly coalesce with nanoparticles, including the nanoparticles of interest, requiring careful design of experiments. Possible methods of discriminating between exposure to engineered nanoparticles and to ambient incidental nanoscale particles will be discussed later. While discrimination will facilitate analysis of exposures, effective control of both engineered and incidental nanoparticles is essential for effective occupational health and safety management.

Ideally, according to [21], the equipment for taking the occupational hygiene measurements should be:

- portable;
- capable of measuring multiple nanoparticle characteristics (particle count, mass, surface area, charge, size distribution, differentiate engineered from background particles, temporal variation etc.);
- capable of obtaining breathing zone samples;
- capable of being used in industrial settings;
- battery-powered;
- real-time;
- relatively inexpensive.

At this time there is not a single instrument that meets all of these criteria.

A summary of currently available instrumentation is provided in Table 1, which is an updated version of that found in the ISO/TR 27628:2007 on Ultrafine, nanoparticle and nano-structured aerosols – Exposure characterization and assessment.[22] Some of the following sections contain information taken from ISO/TR 27628:2007, which will be updated periodically and might contain more up to date information than this Technical Report.

Table 1 — Instruments and techniques for monitoring nanoaerosol exposure.

Metric	Devices	Remarks
Mass directly	Size selective static sampler	The only devices offering a cut point around 100 nm are cascade impactors (Berner-type low pressure impactors, or Microorifice impactors). Allows gravimetric and chemical analysis of samples on stages below 100 nm
	TEOM®	Sensitive real-time monitors such as the Tapered Element Oscillating Microbalance (TEOM) might be useable to measure nanoaerosol mass concentration on-line, with a suitable size selective inlet.
Mass by calculation	ELPI™	Real-time size-selective (aerodynamic diameter) detection of active surface-area concentration giving aerosol size distribution. Mass concentration of aerosols can be calculated, only if particle charge and density are assumed or known. Size-selected samples might be further analyzed off-line (as above).
	DMAS	Real-time size-selective (mobility diameter) detection of number concentration, giving aerosol size distribution. Mass concentration of aerosols can be calculated, only if particle shape and density are known or assumed.
Number directly	CPC	CPCs provide real-time number concentration measurements between their particle diameter detection limits. Without a nanoparticle pre-separator, they are not specific to the nanometre size range. P-Trak has diffusion screen to limit top size to 1 µm.
	DMAS	Real-time size-selective (mobility diameter) detection of number concentration, giving number-based size distribution.
	Electron Microscopy	Off-line analysis of electron microscope samples can provide information on size-specific aerosol number concentration.

Number by calculation	ELPI™	Real-time size-selective (aerodynamic diameter) detection of active surface-area concentration, giving aerosol size distribution. Data might be interpreted in terms of number concentration. Size-selected samples might be further analyzed off-line.
Surface-area directly	Diffusion Charger	Real-time measurement of aerosol active surface area. Active surface area does not scale directly with geometric surface area for particles larger than 100 nm. Note that not all commercially available diffusion chargers have a response that scales with particle active surface area for particles smaller than 100 nm. Diffusion chargers are only specific to nanoparticles if used with an appropriate inlet pre-separator.
	ELPI™	Real-time size-selective (aerodynamic diameter) detection of active surface-area concentration. Active surface area does not scale directly with geometric surface area for particles larger than 100 nm.
	Electron Microscopy	Off-line analysis of electron microscope samples can provide information on particle surface area with respect to size. TEM analysis provides direct information on the projected area of collected particles, which might be related to geometric area for some particle shapes.
Surface area by calculation	DMAS	Real-time size-selective (mobility diameter) detection of number concentration. Data might be interpreted in terms of aerosol surface area under certain circumstances. For instance, the mobility diameter of open agglomerates has been shown to correlate well with projected surface area.[22]
	DMAS and ELPI™ used in parallel	Differences in measured aerodynamic and mobility can be used to infer particle fractal dimension, which can be further used to estimate surface area.

5.3.2. Mass concentration

Mass concentration can be determined by a number of direct reading instruments utilizing collection of particles on filters (aerosol samplers, cascade impactors and oscillating microbalance) and resonator crystals (piezobalance). It is also possible to derive estimates of mass by calculation using a tandem of instruments such as Electrical Low Pressure Impactor and Differential Mobility Analyzing System (see Section 5.3.5).

5.3.2.1. Filter sampling

There are no commercially available workplace aerosol samplers with a 100 nm size selection cut point, although it should be possible to design and test a suitable device. There is very little data on expected mass concentrations of nanoparticles in workplaces but it is expected that high flow rates of about 10 l min^{-1} will be required to collect sufficient mass of nanoparticles in an 8 hour shift to be above the limit of quantification for weighing. At these high flow rates it can be expected in principle to operate existing devices such as impactors and cyclones to provide a cut point at 100 nm.
Analytical techniques other than gravimetric could be also used to characterize mass concentration of nanoparticles. Examples, are NIOSH 7300 method for metals utilizing inductively-coupled argon plasma combined with atomic emission spectroscopy analysis and NIOSH 7500 method for silica utilizing X-ray diffraction analysis.

5.3.2.2. Cascade impactors

An alternative approach that has been used in both workplace[23,24] and environmental[25] studies is to use a low-pressure cascade impactor (e.g. Berner-type) or micro-orifice cascade impactors. Both of these devices use inertial impaction to separate particles into discrete fractions according to their aerodynamic diameters and have two or three stages in the nanoparticle size range. In both devices, the masses of nanoparticles can be assessed by weighing the collection substrates before and after sampling, plotting the full size distribution and making a cut at 100 nm or whatever particle size is considered to be relevant for particles of nanostructured materials. These will be described in 5.3.5.2.

5.3.2.3. Oscillating and piezoelectric microbalances

An alternative is to use the Tapered Element Oscillating Microbalance (TEOM).[26]. The TEOM principle (developed initially for measuring the mass of particles in space) involves the use of a small filter which is located on the tip of a tapered glass tube which forms part of an oscillation microbalance. The oscillation frequency of the microbalance changes with the mass of particles collected on the filter. The devices are widely used to continuously monitor ambient levels of PM_{10} and $PM_{2.5}$ aerosols in national air quality networks and have proved to give reliable information on particle levels for compliance with national air quality directives. Consequently, with a mass detection limit of 0.01 µg, they were considered to possibly have adequate measurement precision (± 5 µg m^{-3} for 10 minute averaging times and ± 1.5 µg m^{-3} for 1 hour averaging times) for the measurement of nanoparticles in workplaces. In using this instrument careful consideration needs to be given to select a pre-separator for the TEOM to match the size of nanoparticles being studied and to change the collection filter to one that has high efficiency for nanoparticles.[27] Personal versions of the TEOM instrument have been developed, for example for sampling respirable dust in coal mines.
Operation of piezoelectric microbalance (or piezobalance) is based on changes in the resonance frequency of piezoelectric crystal as a function of its mass. By monitoring resonance frequency against a second crystal, mass deposited on the crystal can be continuously measured thus providing information about mass concentration of particles.[28,29] Airborne particles can be deposited on the crystal surface by either electrostatic precipitation or by impaction.[30] Collection efficiencies of either of these mechanisms are a function of particle size and particle properties and should be determined to achieve quantitative measurements. Quartz crystals have sensitivities of several hundred hertz per microgram which translates into the ability to measure the aerosol mass concentration of 100 µg/m3 to within a few percent under one minute.[30]

5.3.3. Number concentration

5.3.3.1. Condensation particle counters

The most widely used instrument for determining the number concentration of nanoparticles is the Condensation Particle Counter (CPC). This device exploits vapor condensation on nanometer size (and larger) particles in order to grow the particles to a size range that can be detected optically.

The convective cooling laminar flow CPC is the most widely used and is also commercially available from a number of manufacturers in models with different lower particle size cut-offs. Particle laden air is drawn into the instrument at constant air flow, which is saturated using warm vapor (typically butanol, isopropanol or water). The saturated flow is then taken to a cool condenser tube in which the vapor is depleted onto the tube surface. However, as the flow cools, there will be regions in the flow where the vapor becomes supersaturated and condenses onto particles, which grow to large droplets. The detection limit at small particle diameters depends on vapor properties, operating temperatures (which determine the super-saturation), flows and geometries of the instrument. Devices using butanol are available with detection limits down to 3 nm, while isopropanol has successfully been used in portable instruments with a lower detection limit of 10 nm, and water is used in a commercially available instrument with a similar lower detection limit.

5.3.3.2. Electrometers

A second instrument type that is sensitive to nanoparticles is an electrometer. This instrument detects the charge carried by aerosol particles and therefore its use depends on knowing the charge on individual particles in an aerosol flow. Known charge distributions are possible to obtain using chargers or neutralizers with known characteristics. However, as charging efficiency is strongly a function of particle size, accurate information of the concentration of nanoparticles is difficult to obtain using an electrometer alone. An electrometer in series with a mobility analyzer enables the determination of the size distribution of nanoparticles. In practice, the electrometer is often used to calibrate other instruments, especially CPCs due to good detection efficiency at nanoscale size range.

5.3.4. Surface area concentration

Measurements of particle surface area have been possible for some time using the BET method.[31] However, it requires the collection of relatively large amounts of particles (up to 50 mg have to be collected for BET analysis),[32] and measurements are influenced by particle porosity (which might or might not be important) and collection/support substrate – particularly where the quantity of material analyzed is small.

The diffusion charger measures the Fuchs or active surface area of the aerosols from the attachment rate of positive unipolar ions to particles, from which the aerosol active surface-area can be inferred.[33] However, particle losses affect measurements and, therefore, the instruments show a size dependency, which has to be determined experimentally and compared with the needed response.[34] The sampled aerosol passes through a weak plasma created by a corona discharge device where it mixes with the unipolar air ions produced by the corona. The air ions diffuse and attach to the exposed surface of the particles. The excess unattached ions are removed by a collecting electrode and the particles with attached charges, are collected on a HEPA filter within a Faraday cup electrometer. The current produced by the charged particles is measured by a sensitive electrometer and related to the surface area of the sampled particles. Diffusion charging surface area monitors are available from a number of companies and typically have quoted ranges of 0 – 2000 μm^2 cm^{-3} and sensitivities of 1 μm^2 cm^{-3}.

Two real-time surface area instruments critically evaluated recently[34] do show active surface area response to particle diameter in the range of 20 – 100 nm.

Also, below approximately 100 nm for open fractal-like particles and spherical particles, active surface area measured by diffusion chargers has been found to correlate well with geometric surface area as measured by Differential Mobility Analyzing System (see section 5.3.5.1) and with projected surface area as measured by Transmission Electron Microscopy.[34] The challenge with the diffusion charging method is that for particles larger than 100 nm mobility diameter, the diffusion chargers increasingly underestimate the aerosol surface area with increasing particle size,[34] as is anticipated from theory. Research is needed to establish whether this degree of underestimation is significant in relation to engineered nanomaterials' exposure and health effects.

New instruments are being introduced which use a particular configuration of an aerosol charger to simulate the amount of material expressed as surface area deposited into the tracheobronchial and alveolar regions of the lung. This is in addition to other surface area instruments (described above) that measure the total active surface area. These new instruments draw the aerosol through a cyclone with a 1 µm cut point and then into the mixing chamber to mix with the ion stream. The charged aerosol is passed through an ion trap. The voltage on the ion trap is altered such that it acts as a particle size selector to collect both the excess ions and particles that are not of an electrical mobility state (surface area size) corresponding to either the tracheobronchial or respirable aerosol fractions. The electric charges on the penetrating particles are then measured by the electrometer.[35] This new method has the potential to provide a measurement that correlates with deposited aerosol surface area in the lungs. Models available presently on the market provide static rather than personal sampling. The calibration of these instruments is done only for one breathing condition (nose only and activity level of light exercise) of workers, i.e., reference condition.[36] The calibration to reference conditions does not account for factors such as level of worker activity, worker's age and sex or pre-existing lung disease which might markedly influence particle deposition. It might also not represent real exposures of different people performing different activities in the workplace. Thus the correlation of data provided by this instrument to actual deposited particle surface area in workers' lungs needs to proceed with caution. Comparisons with other instruments to assess the instrument performance can, for example, be made by calculating the deposited surface area, based on similar lung deposition models, from size distribution measurements with electrical mobility spectrometers. Recently performed comparisons for dioctyl sebacate, sodium chloride and diesel soot particles have shown good agreement.[37] It was shown that neither the level of activity nor gender has a major impact on the deposition curves and thus the exposure.[38] Only the dose is a function of breathing frequency and tidal volume. The dose, however, can be inferred from the measured exposure data based on the breathing pattern. This might also allow for a more personalized dose analysis. At present, research is underway indicating that calibration factors might be used to adapt the instrument to breathing behaviour, gender and age other than the reference condition.

5.3.5. Nanoparticle size distribution measurement

5.3.5.1. Measuring size distribution using particle mobility analysis

The most common instrument used for measuring size distributions of aerosols of nanoparticles is the Differential Mobility Analysing System (DMAS). The DMAS is capable of measuring aerosol size distribution in terms of particle mobility diameter from approximately 3 nm up to around 800 nm, although multiple instruments typically need to be operated in parallel to span this range. However, there is a challenge in measuring size distributions of some engineered nanoaerosols, such as single-walled carbon nanotubes. A recent study has reported anomalous instrument responses above certain voltages when characterizing aggregates of airborne carbon nanotubes using an electrical mobility analyzer.[39] Problems were reported, when measuring nanoparticle penetration in filter media. If the system was not operated with a special cleaning procedure, phantom particles below approximately 50 nm were recorded.[40] Thus, care needs to be exercised in order to obtain correct size distributions when measuring nanometer-diameter conducting fibrous material, high particle concentrations and aggregates/agglomerates by electrical mobility analysis. DMAS comprises a Differential Electrical Mobility Sizer (DEMS) to separate the particles according to the electrical mobility diameter followed by a CPC or an electrometer to count the particles. Particles enter a pre-selector with a cut-point at 1 μm, then enter into a region where they are charged to Boltzmann equilibrium by passing them through a bipolar ion cloud formed from a radioactive source. They then pass through a well-defined electric field in the DEMS. The charged particles move between the electrodes, and those with a specific mobility are sampled from a small outlet at the exit of the electrodes, from where they are counted by a CPC or electrometer. By scanning or stepping the voltage between the electrodes, particles with electrical mobilities corresponding to a range of particle diameters can be counted sequentially, allowing the aerosol size distribution to be determined.

The sequential scanning or stepping of the voltage takes a significant time, with the fastest conventional scan speeds being about one minute, which is suitable provided that the process being monitored does not change within this timescale. However, there are many situations within the workplace environments where this might not be the case. If rapid fluctuations of the nanoaerosols appear, the use of a buffer vessel of a few liter volume is recommended to keep the concentration stable for one scan. In case of periodical processes shorter than the scan time, multiple, sequential scans can be averaged in order to get a stable size distribution.

For applications requiring rapid analysis due to temporal variation, fast mobility-based particle spectrometers have been developed which use a parallel array of electrometer-based sensors to count the size segregated particles. Measurements might be made with a time resolution of one second or less, and operation at ambient pressures reduces evaporation of volatile particles. The instruments might be limited to measurements at relatively high aerosol number concentrations and some instruments are available with on-board dilution for very high concentration measurements. The lack of a radioactive source might make them a viable alternative to the DMAS in many workplaces. Research is currently being carried out to develop more compact and therefore cheaper aerosol mobility classifiers relying on particle migration across an opposing air flow.[41]

The DMAS is limited in its widespread application in the workplace due to its size, expense, complexity of operation, the need for two or even three instruments operating in parallel to measure wide aerosol size distributions, and the use of a radioactive source to bring the aerosol to charge equilibrium. However, if nanoparticles are the only airborne particulate of interest, a single instrument might be sufficient.

5.3.5.2. Measuring particle size distribution using inertial impaction

Cascade impactors are widely available in a number of configurations, allowing either personal or static sampling with a range of particle size cut points. Personal cascade impactors are available with cut points of 250 nm and above, and thus are only able to provide very limited information on size distribution in the nanometer size range. Static cascade impactors are available with lower cut points in the nanometer size region, low pressure impactors or multi-orifice impactors.

A number of low pressure cascade impactors are available. These instruments require vacuum pumps to provide the necessary air flow and so are not suitable for personal sampling.

