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Nanoparticles: Actual knowledge about occupational health and safety risks and prevention measures

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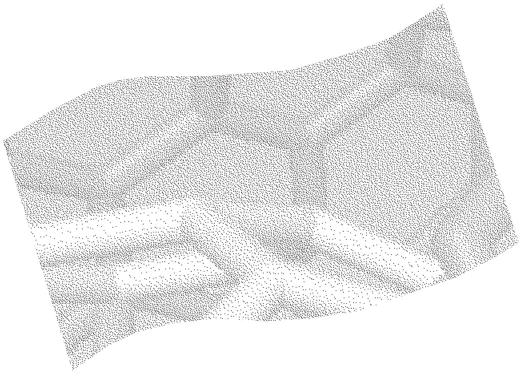
Actual Knowledge about Occupational Health and Safety Risks and Prevention Measures



STUDIES AND RESEARCH PROJECTS

REPORT

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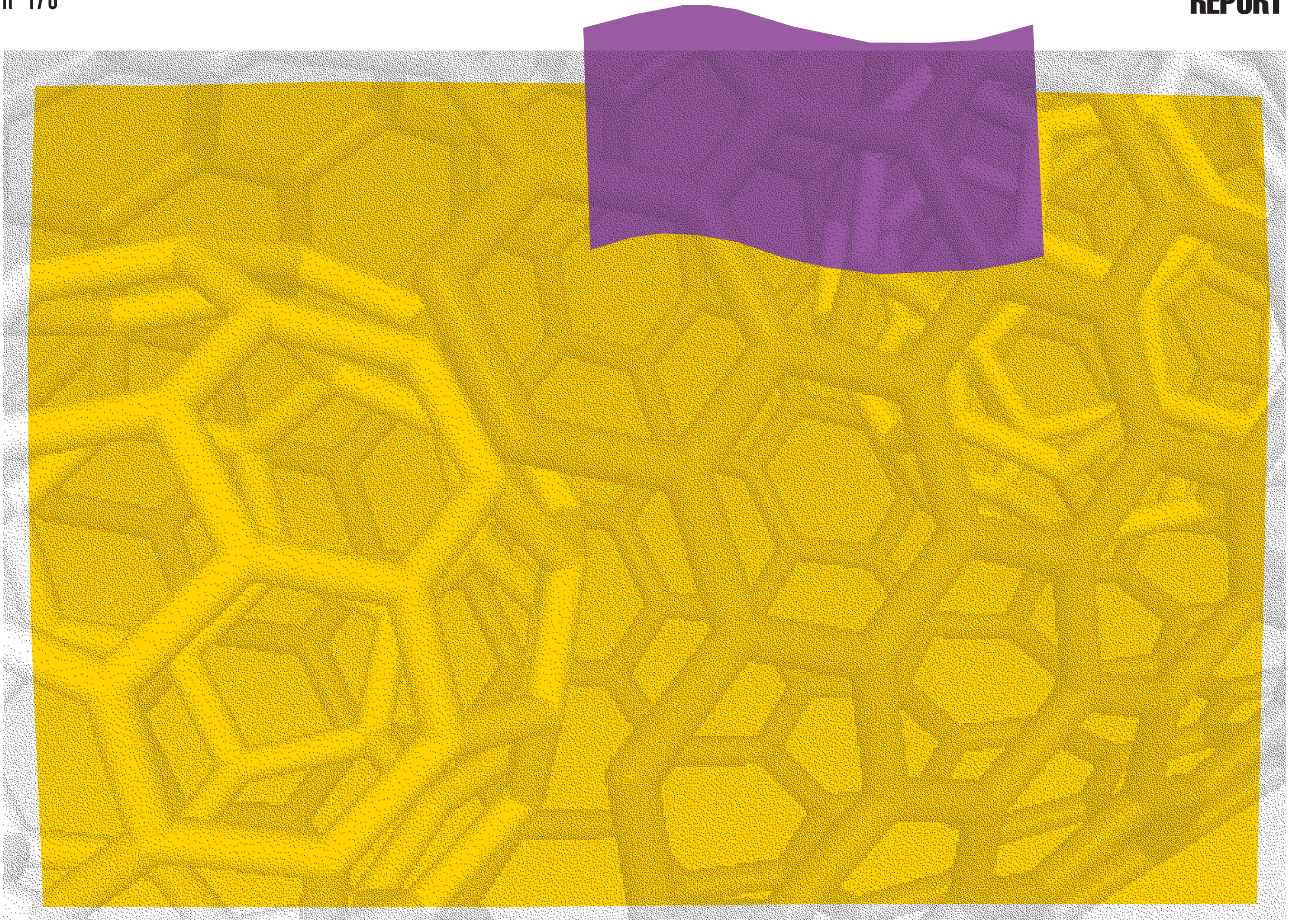
R-470



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Actual Knowledge about Occupational Health and Safety Risks and Prevention Measures

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STUDIES AND RESEARCH PROJECTS

REPORT

This document is a complete translation from the IRSST Report R-455 :
« Les nanoparticules : connaissances actuelles sur les risques et les mesures de prévention en santé et en sécurité du travail »

This study was financed by the IRSST. The conclusions and recommendations are those of the authors.

SUMMARY

New materials with unique properties

A new industrial revolution based on nanotechnologies is underway. The enthusiasm for these technologies is sweeping the planet, generating several billions of dollars of investment annually in research and development (R&D). Using current technologies, we can handle materials and synthesize products at the atomic level; nanoparticles demonstrate properties that are completely different from products with the same composition but larger dimensions. The era of nanomaterials and nanotechnologies promises to be one of major scientific developments and breakthroughs that in the not too distant future will permanently affect our everyday lives. Several of these products are already being used and many organizations foresee annual world markets, beginning in 2015, of the order of US 1,000 billion dollars. Welcome to the nanoworld, where everything occurs at the level of the nanometre (nm), that is, a billionth of a meter (10^{-9} m).

Nanotechnologies cover a broad, multidisciplinary field in which, globally, research activity and the setting up of industries have grown extremely rapidly over the last decade. Physicists, chemists, biologists, engineers, electronics technicians and various experts specializing in materials, processes and applications are working together on objects of nanometric proportions. Nanoparticles can be produced by a whole series of chemical, physical or biological processes, some of which are totally new and innovative, while others have existed for a very long time.

New technologies allow us to build new materials, atom by atom. This often endows the materials with properties that are very different from ordinary materials. Nanoparticles and nanotechnologies do not simply represent another step towards miniaturization. At the “nano” level, the behaviour of particles is dominated by quantal effects. The particles may be confined to a small structure, distributed over large surfaces or demonstrate an entire series of unique phenomena and properties not encountered in larger materials.

We need to bring together existing knowledge

The main objective of the present assessment is to bring together current scientific knowledge on nanoparticles, while paying special attention to their health risks and to ways of protecting Quebec workers from exposure to nanoparticles produced in new ways. Our review takes into account the new nanoparticles (carbon nanotubes, fullerenes, quantum dots, nanopigments of titanium dioxide and certain metals of nanometric dimensions) but excludes products of nanometric dimensions generated by combustion during various industrial processes (diesel exhaust emissions, soldering fumes and fumes from various industrial processes), and products of nanometric dimensions already manufactured on a large scale, such as silica fumes.

Developing new products

Research pertaining to the production, marketing and use of the new nanomaterials is extremely important and is a vehicle for the strategic objectives of sustainable economic development, especially in Asia, Europe, the United States, Canada and Quebec. Potential uses for nanoparticles are foreseen in a wide variety of sectors, including the biomedical field, the

metallurgical industry, agriculture, textiles, coatings, cosmetics, energy, catalysts and electronics, etc. Chemical-resistant materials, self-cleaning windows, medication transmitted directly to affected sites and graffiti-resistant paintings constitute but a few possible applications.

Hundreds of Quebec workers may already have been exposed

In Quebec, there are about 200 professor-scholars active in the field and over 1000 students dispersed among almost all the universities, certain CEGEPS and several research centres. Most of these individuals have potentially been exposed to nanoparticles. About forty Quebec firms are either currently active in the production of nanomaterials or are in the introductory phase. This is four times as many as there were barely three years ago. We must also take into account that Quebec imports nanoparticles for use in a variety of sectors, including textiles, where workers and users have already been exposed.

The principal health impacts

While research on developing new products, setting up industries and marketing has been bubbling over with excitement for more than a decade, research aiming to improve our understanding of the health impacts of occupational exposure, and of the links between nanoparticles and industrial safety, are far less advanced. Nonetheless, there is a body of knowledge clearly demonstrating that nanometric particles are more toxic than larger particles (with micrometric dimensions) of the same substance. Thus, this data supports the recommendation that we should treat nanoparticles of a particular substance as a new product with its own toxicity.

The principal way these particles are absorbed in an occupational setting is via the respiratory route, as are other dusts. Toxicological studies clearly demonstrate that the very small size of nanoparticles plays a key role in its toxicity, especially when the particles are non-soluble or only slightly soluble. First, the location in the lungs where they are deposited varies greatly and is a function of the granulometry of the particle. Thus, particles measuring one nm cannot reach the pulmonary alveoli; they are deposited in the upper regions of the lungs. Particles measuring five nm are deposited relatively evenly in the nose and pharynx, the windpipe and bronchial tubes and, lastly, the alveoli. More than 50% of nanoparticles measuring 20 nm are deposited in the alveoli. Second, toxicological studies have shown that the toxicity of a nanoparticle is related to the surface area of the particle, not to its mass. Third, surface properties, the ability to induce free radicals and the ability to release certain ions can also have a considerable influence on toxicity. Several pulmonary effects have been documented, including the ability of certain nanoparticles to induce pulmonary granuloma. Currently available data seems to indicate that absorption through the skin is limited.

Translocation, that is, the ability to move to other sites in the body, is another important characteristic of insoluble nanoparticles. The latter are able to traverse the pulmonary epithelium and reach interstitial sites; they then enter the bloodstream, which distributes them throughout the body. These particles can even go directly to the brain, though they take a variety of routes; nanoparticles that are caught in the nose go to the brain via the olfactory nerve. Nanoparticles can even cross intestinal, cellular and placental barriers. The pharmaceutical field is pinning many of its hopes for therapy on the fact that certain nanoparticles are able to cross the blood-brain barrier and enter the brain directly.

Certain nanoparticles modify blood parameters and accumulate in particular organs, including the liver and the spleen. Epidemiological studies reveal a significant correlation between the rate of mortality due to cardiorespiratory disease and the content of particles of nanometric dimensions present during air pollution episodes.

Quantitative evaluation of the health risk to workers

The significant lack of scientific knowledge obliges us to confront a major uncertainty concerning the risks raised by nanoparticles. Currently, in spite of the fact that numerous toxic effects on animals have been demonstrated, quantitative evaluation of the risks associated with any of the new nanomaterials is almost impossible to carry out. Nonetheless, toxicological research is underway and several of its results have already been published. One IRSST report (Ostiguy et al., 2006) details all listed toxicological knowledge specific to nanoparticles.

Synthesizing nanoparticles

Four major processes are employed in synthesizing the new nanoparticles: gaseous phase, vapour deposition, wet chemistry and grinding. Several of the processes for producing nanoparticles are similar to existing chemical production processes.

Limits to current knowledge

In considering the occupational health and safety risks related to nanoparticles, currently available information allows us to conclude that:

- the four principal production processes can result in occupational exposure by way of the pulmonary, cutaneous and ingestion routes;
- gaseous phase processes present the greatest potential for exposure during the nanoparticle synthesis stage. On the other hand, all of the processes may result in exposing the worker via the three absorption routes; the exposure occurs during the stages of recovery, bagging and manipulation of powders, which often consist of one or another of the agglomerated nanoparticles;
- to avoid the aggregation of particles, several processes include a post-synthesis stage designed to modify the particle surface, frequently by covering it with another organic or inorganic substance; this operation has an impact on the toxicity of the nanoparticle;
- at present, the tools normally used in industrial hygiene to evaluate the exposure of workers are ill suited to the applications of nanoparticles in an occupational setting. Currently, the data found in the literature cannot be used to estimate the exposure of researchers, students and workers. The little data available suggests that exposure during the manipulation of powders may be considerable.
- current scientific knowledge on nanoparticle toxicity is inadequate for carrying out quantitative risk assessment.

- due to their large specific surface area, several nanoparticles have significant reactivity potential that can result in fires or explosions; specific preventive measures must be introduced to avoid these kinds of events.

Several research organizations working in occupational health and safety or in environment such as the National Institute for Occupational Safety and Health (NIOSH) and the Environmental Protection Agency (EPA) in the United States, the Health and Safety Executive (HSE) in England and the Institut National de Recherche et de Sécurité (INRS) in France are presently carrying out research to develop new knowledge to facilitate quantitative risk assessment for worker exposure.

Much research is still needed to fully understand the effects of human exposure to nanoparticles. It should allow us to fill several major gaps in our knowledge, since:

a) current knowledge on the toxicity and means of absorption of these products is very limited;
b) tools allowing us to evaluate occupational exposure must be adapted to the required measurement characteristics based on nanoparticle toxicity;
c) we need to measure real life exposure;
d) the effectiveness of the means of control and of body coverings must be evaluated.

Prevention is the key

There are several unknown factors in controlling occupational exposure to nanoparticles. Existing approaches such as respiratory protection during inhalation should be effective, but their effectiveness remains to be proved. Controlling exposure through ventilation at source, or through general ventilation, is difficult since nanoparticles tend to behave like gases rather than solids. The practical effectiveness of these kinds of systems must be carefully documented. There is almost no data on personal protection along the cutaneous route. Disposable clothing of the Tyvek® type is recommended in environments where methods employing other existing personal protective equipment do not provide adequate protection. High–efficiency chemical cartridges should provide effective respiratory protection.

Even in the absence of the body of knowledge needed to evaluate the risk, and to assess the effectiveness of the available means of control, several countries have begun to legislate to protect workers from potential exposure. In so doing they hope to prevent an increase in occupational disease. Until the impact of these products on the environment and humans is adequately documented, strict preventive measures should be taken as a precaution to limit emissions, both within and outside of the work environment.

Conclusion

While much research is underway to develop and market nanoparticles, research designed to evaluate the potential risks of these products for nanotechnology workers is still in its early stages. Information currently available suggests that these products might be toxic and that current protection methods might not be as effective as previously thought. NanoQuebec estimates that in Quebec alone about 2000 persons, mainly in the academic community, work with nanomaterials, making the group the largest population potentially exposed to these materials. The pace of growth in this industry is accelerating, and Quebec now has about four times as many companies as it did barely three years ago. Nanoparticles are also imported, though we have very little information either on the way they are used or on the conditions in which they are implemented and the workers exposed.

Recommended follow-up

To prevent an increase in occupational disease, the introduction of strict preventive measures should be promoted among all of these clienteles. The evaluation of occupational exposure should be documented. It would be advisable to regularly monitor the progress of scientific knowledge related to the toxicology and industrial hygiene. This would be an effective way of informing and providing support for Quebec workers — as part of the objective of preventing an increase in nanoparticle-related occupational disease.

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1. INTRODUCTION

The prefix *nano* means a billionth (10^{-9}). Thus, a nanometre (nm) is a billionth of a metre. Nanotechnology is concerned with the creation or manipulation of particles and materials whose minimum dimensions are nanometric, though normally less than 100 nm. These materials may be produced from the structured organization of groups of atoms and molecules or by reducing macroscopic materials to a nanometric scale (Aitken *et al.*, 2004).

While the development of nanotechnologies is a very modern, multidisciplinary science, the manufacture of nanomaterials, both by nature and by humans, dates from time immemorial. Indeed, several natural structures, including proteins and the DNA diameter fit the above definition of nanomaterials, while viruses represent the smallest naturally occurring functional nano-objects. To illustrate the orders of magnitude involved, the diameter of a DNA molecule is of the order of 2 to 12 nanometres (nm), a red blood cell has a diameter of 5,000 nm and a human hair a diameter 10,000 to 50,000 nm (www.nano.gov). Romans in the pre-Christian era were already introducing metals with nanometric dimensions in glass-making; a cup describing the death of King Lycurgus (circa 800 BC) contains nanoparticles of silver and gold; when a light source is placed inside the cup, its colour changes from green to red (Poole and Owens, 2003). The colours of certain Mayan paintings stem from the presence of metallic nanoparticles, as does the lustre of Italian Renaissance pottery (Ambassade de France, 2004). The stained-glass windows of the great medieval cathedrals also contain metallic nanoparticles. Photography, which was developed in the 18th and 19th centuries, provides a more recent example of the use of nanoparticles, which in this example is made up of particles of silver sensitive to light (Poole and Owens, 2003; Ratner and Ratner, 2003).

Due to their low granulometry, many condensation products deriving from the combustion process contain nanoparticles; these include diesel gases, industrial furnace emissions and welding fumes. In 1993 alone, synthesis through flame pyrolysis of six million tonnes of carbon black with a high specific surface area produced carbon powder of nanometric dimensions (IARC, 1996). Combustion or flame pyrolysis is also used in the mass production of silica fume, ultrafine titanium dioxide particles and ultrafine metal particles, all of nanometric dimensions (Aitken *et al.*, 2004). In addition, the definition of nanoparticles based on size, allows us to include colloids and soils that have been used for over a hundred years. In 1857, Faraday, had already described the use of colloidal gold in his experiments (Aitken et al., 2004). Since then, colloidal science has evolved a lot. The new colloids are used in the production of metals, oxides and organic and pharmaceutical products. Given this broad definition, it is important to home in on the subject-matter of our inquiry.

In 1960, Richard Feynman, the 1965 Nobel prizewinner in Physics, began speculating on the possibilities and potential of nanometric materials, and on the fact that the manipulation of individual atoms could allow us to create very small structures whose properties would be very different from larger structures with the same composition. With the major technological developments of recent decades, it has now become possible to manipulate atoms one by one. It has been demonstrated that these structures do, in effect, have unique properties, which accounts for the interest in research in this field, especially over the last decade. Articles describing nanomaterials may be divided into two major categories (Kohler and Fritzsche, 2004; Holister *et al.*, 2003): a) those that are produced by collecting individual atoms; this is the bottom-up approach, and b) those that are produced by subdividing bulk materials into nanometric sizes; this is the top-down approach. In both cases, their dimensions are smaller than the critical length characterizing most physical phenomena, and this is what gives them their unique properties.

Nanomaterials often demonstrate characteristics such as extraordinary strength or unsuspected electrical, physical or chemical properties that are completely different from those demonstrated by the same products with larger dimensions. The fields with current commercial uses and producing the greatest revenue are mechanico-chemical polishing, magnetic recording tapes, sunscreens, automotive catalyst supports, bio-labeling, electroconductive coatings and optical fibers. The biomedical and pharmaceutical fields, electronics, metallurgy, agriculture, textiles, coatings, cosmetics, energy and catalysts are other sectors with growing applications (www.Nano.gov/html/facts/appsprod.html). Roco (2004) maintains that we are already in the second generation of the nanotechnology age. The first generation dealt with passive nanostructures such as coatings, nanoparticles, nanostructured metals, polymers and ceramics. The current generation deals with active nanostructures such as transistors, amplifiers, targeted drugs and adaptive structures.

Many observers think that nanoparticles and nanotechnologies will constitute the focus of the next industrial revolution. Research in the field is growing very rapidly and all industrialized countries see potential for expansion and applications in numerous fields as well as colossal potential economic spin-offs. Governments and large companies are developing strategies and investing massively in research. For example, Europe has made nanotechnology one of its seven priority project-oriented research areas and is investing 1.3 billion Euros in it for the 2002-2006 period (www.cordis.lu/nmp/home.html). In the United States, the National Nanotechnology Initiative (NNI) budget for 2005 alone amounted to a billion dollars (www.nano.gov). The Government of Canada is currently building a research centre in Alberta that will be dedicated exclusively to nanotechnologies. The federal government is also preparing a national nanotechnology plan. Quebec has set up NanoQuebec to support the transfer and marketing of applications developed in universities, and to increase the use of nanotechnologies in research on problems encountered by Quebec companies in all industrial sectors (http://nanoquebec.ca/nanoquebec_w/site/index.jsp).

Unfortunately, only a very small proportion of research on nanoparticles is concerned with its occupational health and safety risks, or with its threat to the environment and the health of populations. The field of nanomaterials and nanotechnologies cannot be covered exhaustively because it is too vast, too multidisciplinary and is changing too rapidly. Nevertheless, the present report, which is based on a literature review extending to June 2005, is designed to provide an overall portrait of nanomaterials and nanotechnologies as well as their main potential applications. It places special emphasis on the situation in Quebec, the known risks to the health and safety of workers and prevention. Rapid technological changes have already facilitated the start-up of about forty nanotechnology companies in Quebec (http://nanoquebec.ca/nanoquebec_w/site/index.jsp). Further efforts must be made in the area of health and safety know-how transfer to effectively support Quebec companies and research teams investigating ways to protect the health and safety of workers producing or using these substances.

2. OBJECTIVES

Nanoparticles can be produced by biological, chemical or physical processes. Several of these processes have been known for a long time, while others are new technologies. Nanoscience may be defined as knowledge and know-how at the atomic and molecular level – involving measuring, observing, predicting and producing – that exploits the new properties that characterize this level. Current research aims to produce new nanoparticles that demonstrate unique properties.

The main objective of the present study is to assess current scientific knowledge of nanoparticles -- produced by either existing technologies or new technologies – to produce new materials. The present study will restrict its focus to an examination of the new categories of nanoparticles. It will place special emphasis on identifying health risks and on methods of prevention that must be implemented if we wish to prevent the spread of occupational disease in the Quebec workplace. An additional goal of the study is to develop Quebec’s expertise in occupational safety and health (OSH) with regard to nanoproduction and nanoparticles. This expertise will provide an effective way to support research teams and companies synthesizing or using these products.