Determination of aerosol size distribution from cascade impactor data requires the application of data inversion routines. The simplest approach is to calculate cumulative mass concentration with particle diameter, and use the data to estimate the Mass Median Aerodynamic Diameter (MMAD) and the Geometric Standard deviation (GSD) of the size distribution. This approach assumes no losses between collection stages, ideal impactor behavior, and a unimodal aerosol with a lognormal size distribution. Cascade impactors are usually used to measure the mass-weighted aerosol size distribution, and so assumptions of particle shape and density need to be made in order to estimate the number or surface-area weighted distribution. As these parameters are rarely quantified, great care needs to be taken in interpreting cascade impactor data in terms of aerosol number or surface-area.

5.3.5.3. Electrical Low Pressure Impactor™ (ELPITM) measurements

The Electrical Low Pressure Impactor™ (ELPI™) combines inertial collection with electrical particle detection to provide near-real-time aerosol size distributions for particles larger than 7 nm in diameter.[42] Aerosol particles are charged in a unipolar ion charger before being sampled by a low pressure cascade impactor discussed in section 5.3.2.2. Each impactor stage is electrically isolated, and connected to a multi-channel electrometer, allowing a measurement of charge accumulation with time. As in the case of the diffusion charger (5.3.4), particle charge is directly related to active surface-area. Thus the integrated electrometer signal from all stages is directly related to aerosol active surface-area. The electrometer signal from a single stage is related to the active surface-area of particles within a narrow range of aerodynamic diameters, allowing limited interpretation of the shape of sampled particles. If the particle charging efficiency as a function of aerodynamic diameter is known or can be assumed, real-time data from the ELPI™ can be interpreted in terms of the aerosol number-weighted size distribution. In practice, particle-charging efficiency is determined experimentally. Interpretation of measurements in terms of particle mass concentration or mass-weighted size distribution can also be carried out, although it requires knowledge of the effective particle density as a function of size and correction for particle losses.

As well as allowing on-line measurements of particle concentration and size distribution, aerosol samples collected by the ELPI™ are available for off-line analysis, including electron microscopy and chemical speciation.

5.3.5.4. Calculations of nanoparticle concentrations from size distribution measurements

As well as providing information about the particle size characteristics of the aerosols in workplaces where nanoparticles are being produced or handled, size distribution measurements can be used to calculate integrated nanoparticle exposure levels. For example, frequency distributions, combined with sample volume can be used to calculate number concentrations. With the assumption that the particles are nearly spherical and that their physical diameters are equivalent to their mobility diameters (for DMAS, see below) or aerodynamic diameters (for ELPI, see below), the aerosol surface concentration can be calculated. A method has been also developed to calculate aggregate surface area and volume distributions using the electrical mobility diameter for nanoaerosols.[43] Similarly, with knowledge of particle density, the aerosol mass concentrations can be determined. The accuracy of these estimations is dependent upon the assumptions made about the physical characteristics of the particles.

Ku and Maynard[34] showed that for monodisperse aerosol particles smaller than 100 nm, particle geometric surface areas calculated by DMAS size distributions agree to within ± 20 % of surface area determined by a diffusion charger surface area instrument. However, the relationship diverged for larger particles because the Diffusion Charger (DC) instrument tends to underestimate surface area of larger particles compared to the DMAS. A similar relationship was found by Shi et al[44] for polydisperse aerosols present in the ambient atmosphere. From comparative measurements at two outdoor sites they found good agreement between geometric surface area measurements using the epiphaniometer and the DMAS. It is therefore reasonable to suggest that reliable measurements of geometric surface area can be obtained with DC instruments, provided that suitable pre-selectors are used.

5.3.6. Sample collection for material characterization

Determination of the physical and chemical properties of airborne nanomaterials relevant to their potential effect on human health is often required. Parameters such as particle size, shape, surface area, composition, agglomeration state, crystallinity, solubility and bio-persistence provide the basic information for the exposure

and toxicological evaluation of new nanomaterials. The surface coating on the particles and their electrical charge will also have a significant impact on their state of agglomeration, which will in turn influence their physical behavior and subsequent biological responses. Because particle nanoscale structure affects transport and locations of deposition within the respiratory system and might affect toxicology, it is important to characterize nanoscale structures of airborne materials used for toxicology studies. A new technique for characterizing particle size-dependent nanoscale structure in airborne single-walled carbon nanotube agglomerates utilizing a tandem mobility-mass analysis has been developed.[45,46]

The main analytical techniques routinely available for determining the particle size, shape and composition are high resolution electron microscopies such as scanning electron microscopy (SEM), field emission gun SEM, transmission electron microscopy (TEM), and scanning transmission electron microscopy (STEM), combined with x-ray microanalysis, Electron Energy Loss Spectroscopy (EELS) and electron diffraction. Both SEM and TEM require samples of particles that are uniform in deposit and have minimal particle overlap. This requirement rules out collection by impaction where particles are concentrated in small regions below the impaction jets. For the SEM, particles down to typically 20 nm in diameter can be sampled directly onto SEM supports using electrostatic precipitation. (An upper limit of electrostatic precipitation is given by the geometry of the instrument and can be assumed around 200 nm.) Point to plane electrostatic precipitators combine a charging and deposition field by using a sharp corona needle as one electrode, and a planar collection surface as the second electrode. Sampling efficiency approaching 100 % can be achieved for particles larger than 20 nm. For smaller particles, rapidly decreasing charging efficiency leads to a lower sampling efficiency. Deposits from electrostatic precipitators are generally uniform across the collection substrate, enabling discrete particle analysis in the SEM. A number of electrostatic precipitators are available from instrument manufacturers. Some studies also indicate that passive aerosol samplers can be potentially used to collect nanoparticles for SEM analysis.[47]

For the TEM, it is generally preferable to sample directly onto a TEM support grid, thus avoiding a secondary sample preparation stage. The deposition onto the coated grid can be achieved by thermal precipitation, electrostatic precipitation or direct airflow through the grid. Thermal precipitation is the most suitable collection mechanism as it relies on aerosol particles migrating from a hot region to a cold region, and is particularly effective for particles between 1 nm and 100 nm in diameter. Thermal precipitation can be used to sample aerosols at ambient temperatures by establishing a temperature gradient above the collection surface, and passing the aerosol across the surface. A number of suitable designs have been published[48,49] and they can be built by a reasonable laboratory workshop.

5.3.7. Measurement of high length: width aspect ratio particles of nanomaterials

There is a wide variety of occupationally relevant particles of nanomaterials with high length: width aspect ratio. Among those, one can distinguish elongated particles of nanostructured materials (such as a chain of aggregated nanoparticles) and elongated nano-objects, also referred to as “nanorods,” which are characterized by distinct chemical compositions, structure and geometry (see Chapter 3).

An example of nanorods, which are produced on industrial scale, is carbon nanotubes. Single-walled carbon nanotubes essentially comprise a single layer of carbon atoms arranged in cylindrical structures of diameter about 1 nm and length up to about 1 mm. Carbon nanotubes might also form as multiple concentric tubes of diameters significantly greater than SWCNTs. The extreme aspect ratio of individual nanotubes, together with their potentially low solubility in the lungs might lead to toxic mechanisms analogous to those observed with other fibrous particles such as asbestos and synthetic vitreous fibers. The question might be asked therefore if they should be considered, for exposure measurement purposes, like asbestos fibers and be analyzed by counting with the TEM.

However, unlike asbestos, SWCNTs are very rarely found as single fibers. They are generally produced as convoluted bundles of nanotubes (nanoropes) of diameter from 20 to 50 nm and then form complex clumps and agglomerates, of size between 100 µm and 1 mm, with other nanoropes and other carbonaceous and catalyst materials that are present. Laboratory and field studies by Maynard *et al*[50] have shown that it is extremely difficult to break these clumps and generate aerosols of nanotubes. Normal procedures of transferring SWCNT powder from production vessel to storage bucket and then tipping into a second bucket showed no significant increase in nanoparticle numbers. It was only by using a single component vortex shaker fluidized bed, operating at over 50 % agitation that any significant increase in particle numbers was produced. Although aerosol generation rates of SWCNTs have been shown to be low during handling[50],

published data to date indicate that inhaled airborne SWCNTs might present a pulmonary hazard. Regarding measurement and characterization of SWCNTs, it is noticeable that physico-chemical properties of SWCNT aerosol particles released while handling unprocessed SWCNTs might vary significantly by particle size and production batch, and that evaluation of potential health hazard needs to account for this.[45] However, for certain applications, manufacturers are currently trying to prevent nanoparticles from agglomerating by using some form of surface coating or other techniques. In addition, there is no information on the size distributions of particles released from the cutting, sanding or abrading of products that incorporate nanotubes bound into the matrix of the material (composites, tires, etc.). Therefore at the moment there is no reason to suggest that nanotubes should be treated like asbestos fibers for exposure assessments, but it would be wise when monitoring levels of nanoparticles in workplaces where carbon nanotubes are being produced or handled to investigate samples collected for TEM analysis for discrete nanotubes. Finally, a careful watch should be kept on developments in nanotube production, and knowledge shared of any evidence of discrete airborne nanotubes found in workplace air.

Only one study on exposure assessment at a carbon nanofiber handling facility has been published.[51] Measurements made with real-time instruments (CPC, diffusion charger, aerosol photometer and ELPI^{TM}) indicate that most processes did not release substantial quantities of carbon nanofibers when compared to background particle measurements. However, some processes (wet sawing of composite material and the transferring of carbon nanofibers to a mixing vessel) did elevate area airborne particle (from 300 nm to 2 500 nm diameter) mass concentrations up to 0.16 mg/m^3 shown by aerosol photometer. In addition, air and surface samples were collected with a vacuum sampling method on high purity quartz-fiber filters and analyzed for total carbon using a thermal-optical analysis technique, which indicated up to 1.1 mg/m^3 in total carbon for inhalable fraction. A point-to-plane electrostatic precipitator was used to collect sample for TEM examination for particle size and shape. A few samples exhibited fiber bundles of varying diameters (some larger than 100 nm) and lengths. The majority of fibers appeared as loosely bundled agglomerates, rather than as single fibers.[51]

According to [52], Raman spectroscopy shows the most promise of the spectroscopic methods, SEM is more suitable than TEM, and Atomic Force Microscopy is more suitable than Scanning Tunneling Microscope.

5.3.8. Sampling strategy issues

Until it has been agreed which is(are) the most appropriate metric(s) for assessing exposure to nanoparticles in relation to potential adverse effects, it has been recommended that a range of instrumentation be used to provide full characterization of the aerosols in workplaces where nanoparticles are being produced, handled or used to make new materials.[53] This requires a large number of instruments, which is not conducive to the normal personal sampling procedures required to assess personal exposure for compliance with any exposure limit or for epidemiological purposes.

However, new instruments are being continuously developed and there are small portable instruments for particle number concentrations, particle surface area concentrations and health-related surface area concentrations. While most of instruments are not yet truly personal, they are compact enough to be carried from location to location in the workplace and to be sited close to the worker at each location. Currently however, these instruments do not provide enough information for full characterization of the workplace, so static instruments such as the DMAS, ELPI^{TM} and devices for collecting particles for physical and chemical characterization should be included. Care should be taken in setting these static samplers as aerosol characteristics can change with distance from source, leading to spatial and temporal variation of nanoaerosol mass and number concentration. This is especially true for hot processes leading to particle nucleation from vapor that will often lead to variations in emission rate and concentration over time.

To improve the comparability of exposure data, the accepted practice of giving personal exposure as an eight-hour-shift value should also be observed in the case of nanoaerosols. In consequence, wherever possible exposure measurement results concerning shorter measurement intervals should be converted into shift data by time weighted recalculation. In all cases, where short-term exposure itself is the target of investigations, the time base of measurements needs to be documented. A time base of 15 minutes for short-term exposure measurements is recommended as it is generally used in occupational hygiene.

Selection of the most appropriate sampling location or locations is a key factor for a reliable interpretation of data in view of personal exposure. This requires analysis of tasks carried out by workers using or handling nanomaterials, identification of all the potential nanoaerosol-emitting sources in the workplace and an understanding of the ventilation system in the workplace to determine the potential for cross contamination. This could be a significant problem for nanoparticles as they will remain airborne for considerable periods of time and be easily dispersed by the air currents in the workplace. For single sources, the relationship between aerosol emission and work activities should be clear, enabling the reliable assignment of exposure levels to be made.

However, unless the workplace is operating under clean room conditions or has high efficiency filters on the inlet air through well defined inlets, outdoor sources of nanoaerosols (e.g. vehicle exhausts, other industrial activities, power stations, etc.) will penetrate indoors and result in overestimation of the levels of nanoparticles emitted from the process under investigation. This will inevitably lead to an overestimation of the worker exposure to nanoparticles derived from that process. One way to overcome this problem is to determine ambient or background particle counts prior to the commencement of manufacturing or processing of the nanoparticles. However, it might not be possible to subtract the background particle counts from the exposure level counts since the background counts may fluctuate with time. Another method is to carry out simultaneous measurement of background concentrations using a duplicate set of monitoring equipment to monitor outside the workplace, and to subtract the outdoor levels from those measured inside the workplace. However this can be expensive and assumes that the ambient particles do not change during transport into the workplace.[53]

Alternatively, differences in composition between nanoparticles generated in the workplace and those combustion particles in the outdoor air can be used for discrimination purposes. If the composition of the engineered nanoparticles is known, and the constituent elements are not likely to be found in outdoor air, then the proportion of the engineered particles in the total particle field counted by TEM and analyzed by x-ray microanalysis can be determined. This ratio can then be used to calculate the surface area concentration of the engineered nanoparticles in the total surface area concentration values for all airborne nanoparticles detected. The accuracy of this approach will obviously depend upon the engineered nanoparticles having at least one detectable element that is not present in outdoor aerosols. This proposition has not yet been fully tested.

5.4. Dermal exposure assessment

5.4.1. Sampling

Sampling of nanoparticles deposited on skin in the workplace can be accomplished by adapting well established sampling methods developed for chemicals.[54-56]

The direct assessment of dermal exposure to nanoparticles can be accomplished by measuring the amount of the nanoparticles in contact with the skin over a period of time. The methods developed for such purposes entail either the removal of accumulated contaminants from the skin[57] or interception of the material as contact occurs. The removal methods include uncertainties in the removal efficiency and require that the duration of contact be evaluated through independent means. Uncertainty is introduced by the interception methods through the use of materials that usually do not mimic the adherence characteristics of the skin accurately. These methods are summarized in the following subsections.

5.4.1.1. Removal procedures

Rinse method. Various solvents (for example, solutions of surface active compounds) can be used to rinse the exposed skin and remove accumulated nanoparticles. These solutions can then be analyzed for the presence of nanoparticles, followed by chemical, particle size and shape analyses.

Wipe method. Solvent impregnated materials can be used to wipe the skin and remove residues. The wipe material is then analyzed for the nanoparticles of concern. For example, metal concentrations might be measured using ICP-MS; other analytical methods would likely be required for most nanomaterials.

Tape stripping method. Adhesive tape can be applied to the skin for purposes of removing contaminant nanoparticles both from the surface of the skin and from within the skin. ICP-MS or other analytical techniques can be used to estimate the amount of residue including nanoparticles removed with the tape.

5.4.1.2. Interception procedures

Patch method. Patches made from various materials such as cotton or polyester gauze, alpha-cellulosic paper, polyurethane foam, or polypropylene film can be placed on the body to collect nanoparticles as contact occurs. The method requires some fairly extensive assumption, and in the occupational setting, it has been proven to be useful for screening purposes but is limited as a quantitative method. It is generally believed that amounts of contaminant recovered by either removal or interception methods do not accurately correspond to amounts of contaminant deposited on the skin. Collection efficiency is considerably lower via removal[58] than interception methods.[59] Results of these methods are more a reflection of skin loading than actual exposure; thus, measurement results at best provide indices of relative exposure.

Glove method. Absorbent gloves can be used to collect nanoparticles contacting the hands.[59-61]

Whole body dosimetry. This method involves the use of clothing covering the whole body (usually cotton, long underwear tops and bottoms and socks) to trap nanoparticles. A problem with this method is the difficulty in extracting nanoparticles from such a large collector. An advantage of this method over the patch method is that it is less likely to miss areas where exposure might occur. Another approach that can be used to estimate exposure is by using patches that are placed on multiple anatomical regions of the body.[62]

5.4.1.3. Other procedures

Fluorescent tracers. This procedure involves modifying the nanoparticles of concern with a nontoxic fluorescent tracer and then using video imaging to identify and quantify the points where the nanoparticles contact the skin.[63]

Contaminated surfaces. Contaminated surfaces, such as tools and equipment, represent another category of sampling. According to Fenske,[64] surface sampling can be considered a first approximation of personal dermal exposure. This observation supports the value of controlling the migration of nanoparticles in the workplace.