3. METHODOLOGY

While working out the protocol for the present assessment, the authors perused the available information on nanoparticles. They saw that there was a limited number of studies in the scientific literature facilitating estimates of risks. There was also a very limited ability to determine worker exposure to nanoparticules using the new methods. Consequently, they decided to conduct their assessment based on:

- analysis of the scientific literature that uses approaches commonly used for this type of research; these approaches are found in journals with peer committees. The IRSST Information Library and the CSST Information Resource Centre conducted the literature search. The principal data banks and search engines consulted were MedLine, Toxline, PubMed, Inspec, Coppernic, Embase, Ntis, Ei, Compendex, SciSearch, Pascal, Alerts, Teoma and Scirus. A number of keywords (in both French and English) were used, including nanotoxicology, nanotechnology, nanoparticle, nanomaterial, health effects, toxicity and toxic. This information was particularly useful in documenting the toxicity of nanoparticles;
- an Internet search, primarily to document (i) the types of processes facilitating the manufacture of these products, and (ii) the description of these products, their properties and their potential uses;
- the use of scientific reviews by recognized committees of international experts in the fields of nanoparticles and nanotechnology;
- information collected from Quebeckers directly involved in the nanotechnology field;
- discussions with the editorial committee of the report.

4. TERMINOLOGY, CLASSIFICATION, CHARACTERISTICS AND PROPERTIES OF NANOPARTICLES

4.1 Terminology

In industrial hygiene, the size of particles forming a solid aerosol is very important, because the behaviour of particles in the air, the exposure control strategies and the possibility of breathing in these particles, which can then be deposited at various locations in the pulmonary system are directly related to the aerodynamic behaviour of these particles, and thus to their dimensions. Thus, document EN 481 of the European Committee for Standardization (1993) gives clear consensus definitions of inhalable, respirable and thoracic dusts.

However, the scientific literature related to the nanoparticle field does not currently allow a single definition to be reached regarding the dimensions of these particles. Moreover, while ultrafine particles and nanoparticles occupy comparable granulometric domains, each author proposes a range of different dimensions (Brouwer, 2004; Jacobson and Seinfeld, 2004). Nonetheless, the majority of authors consider that nanoparticles are smaller than 100 nm. With such a broad definition, nanoparticles could be classified in three main categories: nanoparticles of natural origin, those already produced for decades in large quantities, and finally, those produced by new technologies. The European Commission (2004b) proposed that a distinction at least be made between free nanoparticles (those that will be discussed in this document) and bonded particles, which are less likely to cause health risks due to their inability to be bioavailable.

Among the nanoparticles of natural origin, some are of biological origin, including DNA with a diameter of around 2.5 nm and some viruses (10 to 60 nm) and bacteria (30 nm to 10 µm), while others are of mineral or environmental origin. For example, these include the fine fraction of desert sand, oil fumes, smog, fumes originating from volcanic activity or from forest fires, and certain atmospheric dusts. Among the nanoparticles of human origin, some well-known industrial processes, such as synthesis of carbon black by flame pyrolysis, result in highly agglomerated particles, the basic components of which have nanometric dimensions (IARC 1996). Other materials are also produced on a large scale for commercial purposes by high-temperature processes. For example, silica fume, ultrafine titanium oxide particles and ultrafine metals (Aitken *et al.*, 2004; Teague 2004). Flame hydrolysis and plasma deposition processes are already commonly used in the metal recovery industry. Paint pigments often have dimensions of 80 to 100 nm. Moreover, welding generates a plume of fumes, the elementary particles of which have dimensions of 10 to 50 nm before agglomeration. Combustion processes (diesel, gasoline, barbecue, coal and several industrial processes) also produce nanoparticles of 7 to 40 nm (Teague, 2004).

Many major existing applications use nanometric particles derived from conventional chemical processes. For example, the automobile sector uses catalytic converters based on recovery of precious metals, such as platinum or palladium, which presents large specific surface areas. This allows rapid and efficient combustion of vehicle exhaust gases. Nanoparticles derived from clay strengthen and increase the resistance of plastic widely used in manufacturing composites. Such composites are already found in the exterior panels of road vehicles, bumpers, underbodies or dashboards, etc. Zeolite-based catalysts are materials with pores of less than one nanometer, which, in 2001, were already used for annual processing of over seven billion barrels of petroleum and chemicals.

Within the context of this report, the authors considered four complementary definitions of nanoparticles. According to Kohler and Fritzche (2004), "nanostructures or nanoparticles are defined according to their geometric dimensions induced by external forming processes, so that the forming, orientation and positioning are achieved in relation to an external reference system, such as the geometry of a substrate. Nanostructures must have at least one dimension of less than 100 nanometers and may have two or three". According to the ISO (2004), a nanoparticle is a "particle with a small enough diameter for the physical and chemical properties to differ measurably from those of bulk materials. The rated maximum but non-exclusive diameter is 40 nm". These definitions agree with the one adopted by the US National Nanotechnology Initiative (2004), namely that nanotechnology represents research and technology development at the atomic, molecular and macromolecular levels in the length scale of approximately 1 to 100 nanometers; the creation or use of structures, devices or systems that have novel properties and functions because of their size; the capacity to control and manipulate at the atomic scale. Finally, the definition of the Royal Society and the Royal Academy of Engineering (2004) is probably the one that best summarizes the contribution and novel aspect of nanomaterials. It considers that nanoscience is the study of phenomena and the manipulation of materials at the atomic, molecular and macromolecular scales, where the properties differ significantly from those on a larger scale.

The properties of nanostructures are thus more directly related to those of individual molecules than to those of bulk material (Kohler and Fritzche, 2004; Royal Society and Royal Academy of Engineering, 2004). This situation leads to very different, even unique, properties of nanoparticles. The very principles of chemistry and classical solid state physics must be replaced by quantal approaches, based on the probabilities where each atom and each molecule can play an important role and where the interactions among them have a major impact on the behaviour of the whole. Thus, the classical mechanical parameters of solids no longer prevail, but the individual molecular and atomic dimensions and the interactions determine the arrangement, stability, flexibility and function of nanostructures.

Two main factors may be responsible for the changes of properties observed in nanoparticles: a much greater relative surface area per unit of mass and a predominance of quantal effects. The first of these factors is responsible for the changes in reactivity, which can increase considerably as particles decrease in size. The second factor, observed in particles of a few dozen nm, explains the changes in terms of optical, electrical, mechanical and magnetic properties (Brouwer *et al.*, 2004, Royal Society and Royal Academy of Engineering, 2004).

> "*Conceptually, nanotechnology refers to science and technology at the nano-scale of atoms and molecules, and to the scientific principles and new properties that can be understood and mastered when operating in this domain. Such properties can then be observed and exploited at the micro- or macro-scale, for example, for the development of materials and devices with novel functions and performance*"(European Commission, 2004).

4.2 Classification

Given the document's general objective and that production of new nanomaterials is a very active research field, only the most common products will be described briefly. For more details, it is recommended that you consult the special edition of the Journal of Materials Chemistry regarding preparation of nanomaterials (Rao, 2004). Rao et al. (2004) have also published a volume describing the theory, synthesis, properties and applications of these products.

Briefly, nanomaterials can be classified in terms of dimensioning of the nanostructures involved (Royal Society and Royal Academy of Engineering, 2004). Thus, quantum dots or nanocrystals, fullerenes, particles, precipitates, colloids and catalysts are confined to the three-dimensional nanometric domain. Nanotubes, dendrimers, nanowires, fibers and fibrils have two nanometric dimensions, while surface coatings, thin films and interfaces have only one nanometric dimension.

One-dimensional systems, such as thin films or manufactured surfaces, have been used for decades in electronics, chemistry and engineering. Production of thin films or monolayers is now commonplace in the electronic field, just as the use of customized surfaces is common in the field of solar cells or catalysis. These fields are well known and the risks are properly controlled. The properties of two-dimensional systems (carbon nanotubes, inorganic nanotubes, nanowires and biopolymers) are less understood and the manufacturing capabilities are less advanced. Finally, some 3-D systems, such as natural nanomaterials and combustion products, metallic oxides, carbon black, titanium oxide (TiO_2) and zinc oxide (ZnO) are well known, while others such as fullerenes, dendrimers and quantum dots represent the greatest challenges in terms of production and understanding of properties (Royal Society and Royal Academy of Engineering, 2004).

4.3 Characteristics and Properties of Nanoparticles

Nanoparticles display properties that differ from those of the bulk materials from which they derive. In general, the integration of nanoparticles will seek modification of electrical, mechanical, magnetic, optical or chemical properties. (Hett, 2004). Here are the main examples:

4.3.1 Fullerenes

Fullerenes are spherical cages containing from 28 to more than 100 carbon atoms (see schematic representation opposite). The most widely studied form, synthesized for the first time in 1985 (Kroto *et al.*), contains 60 carbon atoms, C_{60} (Holister *et al.*, 2003). This is a hollow ball composed of interconnected carbon pentagons and hexagons, resembling a soccer ball (Holister *et al.*, 2003; Hett, 2004). Fullerenes are a class of materials displaying unique physical properties. They can be subjected to extreme pressures and regain their original shape when the pressure is released.

These molecules do not combine with each other, thus giving them major potential for application as lubricants. When fullerenes are manufactured, certain carbon atoms can be replaced with nitrogen atoms and form bondable molecules, thus producing a hard but elastic material. Fullerenes, whether modified or not, have also shown major potential as catalysts (Holister *et al.*, 2003). They have interesting electrical properties and it has been suggested to use them in the electronics field, ranging from data storage to production of solar cells (Holister *et al.*, 2003). Incorporating them into carbon nanotubes modifies the electrical behaviour of fullerenes, creating regions with varying semiconductive properties, thus offering potential applications in nanoelectronics. Their properties vary according to wavelength, thus finding applications in telecommunications. Since fullerenes are empty structures with dimensions similar to several biologically active molecules, they can be filled with different substances and find medical applications (Holister *et al.*, 2003).

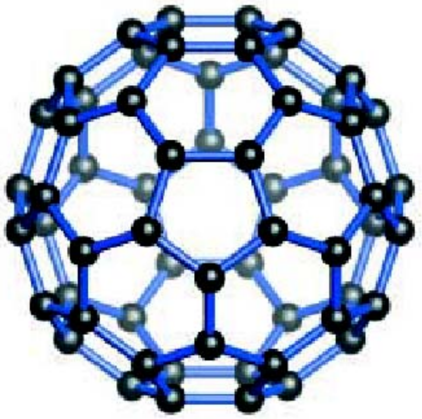
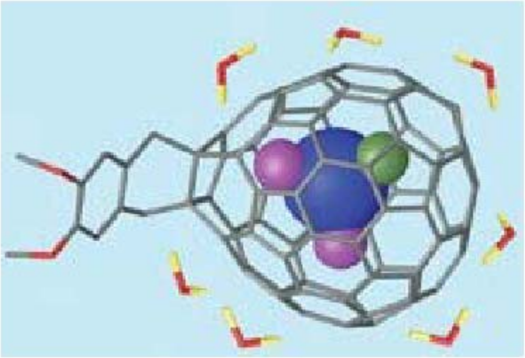


Figure 1 : Schematic representation of a fullerene

Figure 2 : Schematic representation of a modified fullerene



Discovered barely a decade ago, carbon nanotubes are a new form of carbon molecule. Wound in a hexagonal network of carbon atoms, these hollow cylinders can have diameters as small as 0.7 nm and reach several millimeters in length (Hett, 2004). Each end can be opened or closed by a fullerene half-molecule. These nanotubes can have a single layer (like a straw) or several layers (like a poster rolled in a tube) of coaxial cylinders of increasing diameters in a common axis (Iijima, 1991). Multilayer carbon nanotubes can reach diameters of 20 nm (Aitken *et al.*, 2004).