5.4.2. Sample characterization

Electron microscopy can be used to characterize size distribution, number concentration and shape of nanoparticles collected on samplers. In wipe methods, use of mixed-cellulose ester filters as wipes could facilitate such analysis.

Light scattering, laser diffraction, size exclusion chromatography, acoustic techniques and field flow fractionation could be used to characterize size distribution and number concentration,[65] while spectroscopic techniques can be useful in obtaining information about chemical composition and structure of nanoparticles. These techniques can work with rinse sampling methods.

5.5. Dose (internal exposure) assessment

Internal exposure is more directly linked to adverse health effects. However, dose assessment involves analysis of tissues, body fluids, and exhaled air. In occupational settings, less invasive methods such as collection of hair, urine and exhaled air are used most commonly.

Dose can be determined by measuring amount of nanoparticles of interest and/or their metabolites. The term “biomarker” is often used to describe a range of biological effects resulting from interactions between human biological systems and a toxicant. Biomarkers can provide direct evidence for the exposure to a particular toxicant if there is a unique correlation between a particular biomarker and a toxicant. One of the advantages of measuring biomarkers of exposure is that it provides information about combined exposure through multiple routes, including non-occupational. Measurements of biomarkers of exposure are used for screening and monitoring of workers.

Biomarkers of exposure to nanoparticles are in the early development stage complicated by great variety of nanoparticles chemical and physical properties resulting in a wide range of biological responses. Inhalation exposure to poorly soluble low toxicity nanoparticles was shown to cause inflammatory response.[66] For example, nitric oxide in the exhaled air has been proposed as a biomarker of inflammation.[67]

5.6. Discussion

As with all new and emerging technologies, the development of reliable techniques for assessing and controlling exposure to nanoparticles in the workplace will always be working from a position of insufficient knowledge until the suitability of current controls are assessed, the emission rates of nanoparticles from those processes are determined and the exposures of the workforce to those nanoparticles are characterized. Together with information on the toxicity of the nanoparticles to human health, these parameters form the basis of the risk assessment process (see chapter 6. Risk Assessment of Nanomaterials) that informs legislation on its production, sale and use, allows the setting of appropriate occupational exposure limits and leads to guidance on the choice of suitable control procedures.

The area is moving fast and instrument manufacturers are currently developing new devices that they hope will become the mainstay of future nanoparticle exposure assessments. Besides recently-introduced health-related surface area monitors (see 5.3.4), there are a number of developments in the pipeline, including: personal CPCs; small portable diffusion charger surface area monitors; small, portable instruments that provide particle number size distributions (similar to the information provided by the DMAS) and small, portable particle mass monitors. In addition, there are many other long-term developments including a possible portable device that should be able to discriminate between engineered and combustion nanoaerosols. So, assuming that international agreement can be obtained about which metric or metrics is the most appropriate to use as the basis of exposure assessment for inhalation of airborne nanomaterials, then the future looks promising that a suitable sampling methodology will be available. The choice of sampler or monitor depends upon the role for which it is to be used and a device for exposure assessment might be different from that used to determine sources and to assess the efficiency of control systems.

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6. Risk assessment in occupational settings

6.1. Introduction and scope

The present chapter describes the current state of the art of risk assessment for production and processing of nanomaterials. Thus, only occupational settings, e.g., production plants, pilot plants or laboratories, but not consumer product safety or environmental safety, are considered.

A sub-class of nanomaterials, free or unbound nanoparticles, is of particular concern from an occupational safety and health perspective. Nanostructured materials, nanolayers or solids containing embedded nanoparticles, e.g., polymer composites, coatings or finishings can also result in exposures. For example, in field studies it was shown that destructive processing (even using wet-saw) of polymer composites containing nanomaterials generates substantial aerosol release, which includes some aggregated nanofiber material, but there was no evidence of release of unagglomerated nanoparticles.[1] Such aerosols can contain both incidental and engineered nanoparticles. Therefore it is important to properly characterize generated aerosols.

While physical hazards posed by the specific process, e.g., high temperatures, high voltage, etc. can be present in occupational settings dealing with nanomaterials, this chapter focuses more on toxicological hazards and less on fire and explosion hazards. Generally, acute effects should be avoided using typical principles and minimum requirements of occupational health and safety[2,3] provided that acute toxicity information is available for handled nanomaterials. However, health risks due to chronic low level of exposures are more difficult to evaluate and therefore it can be more challenging to establish appropriate exposure mitigation programs.[4]

Risk assessment is typically conducted by safety experts working in close contact with decision makers establishing risk management requirements. Risk assessment analysis requires detailed information both on products and processes. For example, European legislation requires risk assessments specific to individual substances and individual occupational settings.[3,5] Likewise, presently in many countries risk assessment for nanomaterials is conducted according to existing regulations for individual materials and settings.

6.2. Risk assessment for nanomaterials

Risk assessment is an analysis of the potential adverse health effects (current or future) caused by a hazardous agent in the absence of any additional actions to control or mitigate exposure to that agent.

Risk assessment in occupational settings includes several elements: hazard identification, hazard assessment, exposure assessment, and risk characterization.[6-8] The goal of risk assessment is to evaluate whether existing risk in a specific workplace environment is above organization-specific acceptable level of risk and, therefore, to provide information to decision makers about the need to further strengthen risk management approaches.

The components of the risk assessment process and definition are:

- Hazard Identification-identifies those hazards that make a significant contribution to exposure and risk.
- Exposure-Response Assessment-identifies the potential adverse health effects associated with the hazards of concern identified at the workplace.
- Exposure Assessment-evaluates the pathways by which individuals could be exposed to hazards present in a workplace.
- Risk Characterization-incorporates information from the three previous chapters to evaluate the potential risk to exposed individuals at the workplace.

Risk assessment in a specific workplace commonly starts with collection of information on hazard assessment. The process then continues in a logical process whereby hazard and exposure are assessed. Thus the step of risk characterization is the synthesis of hazard and exposure.

The existing structure of risk assessment framework is flexible enough to be adapted to nanomaterials.

6.2.1. Quantitative and qualitative risk assessment

Quantitative risk assessment. Quantitative risk assessment relies on the availability of quantitative exposure data expressed as the probability of exposure or exposure levels and quantitative exposure limits. Exposure limits are developed using dose-response relationships and signify exposure levels at which risk of adverse health effects or risk of an event leading to adverse health effects is below an acceptable level. Examples of exposure limits are Occupational Exposure Limits for specific substances, Minimum Explosible Concentration for explosive dust clouds, and limits of power density for electro-magnetic fields. Another integral component of quantitative risk assessment is measuring and/or estimating actual exposures or probabilities of exposure in the workplace.

Qualitative risk assessment. In the absence of data to utilize traditional quantitative risk assessment methods to evaluate risk, missing information can be obtained using various combinations of expert judgments and extrapolations from existing data for similar materials. In such qualitative risk assessment methods, safety professionals can be required to use their expert opinions in evaluating site-specific risk and in recommending implementation of exposure mitigation options. For example, in “Approaches to Safe Nanotechnology: An Information Exchange with NIOSH”[4] U. S. NIOSH recommends that “the decision to use respiratory protection should be based on professional judgment that takes into account toxicity information, exposure measurement data, and the frequency and likelihood of the worker's exposure.”

More formalized techniques such as “expert elicitation” utilizing a systematic process of formalizing and quantifying experts' judgments about uncertain quantities[9,10] can be used in grouping nanomaterials according to their hazard properties and exposure potential. Such hazard groupings could facilitate the development of techniques utilizing banding to assess risks and recommend appropriate risk management techniques, such as Control Banding (http://www.coshh-essentials.org.uk/). One example of such a risk assessment scheme groups nanomaterials according to their biopersistence, chemical activity and toxicity.[11] Expert opinions can be also systematically utilized within decision analytical frameworks for nanomaterial risk assessment and management, such as Multi-criteria Decision Analysis (MCDA).[12]

Another critical component of a qualitative risk assessment model is regular re-assessment of available hazard and exposure information.

6.2.2. Hazard identification

Hazard identification calls for identifying and monitoring hazards that make a significant contribution to exposure and risk. In this case the focus is on developing a list of pertinent toxic hazards (chemicals or nanomaterials) and physical hazards (strong electro-magnetic fields, high intensity light sources, high level of noise, flammable and explosive materials, high pressures and vacuum, etc). Regardless of engineering controls, low potential of exposures, or low hazard, this step is to identify all hazards that are relevant to potential occupational exposures.

For the identification of the hazard, information can be obtained from typical sources such as specialty literature, Materials Safety Data Sheets (MSDS) and International Chemical Safety Cards (ICSC), vendor information beyond that supplied in the MSDS/ICSC, government and trade association publications and proprietary information or test data. It might be relevant to mention that there is often a lack of nano-specific data or exposure limits. Thus, the information from these sources might not adequately characterize the hazard of specific nanomaterials. When this information is not available from third parties, testing to generate data can be conducted.

The next step includes characterization of the quantity of hazard material or physical agent. The quantity of material handled or physical agent present in the workplace is an important factor affecting exposure potential. Naturally, workplace sites where only small amounts of material are being handled or processed would be expected to have lower exposure potential compared to sites handling larger amounts. Such an analysis of work places facilitates assessment of exposure potential among workers' populations with distinct work duties related to or within exposure-relevant distance to the work process of interest, thus leading to identification of populations of concern.

Hazard identification also includes a survey of individual workplaces, worker procedures, manufacturing processes and the safety measures in place, including use of engineering controls and personal protective equipment, for the description of the exposure and identification of potential for exposure among workers' populations with distinct work duties related to or within exposure-relevant distance to the work process of interest. If such a preliminary survey indicates potential for exposure, further collection and analysis of data to assess workplace exposure can be warranted. As the discussion about relevant metrics is ongoing, multiple tools to characterize exposure to nanoparticles could be employed.[4] Such tools include traditional techniques to characterize mass concentration and airborne particle number concentration. This information might be supplemented by particle size distribution, surface area or chemical characterization data (for further details please see Chapter 5).

6.2.3. Exposure-response assessment

Toxicological hazards. In occupational settings, protection from toxic effects is achieved by reducing exposures to the toxic substance below established “safe” levels resulting in an acceptable level of risk. Toxicological effects can be broadly characterized as threshold and nonthreshold. For the former, it is possible to identify an exposure below which no adverse health effects are observed and for the latter, any exposure results in a non-zero probability of adverse health effect occurrence. For threshold toxicological effects, quantitative determination of “safe” levels includes the following steps:

1) determination of a No-Observed-Adverse-Effect Level (NOAEL) or a “Benchmark Dose” (BMD) using animal or human exposure-response data;
2) extrapolation of animal levels to human levels (recognizing the significant uncertainties introduced by such extrapolations): models translating environmental exposures to dose, such as a human lung dosimetry model, are used to calculate working lifetime exposure concentration.
3) derivation of occupational exposure limits upon consideration of technical feasibility, variability and uncertainties of models and approximations used and acceptable level of risk.

Toxicological properties of nanomaterials might arise from the intrinsic chemical composition of a material, such as those that would originate from bulk material. Apart from that, the scientific community is considering whether there is additional toxicity for nanoparticles due to the particulate nature and due to unique properties associated with the nanoscale.[13] Toxicological studies are also conducted on novel nanomaterials such as carbon nanotubes, which do not have bulk analogues.

The definition, design and standardization of adequate toxicological test protocols for nanoparticles are currently in a developmental stage.[iv] Available international accepted test guidelines (e.g. OECD) should be checked first concerning applicability to nanoparticles and if necessary improvement of these guidelines should be performed. Apart from the obvious toxicological issues, other major challenges being faced during experimental testing would be the representative formation of nanoparticle dispersions as well as their explicit characterization. At relatively high number concentration of particulate matter either in gas or liquid phase, nanoparticles tend to form larger agglomerates very rapidly due to Brownian motion and relatively strong

[iv] In July 2007, ISO TC229 approved the development of a technical report entitled: Guidance on physico-chemical characterization of engineered nanoscale materials for toxicologic assessment.

attractive interactions between nanoparticles. For example, this can occur during unloading of nanoparticles from a production line and packaging. Thus, it is typically uncertain whether exposure occurs to individual nanoparticles or to their agglomerates, even though analytical proof can be furnished that nanoparticles have been released from an emission source.

Multiple toxicological findings have been reported. The existing toxicity studies were sometimes conducted with test materials which were not well characterized, mostly due to the technological limitations. Thus for the time being, a limited amount of representative, validated hazard data derived from toxicological studies in the form of scientific health-based occupational exposure limits are available. And, it is believed that such exposure limits will be available in the near future for only a few engineered nanoscale materials. One of the very few published examples of risk assessment of nanomaterials includes a quantitative risk assessment of ultrafine titanium dioxide, ultrafine carbon black and diesel exhaust particulate.[14] The study utilizes available pulmonary inflammation and lung tumor data from subchronic[15,16] and chronic[17,18] inhalation studies in rats. The data were evaluated using various modeling approaches to estimate the risk of disease in workers exposed to fine or ultrafine titanium dioxide for up to a 45-year working lifetime. The modeling results from dose-response data provide the quantitative basis for developing occupational exposure limits for these nanomaterials. Occupational Exposure Limits were defined, in terms of mass concentration, for Carbon Black, a nanostructured material in the form of agglomerated and aggregated nanoparticles.[19] In another example, a study in mice exposed to single-walled carbon nanotubes by pharyngeal aspiration was used to estimate an equivalent lung dose in humans and the associated workplace airborne concentration.[20] A mouse lung dose linked to adverse lung effects, including a rapid fibrogenic response, was extrapolated to humans by estimating the fraction of airborne particles that would deposit in the human lungs at a relevant workplace airborne concentration.

At this point, given the current paucity of data, hazards based on toxicological properties of nanomaterials have not yet been completely assessed. However it is currently considered that:

- the toxicological properties of nanomaterials cannot always be predicted from the known toxicity of the substance in bulk form alone; and
- for some nanomaterials, mass is not an appropriate metric for characterising exposure and nanomaterial surface area, and number of nanoparticles have been proposed as better alternatives.

Thus, occupational exposure limits based on mass concentration, which are applied for dusting bulk materials, might not be sufficiently adequate for nanomaterials of the same chemical composition.[14,21]

Physical hazards. Very little nanomaterial-specific fire and explosion hazards have been described.[22] Fire and explosion hazards posed by nanoparticles could be more pronounced than those for larger particles or bulk materials and therefore additional tests can be necessary to evaluate flammability, explosivity and reactivity of nanomaterials. Test protocols for these hazards are in place for dusting bulk materials and could be applicable to nanomaterials as well. These protocols include measurement of burning rate, self-ignition temperature and the characterization of the explosive properties. Flammability of nanomaterials can be also evaluated using tests developed for chemicals, for example, using ASTM E-918-83 Standard Practice for Determining Limits of Flammability of Chemicals at Elevated Temperature and Pressure.[23] The explosive properties are analyzed through utilizing the results of the Fallhammer test (mechanical sensitivity, shock) and Koenen test (thermal sensitivity).[24] Therefore, once the physical hazard data is available, risk assessment for fire and explosion hazards could be conducted using existing techniques.

Given the paucity of hazard data for nanomaterials, hazard grouping of nanomaterials based on expert opinions could be implemented. For example, in the European Union system of classification, package labeling includes 1) “indications of danger” classified as very toxic, toxic, harmful, corrosive and irritant and 2) “risk” number to describe the level of hazard.[25] In the Control Banding approach five hazard groups are identified.

Given the great variety of possible nanomaterials and high costs of experiments assessing hazardous properties, computational models (such as Quantitative Structure Activity Relationship like models) predicting hazard properties of novel nanomaterials are expected to play an increasingly important role in risk assessment.

Further information about hazard characterization can be found in Chapter 4.

6.2.4. Exposure assessment

Exposure routes. Exposure to nanomaterials can occur as a result of direct contact. In the case of nanoparticles, the discussion of potential exposure scenarios should consider the liberation potential of the nanoparticles. Liberation potential can be defined as the ability of individual nanoparticles to be available for direct contact with human skin or other organs such as lungs. The following factors are to be considered for the release of airborne nanoparticles: physico-chemical properties and process characteristics. Physico-chemical properties of nanoparticles might include: size, surface coating, charge, dustiness behavior, etc. In considering process characteristics, the conditions of the material should be observed – that is, whether the material is contained in a liquid or solid matrix. Mechanical processing such as stirring, drilling, sawing, milling, grating and cutting can result in release of nanoparticles and particles of nanostructured materials. Other processes which can result in exposures include spraying liquid formulations containing nanomaterials and high-energy treatment of nanomaterials or nano-enabled materials, such as laser drilling or plasma welding resulting in vaporization of treated materials. Additionally, engineering processes, which range from closed contained systems to open air handling, can have a wide range of potential for exposure. Risk of exposure can be also affected by other factors such as incorrect use of and malfunctioning equipment - both manufacturing and exposure mitigating equipment (engineering controls and personal protective equipment); inadequate workplace practices; poor personal hygiene and unsafe individual worker's behavior.

Realistic exposure scenarios need to be identified for exposure assessment. Inhalation and dermal exposure are typically the most common routes of exposure in the workplace. Oral exposure at the workplace is considered less likely (although ingestion is a component of inhalation exposure through mucocilliary clearance and swallowing of inhaled particles). Ingestion might also occur from unintentional hand to mouth transfer after dermal exposure.[2,3] Parenteral exposure could occur accidentally (e.g., needle stick). Some studies have reported that nanoparticles do not penetrate intact porcine skin[26,27], while other studies have shown that nanoscale or microscale particles can penetrate the stratum corneum (particularly with mechanical skin flexing) and reach the dermal and epidermal layers of porcine or human skin.[28,29]

Inhalation exposure can be characterized by applying state of the art analytical methods, such as particle counters and sizers or related methods, while dermal exposures can be characterized using handwipes sampling followed by chemical analysis and electron microscopy. There are several difficulties in applying these methods however, e.g., validation and calibration, adequate consideration of ambient background levels, variations of analytical results due to humidity, and effects of particle aggregation and agglomeration on particle concentration. However, particle size, number and distribution are likely to be important factors. These data might need to be supplemented by surface area or chemical characterization data. (For additional information see also Chapter 5).

In the absence of real-time exposure data, more qualitative techniques can be used to characterize exposure potential. For example, in the Control Banding approach, exposure potential is characterized using three bands (low, medium and high) for the degree of dispersability (dustiness for powders of nanoparticles) and for the amount used in a particular occupational setting.

6.2.5. Risk characterization

Risk characterization includes review and integration of the hazard identification, exposure-response assessment, and exposure assessment steps. Quantitative risk estimates are evaluated for statistical and biological uncertainty. Risk characterization also provides site-specific evaluation of hazard and exposure, whether risks at a specific workplace exceed acceptable levels, and whether there are sensitive populations. Risk management measures might be recommended to reduce risks below acceptable levels. Typical measures might include elimination and substitution of hazardous nanoparticles (though the opportunities to do so might be limited by the unique properties of the nanoparticles) as well as technical measures, e.g., modifications to production processes and/or implementation of engineering controls, organizational measures, e.g., safety procedures, personal protective equipment and individual worker instruction (for further details see Chapter 7).

6.3. Conclusions

Evaluating the risk of exposure to nanomaterials in the occupational setting involves quantitative and/or qualitative risk assessment methods. When there is relatively little scientific information or if a material is unique, only a qualitative risk assessment might be possible. When exposure-response data are available (e.g., in a toxicological or epidemiological study), quantitative risk assessment[8] might be feasible. Presently, quantitative health hazard and exposure data are not available for most nanomaterials. Therefore, health risk evaluation for the workplace currently relies to a great degree on professional judgments for hazard identification, potential exposures and the application of appropriate safety measures.

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7. Control methodologies

7.1. Introduction

This chapter will examine current knowledge on control practices for mitigating or preventing exposure to engineered nanomaterials in the workplace. It does not aim to address health and safety issues or practices associated with nanomaterials generated by natural processes, nanoparticles produced incidentally (e.g. during welding) or associated with potential consumer exposures or uses, though the information should be

relevant to those areas. The chapter will cover control of both health hazards and safety (physico-chemical) hazards, and specific examples of controls used in companies and research laboratories will be presented.

Information in this chapter has been drawn from documents provided by United States, Canadian, Swiss, German, Japanese, United Kingdom and Australian experts,[1-10] and from other sources. Information on current practices is derived primarily from a report by the University of California, Santa Barbara for the International Council on Nanotechnology (ICON) entitled "A Review of Current Practices in the Nanotechnology Industry – Phase two report: Survey of current practices in the nanotechnology workplace".[11] The report presents the findings of an international voluntary survey of current environment, health, safety (EHS) and product stewardship practices in the global nanotechnology industry.

The control of emissions containing nanoparticles in occupational settings is not a new subject. Controls are well established for preventing and controlling exposure to, for example, welding fumes and diesel emissions (which contain incidental nanoparticles). What is new and unique is the need to control exposure to engineered nanomaterials in an increasing number of workplaces. Using existing knowledge for the control of fine and ultrafine particles (including incidental nanoparticles) as a starting point, informed guidance is summarized for the control of engineered nanomaterials.

While it is expected that the controls described in this Chapter should be effective (to some extent at least - some will be very effective) in preventing exposure to engineered nanoparticles in specified situations, to date there is only limited evidence regarding the effectiveness of the control methods. However, based on existing knowledge and information, advice is provided on the likely effectiveness of different control strategies in preventing exposure.

Use of the information on control methodologies can help companies, researchers and other people prevent adverse health and safety consequences during the production, handling, use and disposal of manufactured nanomaterials. This information covers a range of nanomaterials and applications.

7.2. Implication of risk assessment in regard to control methodologies

In considering the appropriate control strategies for nanoparticles in the workplace, it is necessary to consider first the levels of risk associated with the workplace activities. Risk assessment was examined in Chapter 6. Ideally, the control strategy should align with the known risk – as demonstrated in, for example, the *Control Banding*[v] approach, which is the basis of the United Kingdom Health & Safety Executive's *COSHH Essentials* packages and other guidance.[13]

There might potentially be health risks arising from the unique properties of engineered nanomaterials associated with occupational exposure to these materials. There are also potential safety risks of fire or explosion[14] during the manufacture, handling, storage and use of engineered nanoparticles. However at present, there are uncertainties in the extent of the health and safety risks involved in working with nanoparticles, and thus it is not possible with certainty to use knowledge of risks to define control strategies. Also relating to control methodologies, there are as yet no specific workplace exposure standards set for airborne concentrations of free unbound nanoparticles of any type. Exposure standards have been set for substances in a larger particle form, some of which have the same or similar chemical composition to engineered nanoparticles currently being manufactured or used.

7.2.1. Strategies for control

[v] Control banding[12] is a process in which a single control technology (such as general ventilation or containment) is applied to one range or band of exposures to a chemical (such as 1−10 mg/m^3) that falls within a given hazard group (such as skin and eye irritants or severely irritating and corrosive). Four main control bands have been developed for exposure to chemicals by inhalation:
Band 1: Use good industrial hygiene practice and general ventilation.
Band 2: Use local exhaust ventilation.
Band 3: Enclose the process.
Band 4: Seek expert advice.

If we apply the precautionary principle[vi] to nanomaterials, it follows that the lack of scientific certainty about potential health and safety risks associated with engineered nanomaterials should not prevent the utilization of cost-effective preventive measures to mitigate potential risks. The uncertainties about health and safety risks, and the absence of nanoparticle-specific workplace exposure standards, do suggest a precautionary approach is required to control the manufacture, use, storage and handling of nanoparticles. In relation to free nanoparticles and nanotubes, in 2004 the UK Royal Society and Royal Academy of Engineering recommended that factories and research laboratories treat manufactured nanoparticles and nanotubes as if they were hazardous[vii][17]. It has been suggested that strict prevention measures should be taken to limit airborne nanoparticle release into the occupational environment and the environment outside the business,[7] and it is considered important to employ a broad based risk management program to reduce workplace exposures and eliminate workers' exposure wherever possible.[2] It is considered that application of the precautionary principle does not imply that organizations should not use nanoparticles until health and safety hazards are fully understood, but that workers should be provided with appropriate protection taking into account the limited hazard information available.

Choices for the control strategies should be informed by the available understanding of differences between nanoparticles and larger particles, and where nanoparticle-specific information is known, the control approach can be varied according to the properties of the nanoparticles involved. Appropriate work practices should be tailored to the processes and job tasks during which exposure might occur. The choice of strategy should also be informed by methods chosen for the control of incidental nanoparticles.

Research results[18] indicate that total surface area of particles in the lung might be the dominant measure when quantifying the toxicity of poorly soluble dusts[viii]. Preliminary evidence suggests that nanoparticles might be biologically more reactive than larger particles of similar chemical composition per unit mass and therefore might pose a greater health risk when inhaled.[2] Several animal studies suggest that lung pathologies (such as cancers, inflammation, granuloma formation, fibrosis and breathing difficulties) might be expected with exposures to carbon nanotubes and metal oxide nanopowders.[2] Many chemical processes are catalyzed by small quantities of substances, and the efficiency of catalysis is generally a function of the surface area of the catalytic agent.[7] Nanomaterials have large surface areas per unit mass, which might result in increased catalytic activity and in rapid, or even violent or explosive reactions. As for catalysis, due to the high surface area/unit mass, explosivity and flammability hazards might be greater for nanoparticles and particles of nanostructured materials compared with larger particles of the same chemicals, but bulk material properties should also be considered when examining the potential risk.

In regard to nanomaterial-specific information, Chapter 3 described how nanomaterials are not a single group of objects but a multiplicity of shapes, sizes and composition. Given the variation in properties (e.g. general chemical toxicity, shape/size, surface area and surface reactivity), it is reasonable to assume that there might be greater health and safety hazards associated with some nanoobjects than others. For example, specific properties of quantum dots (toxicity of component elements) and carbon nanotubes (morphology) which give rise to concerns about toxicity have been described.[2]

In the future, as health and safety risks are better understood, for some nanomaterials it might be possible to modify prevention measures. With more health hazard information, it might be possible in the future to band risk (and hence controls) effectively based on differentiable health hazards – which might in some cases allow relaxation of strict prevention measures. However, as nanomaterial quantities manufactured, used, stored and handled increase, so the safety risks involved can be expected to increase in some situations.
Measuring and evaluating the effectiveness of prevention approaches is an essential control strategy. However at present, the ability to do so is restricted by limited nanoparticle measurement capability.

[vi] Principle 15 of the United Nations Rio Declaration on Environment and Development[15] states that:
"In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."

[vii] Control of Substances Hazardous to Health (COSHH) defines hazard "in relation to a substance, means the intrinsic property of that substance which has the potential to cause harm to the health of a person, and "hazardous" shall be construed accordingly"[16]

[viii] These experiments were undertaken with TiO_2 and $BaSO_4$ dusts, with mass median aerodynamic diameters of 2.1 micrometers and 4.3 micrometers respectively.

7.3. Examination of control methodologies

7.3.1. Exposure prevention

Exposure prevention measures and appropriate work practices are essential in occupational health and safety, and the production and use of nanomaterials might involve various kinds of risks. Consequently, management, researchers and other employees might give priority to preparing an exposure prevention program designed specifically for the company or research facility.[7] Establishing and implementing an exposure prevention program should be an effective step in protecting the health and safety of employees and other people in the workplace.

A number of organizations have developed specific programs for handling nanomaterials.[11] In developing the exposure prevention program, the company director should (among other things) clearly identify the responsibilities of various individuals in the company and ensure that senior management, research teams and laboratories are involved. A risk assessment approach is needed, with consideration of the specific nanomaterial, its form, toxicity and safety hazards. The approach should be used for each specific task undertaken. A number of organizations working with nanomaterials reported[11] that their exposure prevention program depended on:

- the material form (powder, in suspension/solution or embedded in a matrix)
- specific known hazards (such as flammability, toxicity, carcinogenicity or high reactivity)

Elements of an exposure prevention (risk management) program might include, for example:

- Monitoring and recording the performance and effectiveness of control measures.
- Monitoring workplace exposures to nanoparticles.
- Developing the criteria and procedures for installing engineering controls (e.g. equipment enclosure or local exhaust ventilation) at process locations where exposure might occur.
- Providing: effective training and instruction to the workforce on hazards, operating procedures, equipment manual, procedures for handling nanomaterials, and effective protective measures. The ICON review reported that guideline documents are used by some organizations.[11]
- Obtaining safety data sheets from the producers or suppliers of the nanoparticles used. The safety data sheet should provide indications about health hazards posed by the products, and the protective measures for the workplace. However, examination of current safety data sheets for engineered nanoparticles has shown that information might be incomplete, and using solely the safety data sheet information can result in the implementation of incomplete protection measures.[8]
- Developing procedures describing the types of personal protective equipment that should be used (e.g. clothing and respirators), and when it should be used.
- Developing procedures to include the frequency of changing or washing personal protective equipment (e.g. gloves and coveralls).
- Maintenance of respirator including storage and keeping records where appropriate.
- Developing procedures for cleaning and decontamination of equipment and enclosures etc.
- Seeking expert advice, e.g. from occupational hygienists, to help guarantee a safe working environment.
- Undertaking research projects focused on nanotechnology-based health and safety issues (the research might be undertaken in collaboration with government agencies).
- Benchmarking and sharing practice knowhow with other organizations working with nanomaterials.

The guide for preventing exposure to lead[19] is an example of a guide that sets forth the principle points for consideration in an exposure prevention program designed specifically for controlling exposure to hazardous dusts.

7.3.2. Control strategies

In general, the main approaches to risk control are; elimination of the hazard, substitution of the hazard, engineering control techniques, administrative control systems and use of personal protective equipment. These complementary approaches should be considered starting with the design stage of an industrial process.[20]

In general, the preferred order of options (starting with most preferred) is:
elimination > substitution > engineering techniques > administrative means > personal protective equipment.
In practice, an appropriate combination of these strategies will provide the best approach for a workplace to control exposures.

Control practices for the reduction of inhalable and respirable dust in the workplace are well-known and well-established.[3] The efficiency of these methods for nanoparticles and particles of nanostructured materials has so far been only partially evaluated, but these measures seem useful as a starting point for the development of preventive measures.[8] Some adjustments might be needed to prevent potential exposure to nanomaterials. Generally, organizations working with nanomaterials are using conventional chemical safety methods, with some taking measures beyond those of conventional chemical hygiene.[11] Control measures are also based on the toxicity and physico-chemical properties of other materials handled in the laboratory, e.g. in the ICON review, most respondents indicated their choice of gloves was based on which solvents were being used.[11]

7.3.3. Eliminating the hazards through effective design

Effective process design can make a very major contribution to preventing workplace exposures.[20] In some situations, it can be difficult post-installation to make modifications to correct deficiencies in original design.

Special attention should be paid to positioning of plant, installations, processes, equipment activities and workstations during design. The designer can make a major contribution by:

- recognizing the exposure risk factors specific to the processes and production modes, and then designing to eliminate or at least reduce these exposure risk factors
- designing and recommending control measures

Activities during the design stage include producing the building plans, and planning the procurement, production, packaging, warehousing, shipping and other systems. In addition to taking into account the regulatory requirements and production imperatives, layouts should be designed to eliminate situations involving risks from the process and for the workers. Effective design can help prevent the generation of dusts and aerosols.

In regard to the design of engineering control systems, different processes will produce a range of particle sizes, which might include not only nanoparticles, but also particles of nanostructured materials such as larger agglomerates in some cases. The velocities (face, capture, and transport) necessarily will depend upon the nature of the process and the size range of the particles produced.[21,22] For this reason, the engineering control systems intended to prevent or limit the emission or accumulation of airborne nanoparticles in the work environment, such as enclosure and ventilation, should be designed according to the gaseous and particulate properties of nanoparticles and particles of nanostructured materials.

A fundamental principle of good design is to avoid explosive situations. Dusts having explosive potential are to be avoided. In the worst case scenario, equipment might need to be blast-proofed.[7] Also, where appropriate, building design can incorporate physical separation of workplaces handling hazardous materials.