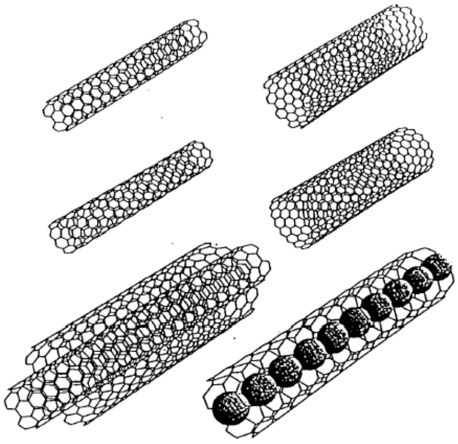


Figure 3: Schematic representation of monolayer or multilayer carbon nanotubes or nanotubes containing other elements

The small dimensions of carbon nanotubes, combined with their remarkable physical, mechanical and electrical properties, make them a unique material (Kohler and Fritzche, 2004; Pautrat, 2003; Ratner and Ratner, 2003). They display metallic or semiconductive properties, depending on how the carbon leaf is wound on itself. The current density that a nanotube can carry is extremely high and can reach one billion amperes per square metre (Pautrat, 2003, Aitken *et al*., 2004), making it a superconductor (Ratner et Ratner, 2003).

Light and flexible, the mechanical strength of carbon nanotubes is more than sixty times greater than that of the best steels, even though they weigh six times less (Ratner and Ratner, 2003, Aitken *et al*., 2004). They also present a very large specific surface area, are excellent heat conductors (Hameed Hyder, 2003), and display unique electronic properties, offering a three-dimensional configuration. They have a great capacity for molecular absorption (Maynard *et al*., 2004). Moreover, they are chemically and thermally very stable (Hameed Hyder, 2003).

4.3.2 Nanowires

Nanowires are conductive or semiconductive particles with a crystalline structure of a few dozen nm and a high length/diameter ratio. Silicon, cobalt, gold or copper-based nanowires have already been produced. They are used to transport electrons in nanoelectronics. They could be composed of different metals, oxides, sulphides and nitrides.

4.3.3 Carbon nanofoams

Carbon nanofoams are the fifth known allotrope of carbon, after graphite, diamond, carbon nanofibers and fullerenes. In carbon nanofoam, islands of carbon atoms, typically from 6 to 9 nm, are randomly interconnected to form a very light, solid and spongy three-dimensional structure, which can act as a semiconductor. Carbon nanofoams display temporary magnetic properties (Health and Safety Executive, 2004b).

4.3.4 Quantum dots

An important field of research for about the past five years, quantum dots (also called nanocrystals or artificial atoms) represent a special form of spherical nanocrystals from 1 to 10 nm in diameter. They have been developed in the form of semiconductors, insulators, metals, magnetic materials or metallic oxides. The number of atoms in quantum dots, which can range from 1,000 to 100,000, makes them neither an extended solid structure nor a molecular entity (Aitken *et al*., 2004). The principal research studies have focused on semiconductor quantum dots, which display distinctive quantal effects depending on the dimensions. The light emitted can be adjusted to the desired wavelength by changing the overall dimension (Aitken *et al*., 2004).

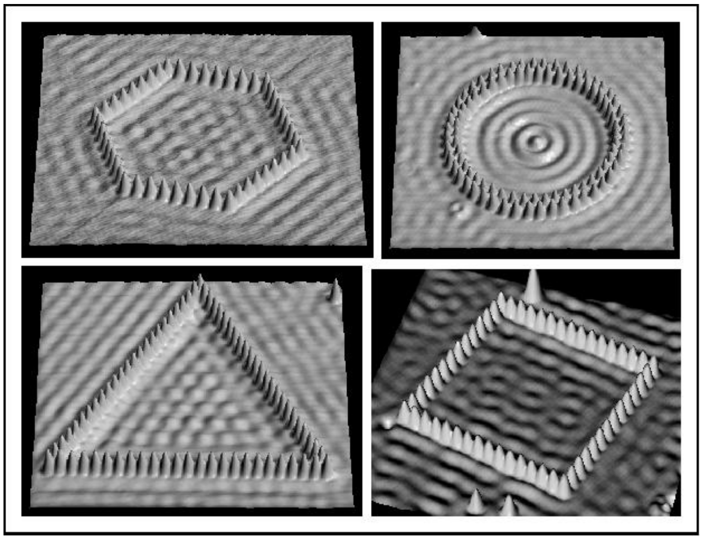


Figure 4 : Different forms of quantum dots show the organization of the individual atoms

4.3.5 Dendrimers

Dendrimers represent a new class of controlled-structure polymers with nanometric dimensions. They are considered to be basic elements for large-scale synthesis of organic and inorganic nanostructures with dimensions of 1 to 100 nm, displaying unique properties. Dendrimers allow precise, atom-by-atom control of the synthesis of nanostructures according to the desired dimensions, shape and surface chemistry. Given that dendrimers can be developed to display hydrophilic or hydrophobic characteristics, their uses can be highly diversified. With different reactive surface groupings, their abundant use is particularly envisioned in the medical and biomedical field (Tomalia, 2004; Goddard *et al*., 2003). Compatible with organic structures such as DNA, they can also be fabricated to interact with metallic nanocrystals and nanotubes or to possess an encapsulation capacity or display a unimolecular functionality (Tomalia, 2004).

4.3.6 Other nanoparticles

Some nanoparticles tend to agglomerate and form structures in chains or with multiple branches. This category normally includes welding fumes, silica fumes, carbon black and other nanoparticles, which are often synthesized by flame pyrolysis. These nanoparticles may include metals, metallic oxides, semiconductors, ceramics and organic material. They may also include composites with a metallic core and an oxide or alloy coating, for example (Aitken *et al.,* 2004). Colloids, which have been known for a long time, are nanometric dimensions. These nanoparticles will not be considered in this study.

4.4 Nanoparticle characterization tools

The characterization of nanomaterials and the understanding of their behaviour is fundamental to the development of new applications and the reproducible and reliable production of nanomaterials. Process nanometrology uses precision instruments with very high sensitivity, capable of measuring at dimensions that are often less than a nanometer. These instruments allow manipulation of individual atoms and measurement of lengths, shapes, forces, masses, electrical properties and other physical properties. They also use electron beam techniques, including high-resolution transmission electron microscopy. Scanning probe techniques include scanning tunneling microscopy and atomic force microscopy. Optical manipulators allow manipulation and measurement of individual atoms (Royal Society and the Royal Academy of Engineering, 2004).

5. DEVELOPMENT, PRODUCTION AND USE OF NANOPARTICLES

Development of nanoparticles and nanotechnologies is currently one of the most active research fields worldwide. Several industrialized countries are making it a strategic priority for sustainable technological, economic and societal development. Indeed, in 2001 it was estimated that the potential world market would reach one thousand billion[1] US dollars by 2015 (Roco and Bainbridge, 2001). In 2003, the British Department of Trade and Industry estimated that there would be a world market of US$100 billion by 2005 (Arnall, 2003). The creation of the US Nanobusiness Alliance, the Europe Nanobusiness Association and the Asia-Pacific Nanotechnology Forum, whose shared objective is to commercialize nanoproducts, clearly illustrates the expected magnitude of these markets and the international competition in the field (Arnall, 2003). Quebec is doing likewise via NanoQuebec.

5.1 Research and development efforts

5.1.1 Worldwide research efforts

A study published in 2002 concluded that, from 1989 to 1998, the rate of increase of scientific publications on nanomaterials increased annually by 27% (Compano and Hullman, 2002). This data indicated that over 30 countries were involved in research in this field, the most active being the United States, Japan, China, France, Great Britain and Russia, which accounted for 70% of publications. Also in 2002, Holister concluded that 455 private companies and 271 academic institutions and government entities were already involved in researching short-term applications in nanotechnology around the world (Holister, 2002). Since then, this field has continued to grow.

Over the past five years, many countries have developed strategic plans and decided to invest massively in nanotechnology research. This will result in an ongoing increase in scientific articles on the subject and a wider variety of research topics. Roco (2001, 2003) reported that government investments had risen from US$432 million in 1997 to over $2.98 billion in 2003. Worldwide research efforts are currently estimated at over US$8 billion for the year 2005 alone, about 40% of which would come from the private sector (Royal Society and Royal Academy of Engineering, 2004; European Commission, 2004; Maynard, 2005). A detailed review of international investments was carried out by Waters (2003) and by the European Commission (2004a). Despite these colossal investments aimed at development of new commercial applications, research in the occupational health and safety field is still in its infancy.

Five leading Asian countries are heavily involved in research into the development of new products: Japan, China, South Korea, Taiwan and Singapore. Japan is the most important Asian stakeholder in the field and has a completely integrated development policy, which the government sees as the key to the country's economic recovery. (Arnall, 2003; Waters, 2003). In 2003, the Japanese government invested the equivalent of US$800 million in the nanotechnology field (Feigenbaum *et al.*, 2004), while the private sector invested an additional $830 million (Waters, 2003). The British Department of Trade and Industry reported, in 2002, that the first

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[1] One thousand billion or one million million

carbon nanotube and fullerene production plants were under construction in Japan (Department of Trade and Industry, 2002).

The European Union's 6th Framework Program (European Commission, 2002), known as Nanoforum, allocated US$1.44 billion for the 2002-2006 period (Waters, 2003) and is seeking to develop a European research and communications network integrating all aspects of nanotechnology, ranging from business to science and information intended for the general public (Hameed Hyder, 2003). In May 2004, the Commission adopted a plan in which it proposed a safe, integrated and responsible European strategy. Following broad consultations of its members, the 7th Framework Program (European Commission, June 2005), proposes to increase the European Union's R&D investments to strengthen Europe's global position in this field.

One of the specific objectives of this European initiative is long-term interdisciplinary research to understand the phenomena involved, master the processes and develop research tools. There is particular interest in nanobiotechnologies, nanoengineering techniques, implications for the fields of health and medical systems, chemistry, energy, optics, food and the environment. This European program also covers production and processing of multifunctional materials, the involvement of engineering for the development of materials, and the development of new processes and flexible and intelligent manufacturing systems. The specific initiatives of several countries must be added to these European efforts. Waters (2003) estimates that the aggregate European investments will range between $3.8 billion and $7.8 billion in 2002-2006. However, private enterprise seems to be much less active than in the United States or Japan. Among the most active European countries are Germany, Great Britain, France, Switzerland, Belgium and the Netherlands. Other European countries are also active in nanotechnology R&D, but their investments are more limited: Ireland, Luxembourg, Italy, Austria, Denmark, Finland, Sweden and Norway.

5.1.2 North American research efforts

In the United States, the National Nanotechnology Initiative (NNI) seeks to accelerate the development of new knowledge in nanotechnology and facilitate its integration into commercially viable technologies (Roco and Bainbridge, 2001; National Research Council, 2002; Hameed Hyder, 2003). This agency, created by the US federal government, supports a major multidisciplinary research program in nanotechnology and specifically covers five kinds of activities: fundamental research, Grand Challenges, the development of centres and networks of excellence, the development of research infrastructures and, finally, ethical, local and social implications and workforce education and training programs in nanotechnologies. More specifically, the NNI is interested in nanostructured materials, manufacturing processes at the nanoscale, detection and protection against chemical, biological, radiological and explosive agents, instrumentation and metrology, the electronic, photonic and magnetic aspects of nanoparticles, healthcare, therapeutic and diagnostic applications, energy conversion and storage, robotics and, finally, processes for improvement of environmental aspects.

When it was created in 2000, the NNI's annual budget was US$422 million (Roco and Bainbridge, 2001). It grew steadily to US$961 million in 2004 with more than 25% allocated to the Department of Defense (Roco, 2004). Of this amount, the NNI, via an agreement with

NIOSH, allocated only US$1.5 million to research in occupational health and safety (Teague, 2004). The NIOSH budget increased to US$3.07 million in 2006 (Castranova, 2006). The NNI coordinates research at 10 federal centres of excellence. In addition, at least 30 American universities have nanotechnology research units and the National Science Foundation includes nanotechnology among its six priority research sectors (Arnall, 2003). Many US States invest in nanotechnology R&D. It is estimated that the private funds invested in R&D in the United States are of the same order of magnitude as public funds (Waters, 2003). In 2003, it was already estimated that 140 companies commercially produced nanoparticles involving 44 different elements of the periodic table (ETC, 2003). A survey conducted in 2004 identifies 875 nanotechnology companies established or in the start-up phase in the United States, offering more than 475 products (Roco, 2004).

5.1.3 Canadian research efforts

Via the National Research Council, Canada has recognized the importance of nanotechnologies and, in 2001, created a National Institute for Nanotechnology, the NINT. It has a $125 million budget for 2001-2005, to which Alberta makes a financial contribution. Although a 10,000 m^2 institute with state-of-the-art equipment is currently under construction in Edmonton, Canada has not yet developed a comprehensive strategic plan allowing coordination of all research efforts at the national level. Nonetheless the NINT Business Development Office is seeking to become a coordinating centre to accelerate the Canadian industry's innovative capacity and successfully launch new nanotechnologies on the market. Apart from the NINT, which is currently located at the University of Edmonton, several major Alberta companies support the nanotechnology research efforts. They include Petro-Canada, SciMed Laboratories, Celonex, BigBangWidth, Westaim Biomedical and Biotools Incorporated (Fiegenbaum *et al*., 2004). The Alberta Government has invested CDN$60 million and has built major facilities for biopharmaceutical technologies (Fiegenbaum *et al*., 2004). Although several Canadian provinces have nanotechnology R&D groups, none seems to have a structured approach at the provincial level, except Quebec. Environment Canada is also showing great interest in nanotechnologies and recently mandated Science-metrix to report on this specific field (Bergeron and Archambault, 2005).

5.1.4 Quebec research efforts[2]

Quebec has established a nanotechnology action plan. Following the report of the Conseil de la science et de la technologie (2001) entitled "Les nanotechnologies: la maîtrise de l'infiniment petit" (Nanotechnologies: mastering the infinitely small) and the overview of nanotechnology research produced by Lebeau in 2001, it has established a nanotechnology action plan. Développement économique et régional et recherche Quebec (2005) is targeting four priority lines of research: biotechnology and pharmaceutical applications, nanostructured materials for the aerospace and automobile industries, photonics and telecommunications, and finally, energy.

Quebec has also established NanoQuebec, which has a mandate to foster the development and enhancement of nanotechnologies and make them an economic and social growth vector. All the major Quebec universities have active nanotechnology researchers (about 200 divided among

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[2] See Chapter 12 for more information on the main Québec stakeholders in the nanotechnology field.

about fifty teams); NanoQuebec posts a detailed directory of Quebec nanotechnology researchers and businesses on its web site (http://nanoquebec.ca/nanoquebec_w/site/index.jsp). A more detailed description of the leading Quebec stakeholders can be found in Chapter 12.

5.1.5 The most actively studied nanoparticles

The most active research in the nanoparticle field concerns carbon nanotubes, which are expected to have a wide variety of applications in numerous fields. In particular, the use of nanotubes is being considered in electronics, in electrochemistry, as mechanical reinforcements for high-performance composites, as cathode ray transmitters, as a means of energy production or hydrogen storage, or as templates for the creation of other nanostructures, such as production of metallic nanowires by filling carbon tubes. The exceptional strength of the bonds uniting the carbon atoms in a nanotube structure makes them an ideal candidate as reinforcing agents in composites. Among the other uses envisioned, carbon nanotubes could be employed as sensors for high-resolution imaging, in nanolithography, in production of nanoelectrodes or as vectors to transport drugs to specific locations in the human body (Kohler and Fritzche, 2004; Danish Institute of Fundamental Metrology 2002; Pautrat, 2003; Ratner and Ratner, 2003).

5.2 Manufacturing processes

Nanoparticles can be synthesized by different approaches. Nanoparticle production can be generally categorized into the bottom-up and top-down methods. In the bottom-up approach, nanoparticles are constructed atom by atom or molecule by molecule. Several strategies are possible to produce such materials, mainly chemical synthesis, self-assembly and positioning of individual nanoparticles. Chemical synthesis is well known and allows production of nanoparticles in very large quantities, while positioning of individual nanoparticles requires microscopy methodologies that are very unproductive. Self-assembly refers to production techniques in which atoms or molecules organize themselves to form an orderly structure on the nanometric scale (Arnall, 2003; Siegel *et al*., 1999). The formation of crystals from a supersaturated solution is an example of self-assembly in which mass production can be envisioned.

In the top-down approach, a large a large structure is gradually scaled down until nanometric dimensions are reached. Etching, precision engineering, lithography and grinding are common approaches. Several of these techniques are commonly used in the electronics industry white rooms, where production and occupational health and safety conditions normally are tightly controlled (Royal Society, 2003; Feigenbaum *et al*., 2004).

In this document, only the approaches most commonly used and likely to subject the works to high exposure during large-scale production of nanoparticles are discussed. The current developments seek to optimize certain specific properties, such as size (diameter, volume, length), granulometric distribution, surface properties, purity, surface coverage, ease of manipulation or performance in a mass production approach.

Four main approaches are currently considered for large-scale production of nanoparticles. They are based on the different mechanisms responsible for nanoparticle formation (Aitken, 2004; Siegel *et al*., 1999; Dresselhaus *et al*., 2001):

- gaseous phase condensation processes, which include flame pyrolysis, high-temperature evaporation and synthesis in a plasma, involving nucleation and evaporation phenomena (bottom-up approach);
- synthesis by evaporation and vapour deposition (bottom-up approach);
- colloid formation by chemical reactions with liquid phase or colloidal solvents, involving controlled precipitation phenomena (bottom-up approach);
- mechanical attrition processes (top-down approach).

5.2.1 Gaseous phase processes

Gaseous phase processes are based on evaporation and nucleation phenomena. Nucleation involves conversion from a vapour phase to a particulate phase. It is observed mainly in condensation of a supersaturated vapour during adiabatic relaxation, rapid quenching of the gaseous flow containing vapour, and/or the chemical reaction of two products. It is said to be homogeneous when the particles formed are composed entirely of the same material found in the vapour phase, and heterogeneous when the condensation occurs on existing particles. After their formation by nucleation, the particles can continue to grow following condensation. Condensation and/or nucleation obtained from combustion or metallurgical processes often form particles with diameters that can range from 1 to 10 nm. In some situations, it is also possible to form larger particles with diameters greater than 100 nm.

Several processes can be used for gaseous phase production of nanoparticles: flame pyrolysis, microwave plasma, thermal plasma, high-temperature furnace flow reactors, pulverization, droplet evaporation and a whole series of methods involving lasers, such as laser ablation, laser-induced pyrolysis and laser vaporization (Kruis *et al.*, 1998; Lebeau, 2001; Swihart, 2003; Aitken *et al.*, 2004).

Since these gaseous phase synthesis methods are based on nucleation of supersaturated vapour followed by growth of a particle by condensation, coagulation and capture, this is a bottom-pup method whereby the nanoparticle is constructed atom by atom. The process chosen will often depend on the desired product. In these processes, vapours are formed by heating a solid, liquid or gaseous precursor in a high-temperature aerosol reactor. Then the vapours are drawn by a vector gas to obtain a supersaturated vapour in a colder zone, allowing condensation. The vapour can be cooled by rapid expansion, by mixing with a colder gas, or by chemical reaction. The method is particularly well adapted to production of metal nanoparticles. This approach also makes it possible to control the morphology of particles or produce oxides by using a vector gas rich in oxygen or nitrides or by using a nitrogen-rich gas.

The supersaturated vapour nucleation process is initiated by the formation of a very small solid nucleus. This grows in size by heterogeneous condensation or by surface reaction, collision and coagulation. Collisions between such particles may produce weakly bonded agglomerates, grouped in chains. Control of experimental conditions allows production of nanoparticles displaying different properties. Several compounds with nanometric dimensions are produced from gaseous phase processes. For example, silica fumes (SiO_2) and ultrafine particles of TiO_2 are produced by flame pyrolysis from oxidation of their chlorides in an oxygen and methane flame. Production of silver, gallium and galena (lead sulphide) nanoparticles has been achieved in the furnace flow reactor, while silicon nanoparticles have been prepared by laser pyrolysis (Aitken *et al.*, 2004).

For readers who want more information about these processes, Kruis *et al.* (1998) and Swihart (2003) explain these production processes in detail, while Aitken *et al.* (2004) summarize them. Kruis *et al.* (1998) consider that the gaseous phase synthesis methods allow good control of nanomaterial specifications, such as dimensions, crystallinity, degree of agglomeration, porosity, chemical homogeneity, purity and stoechiometry, while being well adapted to large-scale industrial production.

5.2.2 Vapour deposition synthesis

These methods are commonly used in the semiconductor field. To summarize, vapour formed by pyrolysis, reduction, oxidation or nitration is deposited, in the form of a film of controlled thickness, on the surface of a semiconductive disk. These techniques can be grouped under the heading of chemical vapour deposition, or CVD. This synthesis method has also been used for production of nanoparticles of TiO_2 (Nakaso *et al.*, 2002), ZnO (Gao and Wang, 2005) and SiC (Honda *et al.*, 2003).

Deposits of nanometric dimensions can also be obtained by physical vapour deposition, or PVD, as in the case of cathode pulverization. With this technique, the layer deposited on the substrate is formed of atoms torn from a cathode by heavy ion bombardment produced by an electrical discharge in a rare gas, generally argon. The most important application of this method in nanotechnology could be the production of carbon nanotubes. This method is currently considered very promising and would allow large-scale production of carbon nanotubes (Singh *et al.*, 2003).