7.3.4. Substitution of raw materials, products, processes and equipment

Substitution is generally a very effective way to reduce risks to health and safety in the workplace. While the unique chemical and physical characteristics of individual nanoparticles are likely to limit possibilities for straightforward substitution of one nanomaterial for another - it is this uniqueness which will likely determine

their application and commercial usefulness, there might be substitution opportunities in processes involving nanomaterials, e.g.:

- Replacing more toxic raw materials with less toxic raw materials.
- Replacing more toxic products with products that are less toxic.
- Changing the physical form of the product or material - use dispersions, pastes, granules or composites instead of dusting powders or aerosols.
- Process changes are very effective risk control methods, for example, changing from dry processes to wet processes, and the use of water can reduce dust emissions at some dry material drop-off or transfer points.[20]
- Substitution of equipment which involves the use or production of smaller quantities of toxic materials, or fewer toxic materials.
- Substitution of equipment to avoid emissions, or to reduce and better control emissions.
- Particle modification, e.g. the coating of quantum dots. In one study, the lack of observable genotoxicity of quantum dots was attributed to a silica coating, which successfully prevented the interaction of Cd, Se, Zn and S with proteins and DNA in the nucleus.[23] A further potential approach which has been examined is the possibility of modifying CdSe metalloid core structures to increase the thermodynamic stability and hence reduce the potential for breakdown into Cd and Se components.[24]
- Consider whether nanomaterials are necessary to the application or product.

7.3.5. Engineering control techniques

For workplaces generally, the choice of engineering control technique should include consideration of the level of risk involved. For example, in the UK's COSHH Essentials approach,[13] the approach recommended for control of airborne contaminants is:

- Highest risk – seek specialist advice
- High risk – use process containment[ix]
- Less risk – use local engineering control (e.g. local exhaust ventilation, LEV)
- Lowest risk – use general ventilation

Currently for engineered nanoparticles and most particles of nanostructured materials there is limited understanding of the level of risk, and it is suggested that in situations where there is risk uncertainty, a precautionary approach should be utilized.

Engineering control systems can be used effectively to control powders and gases, and are in common use in the chemical industry and other industries.[25]

Engineering controls are widely used to reduce exposure to welding fume. A variety of methods for welding fume removal at source might be utilized, e.g. extracted benches, extracted booths, local exhaust ventilation and on-gun extraction.[26] General ventilation, e.g. by dilution ventilation or displacement ventilation might be used to supplement welding fume removal at source by reducing background fume levels. The level of protection provided by these methods is considered to be quite variable and dependent on appropriate use and maintenance. Engineering controls of this type are also used in the carbon black industry, though significant exposure in this industry still occurs.[1]

Engineering controls used in organizations working with nanomaterials are reported in the ICON survey, Figure 3.[11] Not all specific controls were chosen to reduce workers' exposure to nanoparticles (e.g. the control might have been chosen primarily to keep the material clean). Although some organizations detailed

[ix] In this Technical Report, process containment will be considered as an engineering technique.

specialized or modified engineering controls for nanomaterials applications, most reported using commercially available off-the-shelf technologies.

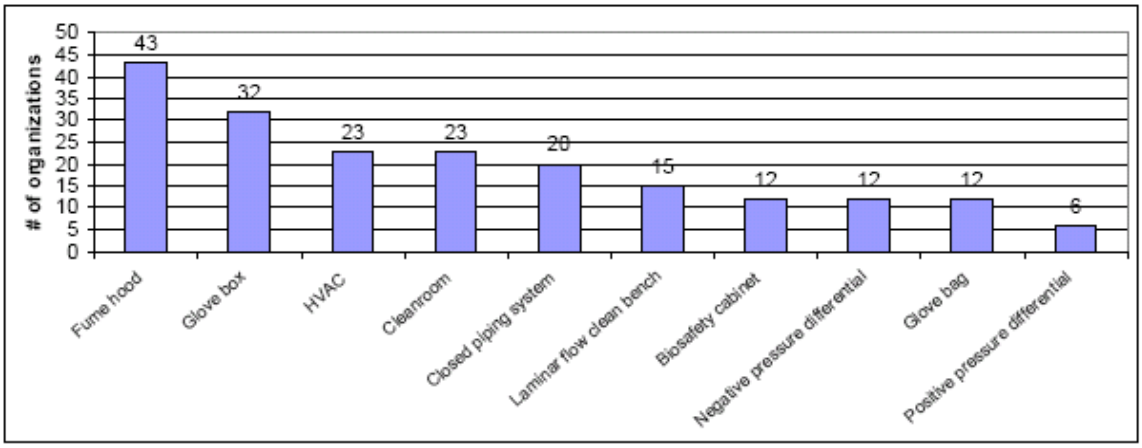


Figure 3 — Reports of "nanotechnology-specific" facility design and engineering controls (from A Review of Current Practices in the Nanotechnology Industry [11]).

7.3.5.1. Closed containment of a process (enclosure and isolation)

Enclosure and isolation of the process can minimize the airborne release of particles into the work environment during production or use. This approach should be considered for processes with a high potential risk to the health and safety of workers. It allows more effective emission control than in open processes, while facilitating treatment of environmental emissions when necessary.

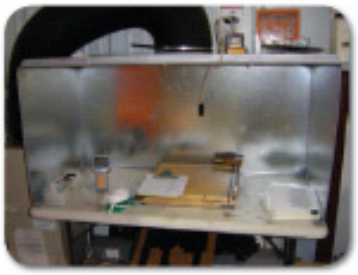
While the level of risk associated with handling most nanomaterials is currently unclear, for materials where there is evidence that indicates it would be prudent to avoid any exposure, a number of containment approaches might be considered. Operations can be performed by isolating the materials in separate, ventilated rooms equipped with a system that avoids any possibility of contaminating other workplaces.[7] Other examples of isolation are; the use of closed-circuit processes, use of robotics and equipment enclosure. In certain situations where the process is too polluting, workers can be isolated in a controlled atmosphere workstation to operate the entire process by remote control. The workers are located in booths or rooms where the air quality conditions are controlled to protect their health and safety.[20]

Maximum protection for the environment and the worker is provided by use of a Class III Biological Safety Cabinet (BSC), which was designed for work with highly infectious microbiological agents and for the conduct of hazardous operations.[27] It is a gas-tight enclosure with a non-opening view window. Access for passage of materials into the cabinet is through a dunk tank, that is accessible through the cabinet floor, or double-door pass-through box (e.g., an autoclave) that can be decontaminated between uses. Reversing that process allows materials to be removed from the Class III BSC safely. Both supply and exhaust air are HEPA filtered on a Class III cabinet. Exhaust air must pass through two HEPA filters, or a HEPA filter and an air incinerator, before discharge to the outdoors. Airflow is maintained by a dedicated, independent exhaust system exterior to the cabinet, which keeps the cabinet under negative pressure. Long, heavy-duty rubber gloves are attached in a gas-tight manner to ports in the cabinet and allow direct manipulation of the materials isolated inside. Although these gloves restrict movement, they prevent the user's direct contact with the hazardous materials. The trade-off is clearly on the side of maximizing personal safety.

In general, source enclosure (i.e. isolating the generation source from the worker) should be effective for capturing airborne engineered nanomaterials, based on what is known of nanoscale particle motion and behavior in air.[5]

Materials such as carbon black, silica fumes, nanoscale TiO_2, metals and nanoscale metallic oxides are normally produced in closed circuit processes,[7] and enclosure and isolation controls are used in practice for handling a variety of different nanomaterial types.[11] In the ICON review, a number of organizations working

with nanomaterials reported the use of cleanrooms (using pressure differentials) with separate and isolated heating, ventilation and air conditioning (HVAC) systems.[11] Organizations also reported the use of glove bags and glove boxes, and closed piping systems to segregate any materials deposited down a drain into a separate collection system. Further information on gloveboxes can be found in the *Guideline for Gloveboxes*.[28] One potential problem reported with glove bags is the build up static electricity charges, which can be problematic for flammable or potentially explosive nanomaterials.[11] Further details of specific enclosure and isolation controls reported are shown in Table 2 below. An example of the use of an enclosing hood with HEPA exhaust is also shown in Figure 4 below.[29]



Enclosing hood with HEPA exhaust constructed to control possible emission of nylon nanofibers during destructive testing.

Figure 4 — Enclosing hood with HEPA exhaust (from NIOSH Progress Toward Safe Nanotechnology in the Workplace[29])

In case of a leak from an enclosed process, primary nanoparticles can escape and disperse through the plant. How much nanoparticle aerodynamic properties resemble those of gases is yet to be determined. But from known relationships,[30] a 10 nm particle is expected to have a diffusion coefficient considerably lower than a nitrogen or oxygen molecule of around 0.3 nm in size.

As the dispersion process progresses, the particles agglomerate and airborne dispersion becomes more difficult. Nonetheless, inhalation exposure to these agglomerates is possible during nanoparticle recovery, bagging and maintenance and cleaning operations.[7]

Table 2 — Details of enclosure and isolation controls reported by facilities (based on A Review of Current Practices in the Nanotechnology Industry [11]).

CONTROL IN PLACE	DETAILS
Air lock and sealed containers for collecting nanomaterials from the reactor.	The reactors operated in a vacuum and collection was done automatically in the air lock, into an environmentally-sealed container. The air lock allowed for any residual particulate matter to be removed by vacuum before removing the sealed container from the reactor. This process was built in-house.
Synthesis of nanomaterials in an enclosed environment.	Vented automatically before opening and also had a self-cleaning burn cycle to eliminate residual material. This device fitted in the fume hood and was engineered in-house.
Clean rooms with positive pressure differentials	The clean rooms had positive pressure differentials that could be exhausted with intermediate spaces of lower pressure between labs and offices.
Portable peristaltic pumps to transfer liquid to waste containers.	Aim is to prevent potential spills and reduce aerosolization of the material. Peristaltic pumps, because they work on positive displacement, are less prone to producing aerosols than conventional high pressure pumps.

Use of distillation system for evaporating solvent from a colloidal dispersion within an explosion-proof enclosure.	This enclosure was designed with concern for the potential for these particular nanomaterials to be explosive.
Using an in-line disperser device, which would open a bag of fine particulate feed stock and transfer the material to the chemical reactor.	This minimizes handling of the dry powder form. The device would mechanically dispose of the used bag into a waste drum. Use of this device within a HEPA filtered enclosure would allow for an exposure and emission-free process.
Remote control set up for the nanomaterial production equipment.	This allowed the equipment to be operated in an isolated environment within a ventilation enclosure. Only certain trained and respirator-equipped individuals would be allowed access to the room for cleaning or maintenance.
Use of safety alarms for nanomaterial production.	Within the closed system were two sensors for changes in oxygen and pressure. If either sensor was activated, the equipment shuts down, which should prevent the potential release of nanomaterials due to a malfunction or accident.

7.3.5.2. Source capture of pollutants, e.g. local exhaust ventilation (extraction)

If the use of closed containments is not possible, then it is best to avoid the formation of dusts or aerosols. However in some processes, it is impossible to avoid airborne release of dusts and aerosols. Source capture of these pollutants (e.g. by using local exhaust ventilation, LEV) is then the method of choice to prevent airborne propagation of these products in the work environment, contaminating all the work areas and being breathed in by workers.[31]

LEV equipment performance is closely linked to the quality and efficiency of design and maintenance, and often of work methods. Ventilation systems should be designed, tested, and maintained using approaches such as those recommended by the American Conference of Governmental Industrial Hygienists (ACGIH).[21,32] It is important for effective containment that the systems be checked daily and records of the checks kept. In-line monitoring should be fitted at key points in the system (e.g. behind the hood, across the filters). The efficiency of new ventilation systems should always be evaluated to ascertain their performance level. Different processes will produce a range of particle sizes, which might include not only nanoscale particles, but larger agglomerates in some cases. The velocities (face, capture, and transport) necessary will depend upon the nature of the process and the size range of the particles produced. A well-designed system should perform very well in airborne engineered nanomaterial applications, provided the aspiration system intake is correctly positioned and an adequate capture velocity is maintained continuously.[33] However if the face velocity is too high, the resulting air turbulence might cause material to escape from the hood, with the risk of inhalation exposure, and nanomaterial powders might be lost to the exhaust system. Before performing maintenance on the equipment, it should be vacuum cleaned using a vacuum cleaner with a high-efficiency filtration system and wet wipe-cleaned.[7]

Reduction by source capture with negative pressure is one of the most effective measures in operations not performed in closed circuits - such as for mixing, recovery, bagging or weighing of products. Source capture is commonly used in welding,[26] cutting and spray metallization processes, among others. These processes, which have been used for many years, generate a significant number of particles of nanoscale dimensions. An example of the use of LEV in nano-operations is for controlling fugitive emissions during precursor mixing at a primary nanoscale oxide production facility,[29] as shown in Figure 5 below.

Local exhaust ventilation controlling fugitive emissions during precursor mixing at a primary nanoscale metal oxide production facility.

Figure 5 — Local exhaust ventilation controlling fugitive emissions (from NIOSH Progress Toward Safe Nanotechnology in the Workplace[29]).

Fume hoods were the most frequently used engineering control for the handling of nanomaterials in the organizations participating in the ICON survey.[11] Fume hoods are used for a variety of different nanomaterial types – nanopowders, carbon nanotubes, colloidal dispersions, fullerenes, quantum dots, polymers, nanowires, nanocrystals and carbon black. Exhaust filtration systems are frequently used with the fume hoods by the organizations working with nanomaterials. A number of different filter types are used in practice - HEPA filters, non-HEPA filters, wet scrubbers primarily for removing water soluble organic materials and sub-micrometer rated cartridge filters that block nanoparticles to less than 10 nanometers.

Biosafety cabinets are designed to protect personnel from potentially harmful agents, and are used in some nano-enabled organizations.[11] Class I and Class II biosafety cabinets both utilize extraction through HEPA filters. Characteristics of biosafety cabinets are shown in Table 3 below.

Table 3 — Comparison of Biosafety Cabinet (BSC) Characteristics (from Biosafety in Microbiological and Biomedical Laboratories (BMBL) 5th Edition, Appendix A).[27]

BSC Class	Face Velocity m/s	Airflow Pattern	Applications	
			Nonvolatile Toxic Chemicals and Radionuclides	Volatile Toxic Chemicals and Radionuclides
I	0.381	In at front through HEPA to the outside or into the room through HEPA	Yes	When exhausted outdoors[a,b]
II, A1	0.381	70 % recirculated to the cabinet work area through HEPA; 30 % balance can be exhausted through HEPA back into the room or to outside through a canopy unit	Yes (minute amounts)	No
II, B1	0.508	30 % recirculated, 70 % exhausted. Exhaust cabinet air must pass through a dedicated duct to the outside through a HEPA filter	Yes	Yes (minute amounts)[a,b]

II, B2	0.508	No recirculation; total exhaust to the outside through a HEPA filter	Yes	Yes (small amounts)[a,b]
II, A2	0.508	Similar to II, A1, but has 0.508 m/s intake air velocity and plenums are under negative pressure to room; exhaust air can be ducted to outside through a canopy unit	Yes	When exhausted outdoors (Formerly "B3") (minute amounts)[a,b]
III	N/A	Supply air is HEPA filtered. Exhaust air passes through two HEPA filters in series and is exhausted to the outside via a hard connection	Yes	Yes (small amounts)[a,b]
[a] Installation may require a special duct to the outside, an in-line charcoal filter, and a spark proof (explosion proof) motor and other electrical components in the cabinet. Discharge of a Class I or Class II, Type A2 cabinet into a room should not occur if volatile chemicals are used.				
[b] In no instance should the chemical concentration approach the lower explosion limits of the compounds.				

A laminar flow clean bench (also called a laminar flow hood) is not a biosafety cabinet. It is not designed to protect personnel or the environment from potentially harmful agents. It is designed to keep material clean. HEPA-filtered air is drawn across the materials and then flows out through the open front of the cabinet, where the worker will be located.

7.3.5.3. General ventilation

General ventilation by dilution in the work environment can draw the contaminants outwards, and if it is the only engineering control utilized, might allow significant exposure of workers to nanoparticles. If the use of LEV for open processes is not practicable, then it might be preferable to use displacement ventilation to reduce background levels, where fume is extracted at roof or ceiling level.