5.2.3 Colloid formation

The first documented use of the colloidal method dates back to Faraday, who first prepared gold colloids in 1857. This very well-known synthesis technique is commonly used in many industrial chemical processes (Holmberg, 2002). To summarize, electrically charged particles are kept dispersed in a liquid by the repulsive forces between them. Colloidal methods allow preparation of large quantities of products and are adapted to nanoparticle production. Current research studies thus seek to establish the conditions allowing production of large quantities of nanoparticles of defined forms with a fairly narrow particle size distribution. This method is based on fairly simple principles, although it may be difficult to control certain reactions uniformly, especially for bigger reactors. This method also offers the advantage of being fairly inexpensive to apply to scale and requiring less energy than other nanoparticle synthesizing processes. The nanoparticles produced include metals, metallic oxides, organic products and pharmaceuticals. These colloids can remain in liquid suspension for distribution or use or can be filtered or dried to produce powders.

5.2.4 Mechanical attrition processes

The only top-down processes considered in this document, mechanical grinding or attrition processes, begin with large particles and break them down until nanometric dimensions are obtained. Attrition thus consists of mechanical reduction of the material's size by friction and high-energy impacts. The powder to be processed is inserted in a receptacle containing larger balls that serve as grinding agents. Using various mechanisms, a large amount of energy is delivered to these balls. The powder trapped between two colliding balls is deformed, first plastically and then elastically, and subsequently split into many pieces.

The mechanical grinding process can be used for several different objectives, such as particle size reduction, conversion into an amorphous structure, particle size increase, particle size modification, mixing or forming alloys of two materials, agglomeration between particles, or modifying or changing the properties of the material. However, the main objective of attrition is particle size reduction (De Castro and Mitchell, 2002). Reduction of the dimensions of materials by grinding is a well-known industrial process allowing production of increasingly fine materials with relatively high production capacity. Production of the finest particles was known as micronization. Production of particles of nanometric dimensions is called ultrafine grinding or nanosizing and is normally performed by a wet process.

The particles obtained by grinding may display nanometric characteristics on two different levels. First, the particles themselves may be of nanometric size. However, this is possible only under certain special conditions and for certain specific materials, such as very fragile ceramics. In all cases, particle size distribution is relatively wide compared to the distributions that may be encountered in the different bottom-up approaches, and mechanical attrition processes generally are not used to produce nanoparticles. Mende *et al*. (2003) thus produced 50 nm carborundum and alumina suspensions with a grinding chamber equipped with perforated rotating plates. Merisko-Liveridge *et al*. (2003) produced drug nanoparticles with low solubility in water and granulometries of around 150 nm. These two studies necessitated stabilization of the solutions to prevent the particles from agglomerating.

The powders produced by mechanical attrition processes are in high demand due to the crystalline structure of the particles. Particles produced by this process display a highly crystalline structure with crystals often ranging from 1 to 10 nanometers, even though the size of the particles is still several microns. Materials displaying a nanocrystalline structure offer major advantages in terms of hardness, fracture resistance and low-temperature ductility, compared to materials with crystals in the micron range (De Castro and Mitchell, 2002).

5.3 Applications of nanotechnologies

The anticipated economic potential of nanotechnologies is phenomenal. It is predicted that a multitude of applications will be found for nanoparticles and affect many sectors of activity. Borm (2005) reports that, in 2003, some 2954 kilograms of single-walled carbon nanotubes were produced worldwide. Japan, which produced 1000 kg, plans to increase its production to 120,000 kg/year over five years.

Several existing or anticipated applications stand out among the fields of application in which nanoparticles will make it possible to improve the performance of existing materials (NanoQuebec, web site; Kohler and Fritzche, 2004; Danish Institute of Fundamental Metrology 2002; Pautrat, 2003; Ratner and Ratner, 2003; The Royal Society and Royal Academy of Engineering, 2004; National Science and Technology Council, 2003; Roco and Bainbridge, 2001; National Nanotechnology Initiative, 2004; US Department of Health and Human Services, web site, 2004; Wood *et al*., 2004; Salata, 2004; Morrison *et al*., 2003; Malsch *et al.,* 2004; EPA, 2003; Feigenbaum *et al*., 2004; Hameed Hyder, 2003; European Commission, 2004a, 2004b; Taylor, 2002). For a detailed description of the potential applications of nanoparticles, readers are advised to consult Hameed Hyder (2003).

- *Automobile and aerospace industries*: reinforced and lighter materials; adhesives; more efficient electrical and magnetic rheological liquids; scratch-resistant, elastic, dirt-repelling exterior paints with colour effects; lighter, faster, safer vehicles; more durable and more reliable roads, bridges, pipelines and railway systems; anticorrosion coatings; sensors optimizing engine performance; ice detectors on aircraft wings, recyclable, longer-lasting tires; incombustible plastics.
- *Electronics and communications industries*: high-density memories and miniaturized processors; new solar cells, batteries and combustion cells; optoelectronic components, including lasers; faster processing speeds; greater data storage capacity; pocket electronic libraries; coupling silica with organic substances; logical digital components; ultra fast compact computers and electronic games with quantum electronics, wires and computers; brightly lit flat screens.
  - *Chemical and materials industries*: multifunctional and more efficient ceramics, pigments, powders and catalysts; lighter and stronger wires; corrosion inhibitors and corrosion-resistant alloys; adhesiveless bonding technologies; new welding technologies; functional layers (thermal insulation, anti-adhesive, antistatic); photoactive and self-cleaning paints, windows and clothing; membranes for separation of materials (water treatment, dialysis); structured catalysts; ultra resistant coatings; extremely hard and resistant cutting tools.
  - *Pharmaceutical, biomedical and biotechnology industries*: new drugs and active agents, including cosmetics, sun creams and protective creams; new antiallergenic medical adhesive surfaces; improvement of existing drugs, customized drugs delivered only to specific organs of the body; biocompatible surfaces for implants; nanoparticle-based oral vaccines; production of magnetic nanoparticles from biological media and production of biocompatible materials; tissue engineering and regeneration; neuron-transistor interfaces.
  - *Healthcare*: Nanomaterials will allow physicians to do a better job of viewing, treating and repairing the body’s interior: the implanting of miniaturized diagnostic media to obtain early diagnoses; in surgery, tissue engineering and implants with nanotechnological coatings that can improve biocompatibility and bioactivity; multifunctional sensors; DNA analysis; manufacturing of ultraprecision devices, analytical and positioning systems, better optical systems; novel means of remedying severe handicaps such as deafness, blindness or certain paralyses; membranes for dialysis; preventive medicine with highly sensitive minisensors, microlaboratories, high-density microchips; early diagnosis, prevention and treatment of cancer; biodetection of pathogens; protein detection, tissue engineering; destruction of tumours by heating.
  - *Energy:* New generation of photovoltaic cells; more economical lighting; batteries and compact combustion cells with large internal surfaces; hydrogen storage in nanotubes;

  quantum dot lasers; more efficient conversion of solar and wind energy; intelligent windows; more efficient insulating materials.

  - *Manufacturing sector:* precision engineering for production of new generations of microscopes and measuring instruments; new processes and new tools for manipulating matter at the atomic level; nanopowders incorporated into bulk materials with special properties, such as sensors that detect imminent failures and monitor measurement controls; manufacturing of biologically inspired materials.
  - *Environment and ecology:* selective chemistry; colloidal membranes; selective catalysts; protection of sensitive organisms and reduction of CO_2 emissions; functional non-toxic layers of multifunctional sensors for environmental depollution; production of ultrapure water from seawater, better use, recovery and recycling of existing resources, more efficient and less harmful pesticides and fertilizers; specific real-time chemical and multi-substance analyzers.
  - *Process security:* compact zeolite reactors; new bonding technologies; production of copies (credit and debt cards, bank notes); adjustment of standards at the atomic scale, self-organized processes; quality control at the atomic scale; manufacturing processes with sensors leading to production with less defects.
  - *Defense:* detectors of chemical and biological agents; much more efficient electronic circuits; much more resistant materials and coatings; light, high-performance textiles that repair themselves; miniaturized surveillance systems; more precise guidance systems.

- Some nanomaterials are already in commercial use (Teague, 2004; Royal Society and the Academy of Engineering, 2003; European Commission, 2004a). Examples include the use of metallic oxides in ceramics, zinc, iron, cerium and zirconium oxides, anti-scratch coatings for lenses, and in certain cosmetics and in sunscreens. It is estimated that the skin protection and skin care market uses 1000 to 2000 metric tons of metallic oxides annually. Clays with nanometric dimensions are integrated into certain materials to increase their strength, hardness, heat resistance and fire resistance. Nanotubes are already used as coating to minimize and dissipate static electricity in fuel lines and in electronics, in electrostatic paints and as flame retardants for certain plastics. Also, bandages, cardiac valves, non-streaking paints and unwrinklable and anti-stain fabrics containing nanometric components are being produced. Exploratory studies are under way to use quantum dots in diagnosis and medical therapy and for self-assembly of nanoelectric structures.

Several composites displaying specific mechanical, optical, electrical or magnetic properties use nanoparticles. For example, monolayer or multilayer carbon fibers would allow control of the conductivity of certain plastics; they would be used in antistatic packaging. Carbon black, part of which has a nanometric dimension, is already widely used to reinforce tires. Composite materials based on nanometric-dimensioned clay and plastic are widely used, particularly for automobile bumpers.

Although certain zeolites, titanium, zinc and iron oxides, carbon black and silica are the only nanoparticles currently produced in high tonnage (Royal Society, 2004), it nonetheless remains that, in the years ahead, nanoparticles will contribute to the improvement of a many products in various sectors. Major advances are expected in the short term in electronics, nanobiotechnology and nanomedicine (Royal Society and Royal Academy of Engineering, 2004).

6. NANOPARTICLES AND HEALTH EFFECTS

Nanoparticles have exceptional physical, chemical and electrical properties. What about their biological properties and interactions with the human body? Do they present a health risk for the workers who produce, handle, transform or use them? This chapter is mainly based on a knowledge assessment produced by our team[3].

Many nanotechnologies pose no new occupational health or safety risk, and most concerns focus on the manufacturing of free nanoparticles not bonded to materials or structures (Royal Society and Royal Academy of Engineering, 2004). This chapter concentrates on the existing data regarding nanoparticles that have not undergone surface modifications. There are two major reasons for modifying nanoparticle surfaces. First, a surface coating is frequently used to prevent aggregation of particles, but little data is available on the toxicity of these coated nanoparticles. Second, many modifications have been made to nanoparticle surfaces to modify their behaviour in the human body and develop new medications. This aspect goes far beyond the objective of this study; we will only touch on it here, since some information could be relevant to the health and safety of workers who manufacture, handle or use these nanoparticles of pharmacological interest.

This chapter is divided into two sections. The first section reports on the toxic effects documented in animals and humans and related to specific nanoparticles. The second section is a general discussion, in which the toxic risk is considered in terms of the target organ and current knowledge of the toxicity of ultrafine particles of the same dimensions as nanoparticles.