7.3.5.4. Air recirculation and filtration

Filtration plays an important role in the control of exposure to airborne particles. High Efficiency Particulate Air filters might be used in engineering control systems to clean the air before returning it to the workplace, or before discharge into the atmosphere. These filters are usually classified as mechanical filters. Current knowledge indicates that a well-designed exhaust ventilation system with a HEPA filter should effectively remove nanoparticles.[5] However, only a limited amount of work has been done to quantify the performance of filters against particles in the nanometre size range[x].

If HEPA filters are used in the dust collection system, they should be coupled to a well-designed filter housing. If the filter is improperly seated, particles have the potential to bypass the filter, leading to filter efficiencies much less than predicted.[34]

To ensure a new air supply for some processes, a fraction of the air used in the collection and filtration systems is also evacuated.[7] This evacuated air can be treated by several filtration stages with, possibly, capture in wet scrubbers or electrostatic precipitators in the final stage. This capture principle, involving electrostatic attraction, is particularly effective for very fine particles. Periodic cleaning of the collection plates is usually accomplished by liquid jet spraying of these plates.

[x] An extension of analysis would be to examine the performance of filters for different types of nanoparticles.

Filtration involves a number of mechanisms by which particles might be captured by filter fibers,[35] giving efficient separation of particles from air. As an aerosol penetrates through a filter, the trajectories of particles might follow the streamline, or be deviated from the streamline (e.g. by diffusion). Mechanical capture of particles can occur by (see Figure 6):

- direct interception, where a particle follows the streamline and is captured if it comes into contact with a fiber;
- inertial impaction, where capture is effected by deviation of a particle from the streamline by its own inertia;
- diffusional deposition, where the combined effect of airflow and Brownian motion brings a particle into contact with a fiber;
- gravitational settling.

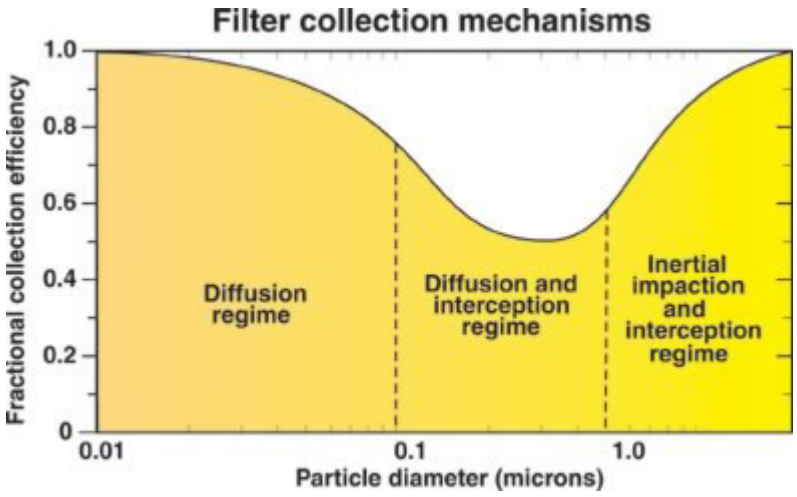


Figure 6 — Fractional collection efficiency versus particle diameter for a mechanical filter (from Guidance for Protecting Building Environments from Airborne Chemical, Biological, or Radiological Attacks[34]).

For some filter types, electrostatic forces will effect capture.

According to single fiber filtration theory, particles larger than 300 nm are collected most efficiently by impaction, interception, and gravitational settling, while particles smaller than 300 nm are collected most efficiently by diffusion or electrostatic attraction.[30] Between 100 nm and 300 nm in size, particles are most likely to flow uncaptured through filters. This is the “Most Penetrating Particle Size” (MPPS), and collection efficiency is lowest.[36-38] The main mechanical filtration mechanisms involved around lowest collection efficiency are diffusion and interception, with the impaction mechanism playing only a minor role.[30,39] The MPPS range can vary due to a number of factors, for example the type of filter media employed and the flow rate.

For particles less than 300 nm, Brownian diffusion is the dominant mechanical mechanism causing particles to impact on filter fibers.[30,33,40] Filtration efficiency due to Brownian diffusion increases as particle size decreases. Brownian diffusion is caused by collisions between particles and the air molecules to create random paths which the particles follow. The random motion increases the probability of a particle contacting one of the filter elements. Once the particle is collected onto a surface it will adhere to it due to the Van der Waals forces.

Current methods for certification of HEPA filters do not routinely require testing at particle sizes below 100 nm. The US Department of Energy's standard, *DOE HEPA Filter Test Program*,[41] an internationally recognized standard, requires that the filter is tested at an aerosol diameter of 300 nm aerodynamic diameter and that the particle collection efficiency is greater than 99.97 %. Given the dimensions and physical properties of nanoparticles, an approved HEPA filter should have filtration efficiency greater than 99.97 % for most nanoparticles.

As described above, due to Brownian diffusion, filtration efficiency will increase as particle size decreases. Research has shown that penetration of nanoparticles through filter media decreased down to 2.5 nm as expected by traditional filtration theory.[38,42,43] As particles approach molecular size (less than 2 nm), they might be less likely to adhere to filter fibers during diffusional collisions, and thermal rebound can occur.[44-46] The filtration efficiency was still found to increases as particle size decreases, but it does not increase as quickly as predicted by traditional filtration theory. In practice, thermal rebound might not be of any significance for the filtration of nanoparticles, e.g. if filters are designed to ensure a sufficient number of collisions.

7.3.6. Administrative means for the control of workplace exposures

Administrative means of control constitute an additional approach to supplement engineering approaches, but are not a substitute for engineering approaches[xi]. Administrative controls can help guarantee industrial hygiene in the working environment, and if necessary, companies and research facilities should seek expert advice from occupational hygienists. In working with nanoparticles, the administrative means to be applied will depend on the type of nanoparticles and other materials involved, and the nature of the work to be performed.

Application of engineering measures might be limited in some situations because, for example, they are not sufficiently advanced technically or they cannot be implemented due to prohibitive costs. In these situations, administrative approaches for limiting the risks of occupational exposure to nanoparticles include:

- modification of work practices;
- minimizing the number of exposed workers;
- limiting access to working areas and restricting access to authorized personnel;
- providing effective personal hygiene measures;
- housekeeping, including routine clean-up of work areas and clean-up of nanomaterial spills;
- use of preventative maintenance, which minimizes the risks of unscheduled interruption of production while assuring safer operations.

7.3.6.1. Recordkeeping

Effective recordkeeping is required to help establish and maintain safe and healthy workplaces. Recordkeeping requirements have been defined in national codes of practice for handling hazardous substances and dangerous goods (with consideration for minor quantities of dangerous goods).[47,48] Records should be kept of:

- induction and training programs;
- risk assessments;
- servicing of and testing of equipment (including fire fighting equipment);
- workplace monitoring;
- health surveillance (records kept confidentially);
- dangerous occurrences and near misses;
- work-related injuries and illnesses;
- workplace engineering controls maintenance, daily checks and examinations;
- disposal records.

[xi] Engineering control methods should always be used according to standard practices

In general (except for confidential records e.g. health surveillance), records should be located conveniently so that managers, employees, employee representatives and public authorities can gain access to information to which they are entitled. Public authorities might also define the length of time records should be kept for, and what actions should be taken if company ownership changes or a company ceases to trade.

7.3.6.2. Training

Effective training and instruction for the workforce is critical to ensure people's health and safety when handling nanomaterials. A number of topics are covered in training undertaken by organizations working with nanomaterials[11] e.g.:

- safe handling of nanomaterials and Standard Operating Procedures (SOP);
- hazards and toxicity;
- personal protective equipment;
- engineering controls and equipment maintenance;
- emergency procedures;
- waste handling;
- definition of nanoparticles;
- environmental release/shipping/customer protection;
- exposure monitoring;
- applicable regulation.

Sources of information and guidelines for training include government agencies (e.g. NIOSH, OSHA, and EPA in the US, the UK Health and Safety Executive, and the Industrial Technology Research Institute in Taiwan), scientific literature and toxicological studies, internet databases, internal expertise, conferences, external experts (e.g. consultants), industry associations and suppliers' Materials Safety Data Sheets (MSDS) and International Chemical Safety Cards (ICSC, see http://www.cdc.gov/niosh/ipcs/ipcscard.html).

7.3.6.3. Reduction of work periods

Reduction of work periods might be applied beneficially under certain conditions, e.g. when working in a hot environment (to avoid heat stress), or in situations where risks cannot be controlled by engineering techniques. For the handling of nanomaterials, this approach should not be widely applicable.

7.3.6.4. Personal hygiene

Effective personal hygiene is needed to help protect the health of workers.[5,7] Particular focus is required when people might be exposed to substances such as nanomaterials which; (a) are known to be hazardous, or (b) might be hazardous. Even in facilities with very efficient engineering controls, some workers could still be exposed to nanoparticles, e.g. during clean-up and maintenance work. Hygiene arrangements for working with nanoparticles are suggested below. The effectiveness is yet to be evaluated, but a number of these approaches are currently used in organizations working with nanomaterials.[11]

Washbasins and showering facilities are needed in the workplace for decontamination of areas of the skin exposed to dust or liquids – for example, prior to leaving the worksite. If there is potential for toxic product spatters or spills, the emergency shower is an indispensable tool to respond as quickly as needed.

Smoking, drinking and eating in the workplace should be prohibited, except in clean areas reserved for this purpose (which are separated from the areas where nanomaterials are handled). To help prevent dermal absorption of nanomaterials, open wounds should be effectively covered.

Facilities for changing clothes should be provided, and clean working clothes should be provided and used. Working clothes and private clothes should be separated. In the presence of highly toxic products, double lockers (one for work clothes, one for home clothes) avoid any risk of contamination outside the work areas.

To prevent transfer of contamination to the home environment, soiled clothing should not be taken home. Clothing must be cleaned safely - working clothes should not be cleaned by the employee, and the use of air jets for cleaning should be prohibited.

In order to prevent transfer of nanomaterials via shoes, sticky mats can be placed at laboratory entrances. These can be sheets of sticky paper adhered to the floor that must be crossed when leaving the laboratory. It is intended that nanomaterials attached to the shoes of employees will stick to the mats and not be transferred to the rest of the building.

Procedures should be in place for disposal of personal protective equipment (e.g gloves and coveralls). Also a procedure should be in place indicating the frequency of changing and washing non-disposable personal protective equipment.

7.3.6.5. Routine clean-up of work areas and clean up of nanomaterial spills

Until relevant information specific to nanoparticles is available, it is suggested that it would be prudent to base strategies for dealing with nanomaterial spills and nanomaterial-contaminated surfaces on established good practices for larger particles.[5] However, use should also be made of available information on nanomaterial exposure risks, and the relative significance of different exposure routes should be considered.[5] Organizations frequently reported using more than one clean-up method (e.g. wet wiping and vacuum cleaning), depending on the nanomaterial and its phase during handling.[11] The effectiveness of the approaches for nanomaterials is yet to be evaluated. Many of the methods used for the routine clean up of powders and liquids are also applicable for the clean up of powder and liquid spills.

Work area clean-up, including removal of dust deposited on the floors, walls and work surfaces, should be performed regularly to avoid any (i) accumulation, (ii) risk of atmospheric re-suspension or (iii) explosion (should the dusts be explosive, as in the case of certain metallic powders).[7] All equipment should be cleaned thoroughly and isolated[xii], as needed, before it undergoes maintenance.

The most frequently used methods for nanomaterial clean-up are wet wiping, vacuum cleaning and dry wiping.[11] Regular[xiii] cleaning of workplaces using wet wiping methods, HEPA-filtered vacuum cleaners, or a combination of both would be suitable for most nanomaterials. Damp cleaning methods with soaps or cleaning oils are preferred.[5] The use of commercially available wet or electrostatic microfibre cleaning cloths might also be effective in removing particles from surfaces with minimal dispersion into the air. Dry wipe is only used by organizations for cleaning up solutions. If vacuum cleaning is employed, care should be taken that HEPA filters are installed properly and bags and filters changed according to manufacturers' recommendations.[5] The performance of any HEPA-filtered vacuum cleaner should be regularly tested to ensure adequacy of seals etc. Standard approaches to cleaning up powder and liquid spills, including the use of HEPA-filtered vacuum cleaners, wetting powders down, using dampened cloths to wipe up powders and applying absorbent materials/liquid traps can be used for nanomaterial spills.

Energetic cleaning methods such as dry sweeping or the use of compressed air should be avoided or only be used with precautions that assure that particles suspended by the cleaning action are trapped by HEPA filters.[5] Clean-up should be conducted in a manner that prevents worker contact with wastes, and the disposal of all waste material should comply with all applicable national and local regulations. A small number of organizations reported that they stored the spilled nanomaterials in separate, sealed waste containers.[11] Given the limited knowledge on the hazards of nanomaterials, cleaning wipes should be properly disposed of as hazardous waste. Drying and reuse of contaminated wipes can result in re-dispersion of particles – therefore, wipes should not be reused.

When developing procedures for cleaning up nanomaterial spills or contaminated surfaces, consideration should be given to the potential for exposure during clean-up.[5] Inhalation exposure and dermal exposure will likely present the most probable routes of exposure. Consideration will therefore need to be given to appropriate levels of personal protective equipment. For inhalation exposure, dusts are likely to present greater inhalation exposure potential than liquids, with liquids in turn presenting a greater potential risk than

[xii] For example, the equipment might be ‘locked out' or electrically isolated for safety.

[xiii] The cleaning frequency needed will vary from workplace to workplace, depending on operating conditions. Cleaning at the end of each work shift might be an appropriate frequency for a number of workplaces.

encapsulated or immobilized nanomaterials and nano-structures. Exposure will be influenced by the likelihood of material re-aerosolization. The use of respirators while cleaning up nano-spills has been reported.[11]

While vacuum cleaning might prove to be effective for many applications, electrostatic forces might make it difficult to remove particles from surfaces.[5] The electrostatic charge on particles will cause them to be attracted to oppositely charge surfaces and repelled by similarly charged surfaces. A similarly charged vacuum brush or tool might repel particles, making it difficult to capture the aerosol or even causing it to be further dispersed. Vigorous scrubbing with a vacuum brush or tool or even the friction from high flow rates of material or air on the vacuum hose can generate a charge. The vacuum cleaners recommended for cleaning copier and printer toners have electrostatic-charge-neutralization features to address these issues.

One organization has reported that it uses a vacuum hose rather than vacuum cleaner to clean up spills of nanomaterials, because the electric motor of a vacuum cleaner has the potential to ignite flammable nanomaterials.[11] Risk of ignition in vacuum lines should be also considered.[49]

For nanomaterials, other methods of equipment decontamination reported are solvent washing, burning, and dissolving using acid and plasma cleaning.[11] A small number of organizations reclaim nanomaterial spills, and two organizations report that they evacuate the area during spill clean-up.

An example of a workplace cleanup and decontamination methodology for highly toxic dusts is provided in the *Summary of good cleanup and decontamination practices for workplaces with beryllium-containing dust*.[50]

7.3.6.6. Waste disposal

Many organizations dispose of their waste nanomaterials through waste management companies.[11] Some dispose of their nanomaterials in separate disposal containers. Labeling of containers should comply with established labeling codes of practice, making appropriate use of available information for the contained nanomaterials (e.g. hazard information from the literature, including research papers). For storage, glass containers, metal containers, and sealed metal drums are used by organizations.[11]

Disposal methods used by organizations that do not dispose of their nanomaterial waste through an external company include:[11]

- treating nanomaterials in-house before disposal;
- recycling all nanomaterials;
- incinerating their waste nanomaterials on-site (all carbonaceous material);
- returning nanomaterials to suppliers.

7.3.6.7. Fire, explosion and catalysis prevention and control

The same principles applying to the management of fine powders, dusts or dusty materials should be considered for nanoparticles, with particular care taken in the case of easily oxidizable metallic dust.[7] However, the effectiveness of methods for nanoparticle fire, explosion and catalysis prevention and control is yet to be evaluated.

Explosion protection measures have been described for dust dispersions (e.g. by OSHA[51]) and for hazardous quantities of larger sized materials,[52] and can be applied to the handling of potentially explosive nanoparticles. For the handling of flammable nanoparticles, following these types of measures has also been recommended.[8] For reactive or catalytically active nanoparticles, contact with incompatible substances should be prevented.[8]

Fire prevention should take into account existing regulations, especially electrical requirements.[7] The design of electrical equipment protection should take into account the fine granulometry and very long settling time of nanoparticles, with dust protection needed[xiv]. In addition, further precautions should be taken regarding the operating temperature of electrical equipment, in regard to the risks of auto-ignition of nanoparticles.

[xiv] For some nanoparticles, the type of protection used to protect equipment from vapors might be needed.

The selection of an extinguishing agent should consider the compatibility or incompatibility of the material with water.[7] Some metallic dusts react with water to form, among other things, hydrogen, which ignites very easily and deflagrates. Chemical powders are available to extinguish burning metallic dust powders. In extinguishing burning metallic dust powders, care should be taken to avoid significant air movement, since this has the effect of putting the metallic dust in suspension, thereby increasing the risk of deflagration. To reduce the risks of fire and deflagration, it might prove necessary to use controlled-atmosphere production and storage processes, using carbon dioxide, nitrogen or inert gas. This might introduce further hazards into the system, notably the risk of asphyxiation.

When working with potentially explosive nanomaterials, there are reports of:[11]

- Anti-static shoes and mats being used in areas where the materials are handled. The shoes reduce the build-up of static charge, which could potentially ignite the materials.
- A distillation system for evaporating solvent from a colloidal dispersion being housed within an explosion-proof enclosure. This enclosure was designed with concern for the potential for these particular nanomaterials to be explosive.

7.3.6.8. Storage

Storing nanoparticles might involve special protection to conserve the products and to ensure workplace health and safety. Suitable records should be kept of all materials stored on site.

Storage containers for nanoparticles and particles of nanostructured materials should accommodate the different granulometric characteristics and reactivity of the particles.[7] The fine granulometry of the materials might result in long settling times and re-dispersion. Reservoirs should be tightly sealed to avoid leakage of the product or contamination of the premises during transport. Appropriate arrangements, some of which resemble those used for storing gases, should be considered.

The small size of the particles (which often tend to agglomerate), provides a very large surface area in contact with the surrounding air, thereby facilitating chemical reactivity. Depending on the product to be stored, a variety of preventive procedures can avert deterioration of the product, and the risk of fire or explosion. Possible solutions include storage in inert gas or in anhydrous conditions. To avoid oxidation, or even explosion in the case of certain metals, nanoparticles often need to be protected from air. In other conditions, it might be possible to surround the nanoparticles in a protective layer of salts or various polymers. These layers can be removed before using the product.[7]

7.3.6.9. Other aspects of prevention

For nano-processes, preventative measures might also need to be developed and implemented to prevent asphyxiation and electrocution. In some current processes using or manufacturing nanoparticles, the risk of asphyxiation is possible due to using large quantities of inert protective gases.[7] There is also risk of electrocution related to the generation of a plasma using high currents.[49]

Procedures for emergency response, including the use of emergency protective equipment and for specialized first aid should also be developed.

7.3.7. Evaluating the work environment

The scientific framework and methods for assessing exposure to nanoparticles are examined in detail in Chapter 5. Monitoring and evaluating the work environment will determine the effectiveness of the control approaches described in Sections 7.3.3 to 7.3.6. Evaluation findings will inform about whether personal protective equipment (PPE) is required.

Regarding the measurement of airborne nanoparticles, currently the direct measurement of personal exposures is difficult because most of the measuring instruments are not designed to be attached to the person. In addition to direct personal exposure monitoring, there exists an alternative method to evaluate the workplace environment - by estimating statistically the personal exposure concentrations from the aerial concentration data measured in the workplace at regular or random intervals. The feature of the described

method is to be able to estimate the arithmetical average concentration and the upper limiting exposure concentration.[53,54]

1) Arithmetical average concentration (C1)
It indicates the exposure concentration of the person who acts averagely at the workplace. The value is estimated using the following formula.

$$\log C1 = \log Mg + 1.151 \log^2 SDg$$

Mg: Geometric Mean of measured concentrations
SDg: Geometric Standard Deviation of measured concentrations

2) Upper limiting exposure concentration (C2)
The value of the upper limiting exposure concentration, which is defined as the level at which only 5 % of all airborne concentrations measured at any time and any place in the unit workplace exceed the exposure limit, is calculated from the following formula[xv].

$$\log C2 = \log Mg + 1.645 \log SDg$$

Using this method, the workplace environment can be evaluated without conducting the measurement of personal exposure concentrations.

7.3.8. Personal protective equipment (PPE)

Engineering and administrative protection measures should be supplemented by PPE, e.g. respirators, protective gloves, protection goggles and full protective clothing, when further protection for workers is needed. In practice, the majority of nanomaterial organizations surveyed in the ICON study recommended their employees or researchers use PPE.[11] Conventional laboratory wear was most often reported as the recommended means of protection.

7.3.8.1. Protection from inhalation exposure – use of filter respirators and air-supplied respirators

The use of filter (air purifying) respirators[xvi] or air-supplied respirators is required to supplement, but not to replace engineering and administrative controls when such controls do not adequately keep worker exposures to an airborne contaminant below a regulatory limit or an internal control target. Respirators should be used as part of a complete respiratory protection program. Preliminary findings have shown that respirators will help provide workers with protection against nanoparticles.

The decision to institute respiratory protection should be based on a risk assessment after all other controls are in place. In regard to risk assessment, there are no specific exposure limits for airborne exposures to nanoparticles. For some nanoparticles, occupational exposure limits exist for larger particles of similar chemical composition, and this general toxicology information should be considered. However, current scientific evidence indicates that nanoparticles might produce a larger biological reaction than larger particles of similar chemical composition for the same mass of material and thus might pose a greater health risk when inhaled.[2]

The effectiveness of engineering, administrative and work practice controls can be evaluated using the measurement techniques described in Chapter 5 (Exposure Assessment). If worker airborne exposure to nanoparticles remains a concern after instituting these measures to control exposure, the use of respirators can further reduce exposures. A respiratory program[xvii] should include the following elements as a minimum:

- an evaluation of the worker's ability to perform the work while wearing a respirator;
- regular training of personnel;
- periodic environmental monitoring;

[xv] Assuming a lognormal distribution of airborne concentrations in the unit workplace.
[xvi] Air purifying respirators depend on filtration as a means of cleaning the air prior to it being breathed by the worker.
[xvii] When respirators are required to be used in the workplace in the United States, OSHA's respiratory protection standard [29 CFR 1910.134] requires that a respiratory program be established.[55]

- respirator fit testing;
- respirator maintenance, inspection, cleaning, and storage;
- selection of respirators made by a person knowledgeable about the workplace and the limitations associated with each type of respirator;
- detailed records of all these elements should be kept.

Information for employees using respirators is provided in U. S. OSHA's respiratory protection standard 29 CFR 1910.134.[55]

Several classes of respirators exist that can provide different levels of protection when properly fit tested on the worker. Assigned Protection Factors (APFs) for respirators have been recommended by a number of organisations (see Appendix 7.1).[56,57] This includes information from U. S. OSHA's *Assigned Protection Factors; Final Rule* (published in 2006).[58] Notes on the advantages and disadvantages of various types of respirators is shown in Appendix 7.2, using information in the *NIOSH Respirator Selection Logic 2004.* [59,xviii].

The collection efficiency of particles by filters was examined in detail in the earlier section on *Air recirculation and filtration* (in Section 7.3.5). The most penetrating particle size (MPPS) for many filters is around 300 nm, but this can vary based on the type of filter media employed, flow rate, and the condition of the respirator. For example, the most penetrating particle size for HEPA class filters can range from 100 nm to 300 nm,[36,38] while for N95 class air purifying respirators containing electrostatically charged filter media it has been found to be around 30-70 nm[61] and around 50-100 nm.[5,62,63] Below the MPPS, filtration efficiency will increase as particle size decreases due to particle diffusion.

Current methods for certification of respirator filters do not routinely require testing at particle sizes below 100 nm. For example, European Standards for respirator filter cartridges[64] and for filtering face pieces[65] require that these systems are tested against sodium chloride aerosols with a mass median diameter of 300 nm, again based on an expectation that this would be the most penetrating size.

Recent research indicates that respirators can offer considerable levels of protection against nanoparticles, but not necessarily the expected levels of protection at high inhalation (or respiratory) flow rates. Manikin-based tests using sealed facepieces showed that the penetration of ~30-70 nm monodisperse nanoparticles through some of NIOSH certified N95 filtering facepiece respirators could exceed the 5 % threshold at high inhalation flow rates.[61] Average penetrations of 5 % and 6 % (with standard deviation of 1 %) were measured at 85 l/min inhalation flow rate for the two types of N95 respirators examined. However, another recent report[66] compared the penetration of sodium chloride particles at 85 l/min flow rate through five NIOSH approved N95 filtering facepiece respirator models using two test methods: a monodisperse aerosol test (20 to 400 nm) and a polydisperse aerosol test similar to what is used for NIOSH certification testing. The average initial penetration levels from the polydisperse aerosol tests ranged from 0.61 % to 1.24 %. Monodisperse aerosol penetrations behaved according to single fiber filtration theory. The most penetrating particle size was found to be near 40 nm. The mean penetration level of 40 nm particles for the five models ranged from 1.4 % to 5.2 % and exceeded 5 % for only two of the respirator models. The rank ordering of the filtration performances of the five respirator models was consistent between the two test methods. The correlation coefficients between the average penetrations from the polydisperse aerosol tests and average penetrations of monodisperse particles of 40, 100, 200 and 300 nm were 0.945, 0.979, 0.996 and 0.994, respectively.

Over a range of particle sizes down to 20 nm, particle penetration through N95 and P100 filtering facepiece respirators and respirator cartridges (two models from each of four categories) was also examined in a recent study by the Battelle Memorial Institute,[63] to assess the effect of particle size and flow condition on measured penetration. The following trends were observed:

- Penetrations varied within respirator groups, i.e. within the group of P100 filters tested, and within the group of N95 filters tested.
- The MPPS for P100 cartridges was generally between 100-200 nm and shifted toward the lower end of this range with increased flow. The MPPS for the N95 cartridges was generally 50 to 100 nm for all

[xviii] IRSST has also published a complete guide to respirator selection and use.[60]

flow conditions, and the MPPS for both P100 and N95 filtering facepiece respirators was 50 to 100 nm.

- For 50 nm particles at flow rates of 85 l/min, mean particle penetrations ranged from <0.0001 % to 0.002 %, 0.7 % to 8.8 %, 0.01 % to 0.048 %, and 2.8 % to 9.7 % for P100 cartridges, N95 cartridges, P100 filtering facepiece respirators, and N95 filtering facepiece respirators, respectively.

The choice of respirator type will depend on the specific task and the materials being handled. It has been reported that a number of filter specifications are used by organizations working with nanomaterials.[11] Cartridge respirators with either a full face mask or a half mask are used by a number of organisations. Some organizations indicated that disposable particulate respirators are recommended for employee use while working with nanomaterials.[11] Some disposable particulate respirators are N/R/P/95/99/100 U. S. NIOSH-Certified filtering facepiece respirators, but some inexpensive masks might be largely untested and not certified by any recognized body. Masks and respirators that are not certified should not be relied upon for protection against nanoparticles. Users cannot be assured that they provide a certain level of protection.

It has been recommended that respirators should be used when handling powders (particularly when working with larger amounts), and for maintenance work on production machines.[7] An example of the use of respirators for sampling and data collection during a mixing operation is shown in Figure 7 below.[29] Individual airway protection equipment used in locations where nanomaterials are produced in the particulate form should be particularly efficient. Wearing a full-face mask with high-efficiency filters (over 99.97 % efficient) has been recommended by some.[7]

Figure 7 — Use of respirators for sampling and data collection during a mixing operation (from NIOSH Progress Toward Safe Nanotechnology in the Workplace[29]).

The frequency of cartridge change-out and/or facepiece respirator disposal should be carefully considered, and should occur before workers have difficulty breathing or can smell chemical vapors, or the filter is clogged. Change-out/disposal schedules should be more frequent at higher scales of production and among organizations that work with nanomaterials in the dry powder form.

Often, the determining factor which governs the effectiveness of Respiratory Protection Equipment (RPE) against particulate challenges is not absolute penetration through the filter, but rather face-seal leakage which bypasses the device. Face seal leakage is dependent on many factors including the fit of the mask to the face, duration of wearing and work activity. User comfort and equipment maintenance are also issues with RPE. Since it is expected that nanoparticle aerosols will have high mobility, it is possible that some leakage will occur, although no more than might be expected for a gas,[1] noting that aerosol particles attach firmly to any surface they contact.[30] Numerous studies on mask leakage have been conducted on larger particles and on gases/vapors. For example, work done by researchers at the U.S. Army RDECOM on a head-form showed that mask leakage (i.e., simulated respirator fit factor) measured using submicrometer aerosol challenges (720 nm polystyrene latex spheres) was representative of vapor challenges such as sulfur hexafluoride and isoamyl acetate.[67]

A higher level of protection is assured by using a Powered Air-Purifying Respirator (PAPR), which includes high-efficiency filtration and a pump supplying filtered air to a full-face mask.[7] The air current generated on the wearer's face might increase the level of protection by maintaining positive pressure inside the mask. This results in greater comfort for the worker and minimizes exposure when the mask seal is imperfect. In cases where the APF of the PAPR is insufficient, or where the concentration is Immediately Dangerous to Life or Health (IDLH), airline respirators or self-contained breathing apparatus are necessary.

7.3.8.2. Dermal protection

Dermal exposure might occur during the manufacturing, use and handling of nanoparticles. During nanomaterial manufacturing, exposure is most likely to occur in the product recovery and packaging stages, and from surface contamination e.g. during general maintenance of workplaces and equipment. Use of Skin Protective Equipment (SPE) is recommended where the possibility of dermal exposure cannot be excluded at all times. However, because of the small diameters of nanoparticles, the various kinds of SPE might have limited effectiveness. For example, research conducted under EU Nanosafe2 project (www.nanosafe.org/node/907) showed that nanoparticles might penetrate through commercially available gloves, and therefore, it is recommended to use at least two layers of gloves. Non-woven fabrics seem much more efficient against nanoparticle penetration. Thus, it is recommended that protective clothing made of cotton fabrics are not used (www.nanosafe.org/node/907).

Some soluble nanoparticle compounds can penetrate the skin by dissolution and absorption. However, certain insoluble nanoparticles could also penetrate the epidermis and possibly end up in the bloodstream, where they can travel throughout the body.[7] Currently, there is a very limited state of knowledge in regard to potential health risks, and no dermal exposure standards have been proposed. As a precaution, it is preferable to introduce controls to exclude or limit the level of dermal exposure likely to occur.

As for inhalation exposure, the UK's *Control of Substances Hazardous to Health Regulations 2002 (COSHH) (as amended)* provide a framework by which a strategy to prevent or control dermal exposure can be developed.[16] As with control of exposure by inhalation, the first approach is enclosure of the process, and powder handling processes can be enclosed successfully. However, in practice, particularly with products or processes which are in development, the main emphasis might be on investment in the design of safeguards during product synthesis. This might reduce the expenditure on sophisticated control and automation processes to deal with the relatively mundane tasks such as harvesting and packing of nanomaterials. Even where such processes are in place, the requirements for attention to equipment breakdowns and maintenance means that the possibility of dermal exposure cannot be excluded at all times. In these and other instances, protection against dermal exposure typically consists of the use of SPE, i.e. suits, gloves and other items of protective clothing.[1]

Clothing recommended by organizations working with nanomaterials for use by their employees or researchers is shown in Figure 8.[11] Lab coat materials include cotton, nylon and disposable material. Building suits (“bunny suit,” “coveralls”, “working suit”) are frequently disposable, and are recommended instead of lab coats for higher exposures. A range of glove materials are utilized, most often nitrile, latex, and rubber, with other materials including PVC, polyethylene, neoprene, and leather.[11] Long gloves that cover the wrists, double gloves, wrist barriers and gloves with cuffs are all used. Most organizations report their choice of gloves is based on the solvents being used, with choices based specifically on chemical compatibility. A number indicated that the use of glove types was application specific. Other forms of PPE used are hair bonnets and anti-static shoes in areas where there is concern about the explosive properties of the nanomaterials.