6.1 Health risk related to specific nanoparticles

6.1.1 Fullerenes

After intraperitoneal administration in mice, Moussa *et al*. (1997) detected fullerenes (C_{60}) in the blood, liver and spleen, while Tsuchiya *et al*. (1996) showed that they also pass through the placental barrier in mice and are distributed throughout the embryo and the yolk sac. On the metabolic level, C_{60} can reduce the hepatic enzyme activity of glutathion *in vitro* in humans and rodents (Iwate *et al*., 1998). Nelson *et al.* (1993) studied the effects of the application of fullerenes on mouse skin. A subchronic study of initiation and promotion of carcinogenesis showed no effect on DNA synthesis, but there was a slight increase in the activity of an enzyme that promotes epidermal tumours without any observed increase in skin tumours. Sera *et al*. (1996) observed mutagenic activity *in vitro* on three salmonella strains exposed to fullerene C_{60} and to visible light in the presence of a metabolic activation system. Zakharenko *et al*. (1997) did not observe any genotoxic effect of fullerene C_{60} in an *in vitro* test on *Escherichia coli* and an *in vivo* test on *Drosophila melanogaster* larvae. Exposure *in vitro* to fullerene C_{60} (12.5 µg C_{60}-cyclodextin) induces oxidative damage to hepatic microsomes in rats. This damage can be modulated by antioxidants and free radical traps (Kamat *et al.,* 1998).

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[3] Ostiguy *et al*., 2006. Les e*ffets à la santé reliés aux nanoparticules*. IRSST Report R-451, March 2006.

A few studies have been conducted with chemically modified or solubilized fullerenes. Numerous effects have been reported and the toxicity seems to vary greatly with the nature of the functional group (Ostiguy *et al*., 2006).

Oberdörster (2004) studied the effect of fullerenes and a known oxidizing agent, oxygen peroxide, on a fish population. Exposed for 48 hours to a 0.5ppm concentration in water, the researcher noticed a significant increase in lipid peroxidation in the brain.

Our review did not allow us to present a standard toxicological study of pulmonary exposure to fullerenes. We have no significant information on the potential consequences of one-time or repeated occupational exposure to fullerenes. The only possible conclusion is that fullerenes do not seem to show the power of cutaneous irritation. It is difficult to take a position on the oxidative power of fullerenes, since most studies were performed under special conditions.

6.1.2 Carbon nanotubes

An exploratory study of pulmonary function in Guinea pigs, following a single 25 mg inhalation dose of single-walled carbon nanotubes, was performed by Huczko *et al.* (2001). No effect on pulmonary function (current volume, respiratory frequency and respiratory resistance) or bronchoalveolar lavage fluid was observed. Warheit *et al*. (2004) studied the pulmonary toxicity of acute exposure by intratracheal installation with a preparation of single-walled carbon nanotubes in male rats. This was an agglomerated soot containing 50% to 60% nanotubes about 30 nm in diameter, 30% to 40% amorphous carbon, 5% nickel and 5% cobalt. At 5 mg/kg, they reported a high mortality rate (~15%) caused by mechanical blockage of the upper airway, an inflammatory response, an increase in lung cell proliferation and an increase in multifocal pulmonary granulomas. Significant increases in lung weight bronchoalveolar lavage anomalies and pulmonary lavage anomalies were also observed. There was no effect on lung macrophages. The pulmonary response was similar, but less pronounced than in rats exposed to silica.

Lam *et al*. (2004) studied the pulmonary toxicity of acute exposure by one-time intratracheal instillation with three single-walled carbon nanotube preparations in male mice. The three preparations contained purified carbon nanotubes (2% residual iron), non-purified carbon nanotubes (27% iron) and carbon nanotubes containing 26% nickel and 5% yttrium. Silica and carbon black were used as controls and injected in the same doses. No clinical sign was observed at 0.1 mg following exposure to silica or carbon black, but inflammation and pulmonary granulomas occurred in rats exposed to the three types of carbon nanotubes, whether purified or not. The granulomas often were located at the interstitial sites. The researchers observed a high incidence of mortality (5/9) for the nanotubes containing nickel at 0.5 mg but no mortality for the carbon nanotubes containing iron, whether purified or not. Various clinical signs were reported for all these forms of nanotubes following strong exposure, as well as an increase in pulmonary granulomas. No irritation or granuloma was observed for carbon black. High-concentration silica exposure led to a mild to moderate inflammatory response at the alveolar and interstitial levels and a mild granulomatous response at 7 days of exposure. These results, as well as those of Warheit *et al*. (2004), suggest that granuloma formation is associated with single-walled carbon nanofibres, which would then be cytotoxic.

Huczko *et al*. (2001) studied the effects on the skin and eyes of exposure to carbon nanotubes. The application of a filter saturated with a solution containing nanotubes did not cause irritation or allergies in volunteers. Ocular instillation of an aqueous suspension of nanotubes in rabbits did not cause irritation. Shvedova *et al*. (2003, 2004) reported that 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. They concluded that their results indicate that exposure to unrefined single-walled carbon nanotubes can lead to an increase in cutaneous toxicity in exposed workers.

Zheng *et al*. (2003) showed that single-strand DNA (unspecified origin) can unwind *in vitro* around a carbon nanotube of appropriate diameter and electrical properties. Cui *et al*. (2005) showed that single-walled carbon nanotubes could inhibit cell proliferation, induce apoptosis and reduce adherence of renal embryonic cells of human embryos *in vitro.*

Jia *et al*. (2005) performed a comparative study of the cytotoxicity of single-walled carbon nanotubes, multi-walled carbon nanotubes and fullerene C_{60} on alveolar macrophages in Guinea pigs. No cytotoxicity was observed for fullerenes. However, the single-walled carbon nanotubes showed greater cytotoxicity than the multi-walled carbon nanotubes, which led to greater cytotoxicity than quartz. The single-walled carbon nanotubes caused a decrease in phagocytosis at a lower dosage than the one necessary for a decrease triggered by multi-walled carbon nanotubes.

Pantarotto *et al*. (2004) studied intracellular transport of functionalized single-walled carbon nanotubes, i.e. combined with lysine, on human fibroblasts and mice *in vitro.* They showed that they could pass through the cell membrane, accumulate in the cell and end up in the cell nucleus.

The study by Wang *et al*. (2004) shows that hydroxylated single-walled carbon nanotubes administered by the intraperitoneal route distribute throughout the body, except for the brain, pass through several compartments and are retained in the bones. The other routes used (intravenous, subcutaneous and intubation) did not influence the distribution of the hydroxylated single-walled carbon nanotubes. Wang *et al*. (2004) report that 11 days after exposure, about 80% of the hydroxylated single-walled carbon nanotubes administered by the intraperitoneal route had been excreted, with a distribution of 94% in the urine and 6% in the feces. Cherukuri *et al*. (2004) showed that carbon nanotubes could be ingested by peritoneal macrophages in mice. Monteiro-Riviere *et al*. (2005) found carbon nanotubes in the cytoplasmic vacuoles of human epidermal keratocytes *in vitro* (up to 3.6 µm), leading to a decrease in cell viability and a significant increase in interleukin-8, an inflammation marker. Carbon nanotubes seem capable of penetrating the cell and inducing irritation.

Table 1 summarizes the information gathered on the health effects related to single-walled carbon nanotubes. This table, which lists the essential information for quantitative establishment of the risk, clearly illustrates the major limitations related to the lack of currently existing knowledge for carbon nanotubes.

Table 1 : ***Documented health effects for single-walled carbon nanotubes[1]***

Effect	Route			
	Inhalation[2]	**Cutaneous**	**Oral**	**Other**
Toxicokinetic				
Irritation		■ ▲		
Systemic				
Acute	▲			
Intermediate				
Chronic				
Neurological				
Immunological		■		
Development				
Reproduction				
Genotoxic				
Cancer				

[1] Existing studies in humans (■) or animals (▲). Adapted from the Agency for Toxic Substances and Disease Registry (ATSDR).

[2] Including intratracheal instillation.

6.1.3 Organic nanoparticles

Organic nanoparticles generally are materials in which a biological substance is trapped, encapsulated or adsorbed to the surface (Zimmer, 1999). They are interesting because their use in transport and optimal targeting of drugs. Literature reviews of the use of nanoparticle systems for cerebral transport of different drugs have been produced by Kreuter (2001) and Lockman *et al.* (2002, 2003), among others. The different systems (coated or uncoated polymers, etc.) have proven to be an effective tool to help drugs pass through the hematoencephalic barrier (dalargin, doxorubicin, etc.) in several animal species. Tests were performed with various types of nanoparticles: polymeric (Kante *et al.*, 1982; Couvreur *et al.*, 1982; Gibaud *et al.*, 1996; Sakuma *et al.*, 2002), colloidal (Nemmar *et al.*, 2002) and nanospherical lipid (Fukui *et al.*, 2003). The therapeutic results are promising, primarily for polymeric nanoparticles, but the data is inadequate concerning their toxicity in the work environment because of the unusual route taken and limited information concerning their toxicological assessment.

6.1.4 Inorganic nanoparticles

Potential cutaneous absorption of titanium dioxide (TiO_2) contained in sunscreen formulations is a key concern due to the potential production of free radicals and changes in cellular DNA – and thus the potential contribution to the development of cancers.

Report on certain studies that indicate cutaneous absorption in rats, rabbits and humans of the titanium dioxide (TiO_2) contained in sunscreen formulations. However, Lademann *et al.* (1999) did not observe significant cutaneous absorption of coated nanocapsules of TiO_2 (17 nm) beyond the horny layer of the skin of human volunteers. The absence of absorption beyond the horny layer of the skin was also revealed by Schulz *et al.* (2002), who used different formulations, in which the TiO_2 exhibited various dimensions, forms, degrees of compatibility and combinations of ingredients. Their results make it unlikely that there is deep absorption in the dermis and transport of substances in the bloodstream. One of the first and most important studies on the comparison of fine (250 nm) and ultrafine (20 nm) TiO_2 particles was published by Oberdörster *et al.* (1994). In this inhalation experiment conducted on rats exposed to similar concentrations, the authors observed greater pulmonary retention of ultrafine particles. A greater quantity of 20 nm particles was found in the lymphatic ganglia, a phenomenon indicating penetration of the interstitial spaces. Pulmonary clearance of ultrafines was extended and translocation of these particles in the pulmonary was greater. The authors also observed a significant increase in signs or parameters of inflammation with 20 nm particles compared to 250 nm particles. Damage to the pulmonary epithelium, obstruction of the pores of Kohn, development of interstitial fibrogenic foci and alteration of macrophage functions were significantly higher. The specific surface was the parameter that was best correlated to the observed effects. Currently, NIOSH (http://www.cdc.gov/niosh/topics/nanotech/#oshrisks) recommends a lower exposure standard for TiO_2 of nanometric dimensions than for the same product in larger dimensions (NIOSH 2005).

In an experiment performed by intratracheal instillation in rats, Hohr *et al.* (2002) showed an increase of pulmonary neutrophiles, early parameters of inflammation, for 20-30 nm TiO_2 nanoparticles. This effect was not as significant with the administration of 180 nm particles. The authors conclude that the surface of the particles is the determining parameter of pulmonary inflammation. In an experiment intended to evaluate the hemocompatibility of various forms of titanium dioxide (TiO_2), Maitz *et al.* (2003) studied different parameters, such as platelet aggregation and coagulation time, and did not observe any effect of the nanocrystalline form on platelet-rich human plasma.