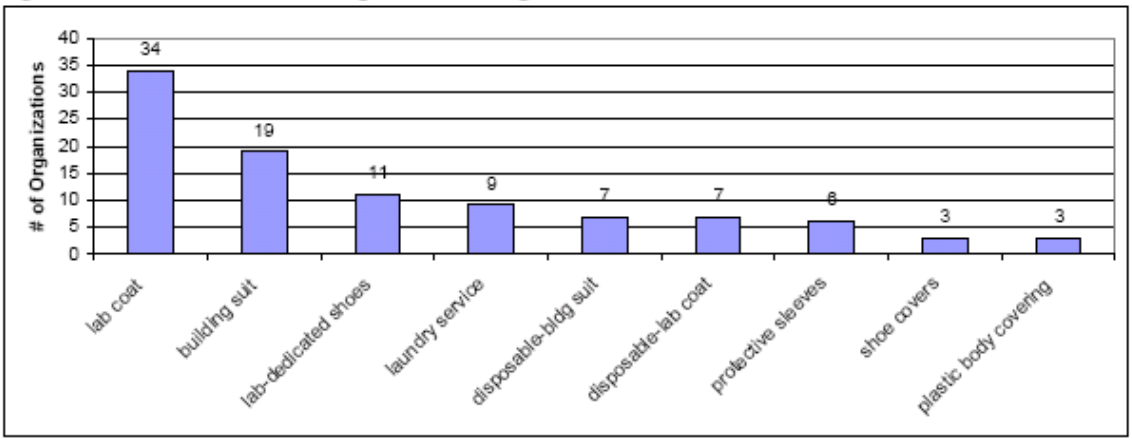


Figure 8 — Clothing recommended by organizations working with nanomaterials (from A Review of Current Practices in the Nanotechnology Industry[11]).

Maintenance of skin protection equipment is an important issue to consider. If in practice it proves difficult to maintain and clean SPE[xix], then there is the option to use disposable clothing, e.g. hooded coveralls, aprons and shoe covers which normally provide excellent skin protection[xx]. The same principle applies to gloves, which are available in a wide range of sizes and resistances to various chemicals, cuts and perforations. In general, deterioration of protective gloves occurs during use, and they need to be changed on a regular basis. Procedures should be in place for disposal of personal protective equipment (e.g gloves and coveralls). Also a procedure should be in place indicating the frequency of changing and washing non disposable personal protective equipment.

Considering the effectiveness of SPE, mechanisms whereby skin contamination might occur when using SPE have been described.[68] These mechanisms are: (i) penetration or permeation through the materials making up the SPE[xxi], (ii) the transfer of substances through direct contact between the SPE surfaces and the skin, (iv) transfer of substances by direct contact of skin with contaminated surfaces and (iv) redistribution of substances by skin to skin contact e.g. as a result of touching the face with contaminated fingers. Transport of contaminants through permeable clothing occurs by aerosol penetration and liquid transport. External air pressure and the “bellows effect” (i.e. the expulsion and entering of air during movement) can be considered to be the driving force for penetration of aerosols through fabric, whereas the mechanisms of liquid transport are capillary penetration, pressure penetration, impact penetration and evaporation-condensation. Mass transport through non-permeable clothing is a diffusion process driven by concentration.

Current European testing for certification of PPE against dermal exposure only takes account of permeation or penetration of the material. However, recently, new tests have been proposed which take account of human factors,[69] involving real workplace SPE performance tests and/or workplace simulations.

Even for powders above 100 nm in size, it is recognized that SPE is limited in its effectiveness to reduce or control dermal exposure.[5] The penetration efficiency (i.e. % penetration) for 10 widely different fabrics (including woven, non-woven, and laminated fabrics) against an aerosol of polystyrene latex spheres with a mean diameter of 477 nm has been examined.[70] Particle penetration measurements ranged from 0 % to 54 %, with the three fabrics exhibiting significant pressure drop (i.e. the least air permeable) all having penetration levels less than 1 %. No information on either the efficacy of SPE against direct penetration of nanoparticles, or the impact of nanoparticles on the probability of failure of SPE due to human factors has been identified. However, some existing clothing standards already incorporate testing with nanometer-sized particles, and therefore provide some indication of the effectiveness of protective clothing to nanoparticles. For

[xix] SPE made from breathable laminates might offer the possibility of washing and re-use for some applications.
[xx] From an environmental viewpoint, use of disposable clothing will probably result in clothing and nanoparticles ending up in landfill, as opposed to nanoparticles ending up in waste water from washing processes.
[xxi] Noting also that actions such as flexing of the material can impact on particle penetration

instance, ASTM standard F1671–03 specifies the use of a 27 nm bacteriophage to evaluate the resistance of materials used in protective clothing from the penetration of bloodborne pathogens.[71]

It has been suggested that penetration of SPE by nanoparticles is likely to be even greater than by larger particles.[7] It has also been proposed that, since it is likely that nanoparticles which escape into the workplace will become widely dispersed, it is likely that the human factor element will be even more critical than for macro size particles,[1] further contributing to SPE being less effective against nanoparticles than against macro size particles.

7.3.8.3. Eye protection

Eye protection is recommended where there is potential for exposure to nanomaterials. Goggles, safety glasses and full-face shields are all used in practice,[11] though the use of a full-face shield was not always recommended for reasons related to the handling of nanomaterials specifically (e.g. it was also recommended when there is increased exposure to solvents or hot material). One organization does not allow the use of contact lenses in the laboratory.

Full facepiece respirators offer eye protection in addition to respiratory protection. They also allow the use of corrective lenses or contact lenses.

7.3.8.4. Preventing ingestion exposure

It is considered that ingestion exposure in the workplace results primarily from hand-to-mouth contact, but might also occur via the mucociliary escalator after inhalation.[2] Ingestion could also occur from swallowing particles trapped in the head airways region. It follows that strategies which tend to reduce dermal exposure to nanomaterials in the workplace will also tend to reduce exposure by ingestion.

7.4. Health surveillance

Health surveillance should be considered for all workers where there is risk of exposure to nanoparticles, and where it has been demonstrated that there is a relationship between exposure to the substance and a measurable biological indicator. It is strongly recommended that a health surveillance program is established for workers if nanoparticles contain chemicals or components for which current guidelines recommend health surveillance.

Given that exposure to very low concentrations of nanoparticles might be widespread, measurable changes in biological indicators from baseline levels, rather than comparison of body burden with the Biological Exposure Index (BEI), might be the most appropriate parameter to examine. The use of health surveillance in this context is as an indicator of whether exposure is occurring, rather than in determining that levels of exposure are safe. Due to the currently limited capability for measuring airborne concentrations of nanoparticles, the use of biological indicators might be a very useful approach in evaluating the effectiveness of control measures introduced.

At this stage, where the impact of nanoparticles on human health is unclear, continuous health checks for workers are particularly important to detect any adverse effects from nanoparticles. Health check records are important evidence in identifying adverse health effects.

It is recommended that a basic worker health monitoring program is established.[72] Such a program should include at a minimum:

1. identifying staff (nanoparticles workers) exposed to engineered nanoparticles of unknown health effects;
2. conducting workplace characterization and worker exposure assessments;
3. providing nanoparticles workers with “baseline” medical evaluations and including them in a nonspecific routine health monitoring program.[72]

It is recommended to ensure that engineered nanoparticle workers are offered periodic medical evaluations that might include routine tests such as pulmonary, renal, liver, and hematopoietic function testing.[72]

7.5. Product stewardship

The types of guidance information provided by organizations supplying nanomaterials to customers are listed below, with the most common form of guidance being the MSDS:[11]

- Material safety data sheets (MSDS);
- Product information sheets;
- Technical instructions;
- Personal interaction;
- Accompanying letter;
- Technical data sheets;
- Specification sheets;
- Certificates of analysis;
- Operation manuals.

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Useful links

Australian Safety & Compensation Council (ASCC). http://www.ascc.gov.au/

DIN. German Institute for Standardization. http://www2.din.de/index.php?lang=en

EPA (US). http://www.epa.gov/

HSE Horizons Scanning - Nanotechnology (UK). http://www.hse.gov.uk/horizons/nanotech.htm

Industrial Technology Research Institute – ITRI (Taiwan) http://www.itri.org.tw/eng/index.jsp

IRSST (Canada) http://www.irsst.qc.ca/en/home.html

NIOSH Nanotechnology (US). http://www.cdc.gov/niosh/topics/nanotech/

OSHA (US). www.osha.gov

SUVA (Switzerland). http://www.suva.ch/en/home_en

Appendix 7.1. Assigned protection factors (APFs) for respirators (from USACHPPM 55-011-1106).[56] A comparison of past and present APFs.[xxii]

Type of Respirator	OSHA 29 CFR 1910.134 (2006)[58]	NIOSH Decision Logic (2004)[59]	ANSI Z88.2 (1992)[73,b]
APR - quarter mask	5	5	10
APR - filtering facepeice	10	10	10
APR - tight fitting half mask	10	10	10
APR-tight fitting full face (if part. filter ≠ N-P-R 100)	50	10	100
APR-tight fitting full face (if part. filter = N-P-R 100)	50	50	100
PAPR - tight fitting half mask	50	50	50
PAPR - tight fitting full facepeice	1000	50	1000[c]
PAPR - helmet/hood	25/1000[a]	25	1000[c]
PAPR - loose fitting	25	25	25
SAR - demand mode - half mask	10	10	10
SAR - demand mode - full facepiece	50	50	100
SAR - continuous flow - half mask	50	50	50
SAR - continuous flow - full facepiece	1000	50	1000
SAR - continuous flow - helmet/hood	25/1000[a]	25	1000
SAR - continuous flow - loose fitting	25	25	25
SAR - pressure demand - half mask	50	1000	50
SAR - pressure demand - full facepiece	1000	2000	1000
Combo SAR/SCBA - pressure demand - full facepiece	----	10000	----
SCBA - demand mode - half mask	10	----	10
SCBA - demand mode - full facepiece	50	50	100
SCBA - demand mode - helmet/hood	50	----	----
SCBA - pressure demand - full facepiece	10000	10000	10000[d]
SCBA - pressure demand - helmet/hood	10000	----	----
[a]Employer must have evidence provided by manufacturer that testing these devices demonstrates performance at a level of protection of 1000 or greater.			
[b]Rescinded in 2003.			
[c]For HEPA filter if used for particulate protection; if less than HEPA, APF=100.			
[d]For emergency planning purposes only.			

[xxii] The U. S. NIOSH assigned protection factor (APF) is defined as the minimum anticipated protection provided by a properly functioning respirator or class of respirators to a given percentage of properly fitted and trained users.[59] The APF values developed by U. S. NIOSH are based in part on laboratory studies and take into consideration a variety of factors including the inward leakage caused by penetration through the filter and leakage around the face seal of the respirator. Numerically, an APF of 10 for a respirator means that a user could expect to inhale no more than 10 % of the airborne contaminant present, whilst an APF of 100 means user could expect to inhale no more than 1 % of the airborne contaminant.

Appendix 7.2. Advantages and disadvantages of different types of Air-Purifying Particulate Respirators - using information from the U. S. NIOSH Respirator Selection Logic.[59]

Respirator type		Advantages	Disadvantages
Filtering facepiece (disposable)		– Lightweight – No maintenance or cleaning needed – No effect on mobility	– Provides no eye protection – Can add to heat burden – Inward leakage at gaps in face seal – Some do not have adjustable head straps – Difficult for a user to do a seal check – Level of protection varies greatly among models – Communication might be difficult – Fit testing required to select proper facepiece size – Some eyewear might interfere with the fit – Respirator must be replaced whenever it is soiled, damaged or has noticeably increased breathing resistance.
Elastomeric half-facepiece		– Low maintenance – Reusable facepiece and replaceable filters and cartridges – No effect on mobility	– Provides no eye protection – Can add to heat burden – Inward leakage at gaps in face seal – Communication might be difficult – Fit testing required to select proper facepiece size – Some eyewear might interfere with the fit
Powered with loose-fitting facepiece		– Provides eye protection – Protection for people with beards, missing dentures or facial scars – Low breathing resistance – Flowing air creates cooling effect – Face seal leakage is generally outward – Fit testing is not required – Prescription glasses can be worn – Communication less difficult than with elastomeric half-facepiece or full-facepiece respirators – Reusable components and replaceable filters	– Added weight of battery and blower – Awkward for some tasks – Battery requires charging – Air flow must be tested with flow device before use
Elastomeric full-facepiece with N-100, R-100, or P-100 filters		– Provides eye protection – Low maintenance – Reusable facepiece and replaceable filters and cartridges – No effect on mobility – More effective face seal than that of filtering facepiece or elastomeric half-facepiece respirators	– Can add to heat burden – Diminished field-of-vision compared to half-facepiece – Inward leakage at gaps in face seal – Fit testing required to select proper facepiece size – Facepiece lens can fog without nose cup or lens treatment – Spectacle kit needed for people who wear corrective glasses
Powered with tight-fitting half-facepiece or full-facepiece		– Provides eye protection with full-facepiece – Low breathing resistance – Face seal leakage is generally outward – Flowing air creates cooling effect – Reusable components and replaceable filters	– Added weight of battery and blower – Awkward for some tasks – No eye protection with half-facepiece – Fit testing required to select proper facepiece size – Battery requires charging – Communication might be difficult – Spectacle kit needed for people who wear corrective glasses with full face-piece respirators – Air flow must be tested with flow device before use

Annex A. Symbols and abbreviated terms

ACGIH	American Conference of Governmental Industrial Hygienists
AIDS	Acquired immune deficiency syndrome
ANSI	American National Standards Institute
APF	Assigned Protection Factor
APR	Air-Purifying Respirator
ASCC	Australian Safety & Compensation Council
ATSDR	U. S. Agency for Toxic Substances and Disease Registry
BAuA	German Federal Institute for Occupational Safety and Health
BEI	Biological Exposure Index
BET	Brunauer-Emmett-Teller

BMD	Benchmark Dose
BSC	Biological Safety Cabinet
CEN	European Committee for Standardization
CNF	Carbon nanofiber
CNT	Carbon nanotube
COSHH	Control of substances hazardous to health
CPC	Condensation Particle Counter
DC	Diffusion Charger
DEMS	Differential Electrical Mobility Sizer
DIN	German Institute for Standardization
DMAS	Differential Mobility Analysing System
DNA	Deoxyribonucleic acid
DOE	U. S. Department of Energy
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
EPA	U. S. Environmental Protection Agency
GI	Gastro-intestinal
GSD	Geometric Standard Deviation
HEI	Health Effects Institute
HEPA	High Efficiency Particulate Air filter
HSE	U. K. Health and Safety Executive
HSL	U. K. Health and Safety Laboratory
HVAC	Heating, Ventilation and Air Conditioning
EHS	Environment, Health and Safety
ELPI™	Electrical Low Pressure Impactor
ICON	International Council on Nanotechnology
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
ICRP	International Commission on Radiological Protection
ICSC	International Chemical Safety Cards
IDLH	Immediately Dangerous to Life or Health
ILO	International Labor Organization
ILSI	International Life Sciences Institute
IRSST	Canadian Institut de recherche Robert-Sauvé en santé et en sécurité du travail
ISO	International Organization for Standardization
LEV	Local Exhaust Ventilation
LPI	Low Pressure Impactor
MCDA	Multi-criteria Decision Analysis
MMAD	Mass Median Aerodynamic Diameter
MPPS	Most Penetrating Particle Size
MSDS	Materials Safety Data Sheet
NIOSH	U. S. National Institute for Occupational Safety and Health
NMAM	U. S. NIOSH Manual of Analytical Methods
NOAEL	No-Observed-Adverse-Effect Level
NOHSC	Australian National Occupational Health and Safety Commission
OECD	Organization for Economic Cooperation and Development
OSHA	U. S. Occupational Safety and Health Administration
PAPR	Powered Air-Purifying Respirator
PPE	Personal Protective Equipment
PTFE	Polytetrafluoroethylene
RDECOM	Research, Development and Engineering Command
RPE	Respiratory Protection Equipment
SAR	Supplied-Air Respirator
SCBA	Self-Contained Breathing Apparatus
SCENIHR	E. C. Scientific Committee on Emerging and Newly Identified Health Risks
SEM	Scanning Electron Microscopy
SOP	Standard Operating Procedures
SPE	Skin Protective Equipment
SUVA	Swiss National Accident Insurance Organization
SWCNT	Single-Walled carbon nanotube
TEM	Transmission Electron Microscopy

TEOM	Tapered Element Oscillating Microbalance
TR	Technical Report
UN	United Nations
USACHPPM	U. S. Army Center for Health Promotion and Preventive Medicine
WHO	World Health Organization

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