An *in vitro* study performed by Lucarelli *et al.* (2004) showed that SiO_2 and cobalt nanoparticles displayed a significant proinflammatory activity on human myelomonocytic cells, while the activity of TiO_2 and ZrO_2 nanoparticles was much less intense. Studying human endothelial cells, Peters *et al.* (2004) arrived at similar conclusions, namely that cobalt nanoparticles show a substantial proinflammatory potential, while TiO_2 and SiO_2 have a lower potential.

In an ingestion study performed in mice, Hillyer and Albrecht (2001) showed the capture of colloidal gold nanoparticles by the intestine, their passage through the blood and their distribution to the brain, lungs, heart, kidneys, intestine, stomach, liver and spleen. This effect was inversely proportional to the size of the nanoparticles. The smaller the particle, the greater the passsage. Paciotti *et al.* (2004) and Hainfeld *et al.* (2004) studied colloidal gold nanoparticle formulations injected intravenously in mice loaded with colon tumour cells (Paciotti *et al.*, 2004) and breast tumour cells (Hainfeld *et al.*, 2004). Nanoparticles were distributed preferentially to the tumour site, without significant accumulation in the liver, the spleen and the animals' other normal organs, which gives reason to believe in the low toxicity of this type of therapeutic formulation. Mice with induced tumours in the Hainfeld *et al.* (2004) had a high survival rate (86%) at one year when the maximum dose of gold nanoparticles had been administered intravenously before radiotherapy. Paciotti *et al.* (2004) concluded that to attain the same antitumoral performance, the nanoparticle formulation required lower doses.

In an *in vitro* study of the trajectories of pharmacological vectors (modified gold nanoparticles), Tkachenko *et al.* (2004) revealed various degrees of particle capture by human cervical and liver tumour cell nuclei and by mouse fibroblastoma cells. The nanoparticles were able to pass through the three cell barriers of the tumour cells – the cell membrane, the endosomal membrane and the nuclear membrane - to reach the nucleus. The researchers do not report any indication regarding the behaviour of healthy cells. Paciotti *et al.* (2004) did not note any general toxicity in mice exposed to the colloidal gold nanoparticle formulation; to achieve the same antitumoral performance, the nanoparticle formulation required higher doses than for larger particles.

To study the distribution of iridium-192 nanoparticles, Kreyling *et al.* (2002) exposed rats to 15 and 80 nm nanoparticle aerosols. After exposure, the authors observed iridium in the animals' liver, spleen, heart and brain, and these phemomena were twice as great for 15 nm nanoparticles. Iridium nanoparticles are insoluble and were not absorbed significantly in the intestine. The authors conclude that there is translocation to the organs, resulting in circulation of nanoparticles through the pulmonary blood vessels.

Oberdörster *et al.* (2002) examined the corporal distribution of 20 to 29 nm nanoparticles of carbon-13 (insoluble) in a rat inhalation study. No elevation in several of the animals' organs was observed (lungs, heart, brain, olfactory bulb and kidneys) for up to 24 hours after exposure. However, the researchers observed a substantial liver accumulation of carbon-13 in animals of the 2 groups, 18 and 24 hours after exposure. The authors explain the hepatic distribution by a translocation of nanoparticles from the respiratory system to the circulatory system and then to the liver. The authors do not exclude the possibility that nanoparticles might have gone down the airway to the upper digestive system, and then been captured by the liver.

In another, longer-term rat inhalation study, Oberdörster *et al.* (2004) studied the cerebral distribution of carbon-13. Analysis of the animals' brains, cerebellums and olfactory bulbs revealed significant capture in the exposed rats, which persisted only in the olfactory bulb. To explain cerebral capture of carbon-13, the authors postulate translocation from the lung to the blood and then passage through the hematoencephalic barrier. Transport from the respiratory zones to the olfactory bulbs, and then translocation by axonal migration to the brain, also may have contributed to transport of nanoparticles.

Zhang *et al.* (2000) studied the effect in rats of intratracheal instillation of the nanoparticulate form of cobalt in comparison with the administration of 5 µm cobalt microparticles. The authors observed much greater signs of pulmonary inflammation and epithelium damage with nanometric cobalt. Zhang *et al.* (2005b) report that Donaldson and his team had shown that nanoparticulate forms (< 50 nm) of titanium dioxide, aluminium oxide and carbon black increased the pulmonary inflammation parameters 10 times more than the administration of fine particles of the same products. The epidemiological evidence (Gardiner *et al.,* 1992) suggests an increased potential respiratory risk in the production of carbon black, where workers potentially can be exposed to particles of nanometric dimensions.

Peters *et al.* (2004), studying the behaviour and viability of human endothelial cells *in vivo*, observe that polyvinyl chloride (PVC), TiO_2, SiO_2, cobalt and nickel nanoparticles were incorporated into the vacuoles of the cells. Cobalt nanoparticles show substantial proinflammatory and cytotoxic potential, while SiO_2 nanoparticles have low proinflammatory potential. TiO_2 nanoparticles display even less potential, although still observable, despite the fact that this substance is often considered biologically inert. PVC and nickel (Ni) nanoparticles do not produce these effects.

6.1.5 Nanocapsules and nanoshells

In an *in vitro* study, Zhou *et al.* (2005) show that use of a nanosphere formulation to administer arsenic trioxide reduces the blood toxicity of this product, employed against bladder cancer, and renders its action more specific to cancer cells. The other studies identified (Aprahamian *et al*., 1987; Cahouet *et al*., 2002; Torres-Lugo *et al*., 2002) focus on the use of nanospheres in the pharmacological field and will not be discussed here.

6.1.6 Quantum dots and nanocrystals

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 their capacity to establish covalent bonds with peptides, antibodies, nucleic acids and other low molecular weight molecules (Smith *et al.,* 2004). The studies reported in the literature deal with the use of quantum dots coated with different substances (Chan and Nie, 1998, cited in Smith *et al.,* 2004; Akerman *et al.,* 2002; Dubertret *et al.,* 2002; Kirchner *et al.,* 2005; Green et Howman, 2005; Lam *et al.,* 2003).

Some of these products seem to be capable of preferentially attacking cancer cells, while the different coatings have a major impact on capture of nanoparticles by different organs. Several *in vivo* studies seemed to show the absence of toxicity of quantum dots for the normal development of non-mammalian organisms. However, according to some researchers, the long-term stability of the complexes and their complete degradation before elimination still have to be evaluated. In an *in vitro* study performed to evaluate the cytotoxicity of CdSe quantum dots for liver cells, Derfus *et al.* (2004) observed that cytotoxicity was quite real and that surface oxidation of the quantum dots produced Cd^{2+} ions, recognized as carcinogenic. Encapsulation of the quantum dots with ZnS tended to reduce this effect and it declined to almost zero with encapsulation by bovine serum albumen.

6.1.7 Scope and limits of current nanoparticle data

Although this section has allowed us to present the results of several studies on the toxicity of specific nanoparticles (fullerenes, carbon nanotubes, quantum dots …), there have been relatively few studies of these nanoparticles. The available data is fragmentary and only covers a tiny fraction of the information required to reach a final conclusion on the toxicity or safety of any specific nanoparticle. The current research should contribute to a better understanding of the potential risks related to these different products.

6.2 Nanometric and ultrafine particles

As already mentioned, the results of the toxicological studies are clearly insufficient to allow a conclusion, yet most studies raise the possibility of health hazards for workers exposed to nanoparticles. These limitations on knowledge of the potential nanoparticle-related risks are especially important in that the rapid development of new products with chemical and physical characteristics specific to targeted use may also lead to specific biological and toxic properties, which will only increase the challenge of risk assessment in all situations.

In such a context, we considered it essential to report the results of the knowledge syntheses on the health effects of nanoparticles, which have been published by recognized bodies or by specialized authors in the field (Aitken *et al*., 2004; Arnall, 2003; Bodegal *et al*., 2003; Bordé *et al*., 2002; Borm and Kreyling, 2004; Christiansen, 2004; European Commission, 2004b; Dreher, 2003; Durrenberger *et al*., 2004; Feigenbaum *et al*., 2004; Health and Safety Executive, 2004a, 2004b, 2004c; Hoet *et al*., 2004a, 2004b; Kirchner *et al*., 2005; Lamy, 2005; Malsch *et al*., 2004; Mark, 2005b; Morrison *et al*., 2003; Oberdörster *et al*., 2000, 2005a, 2005b; Royal Society and Royal Academy of Engineering, 2004).

Our first finding is that the scope of these syntheses often varies and that they conclude, as we do, that there is a shortage of up-to-date data. Like certain of these organizations, the authors of this report have decided to incorporate some of the accumulated knowledge on the toxicity of particles similar in size to the nanoparticles to which certain workers are exposed; they have done so because the scientific literature is relatively rich in information on the toxicity of ultrafine particles. These ultrafine or nanofine particles have an aerodynamic diameter of less than 100 nm and normally are generated as undesirable side products of several processes. For example, they are found in welding fumes, diesel engine emissions and the fumes of many high-temperature operations. They are also often related to atmospheric pollution. It is appropriate to summarize part of the information available on these products so as to have an overview of the current knowledge regarding the toxicity of ultrafine particles of nanometric dimensions.

6.2.1 Principal factors influencing toxicity mechanisms

Kirchner *et al*. (2005) report that three main factors contribute to the toxicity of nanoparticles absorbed by the body. A first toxicity factor would be related to chemical composition. For example, for low solubility nanomaterials, toxic ion emissions related to the partial decomposition of nanomaterials could be favoured by their high surface-to-volume ratio. Secondly, cellular toxicity unrelated to chemical composition results from the potential adhesion of nanoparticles to cells or their cellular incorporation. This could even be true of particles traditionally considered biologically inert. Borm and Kreyling (2004) then focus attention on the effects related to the surface properties of nanoparticles (absorption, bonding and transport) and their dimensions. Finally, Kirchner *et al*. (2005) report toxicity related to the form of nanoparticles, such as the potential that longilinear nanomaterials, including carbon nanotubes, will impale the cell.

To interpret the effects of nanometric and ultrafine particles absorbed by inhalation, Borm and Kreyling (2004) postulate that researchers should focus on the 5 “D’s”: *dose*, *deposition*, *dimension*, *durability* and *defence* mechanisms. In the case of nanoparticles, this *dose-dimension* relationship links toxicity to surface concentration. The *dose* at the pulmonary site determines the potential toxicity, and this dose is determined by the concentration and the *dimensions* of the particles.

Deposition of nanoparticles in the pulmonary tree is extremely dependent on particle granulometry, as we will see a little later. The *durability* of a group of particles will be greater if they are insoluble and cannot be degraded or eliminated by the lung. If there is sustained exposure, there will then be a large local accumulation. The respiratory system has different *defence* mechanisms designed to eliminate undesirable particles. Toxicity often will depend on the efficiency of these mechanisms in taking charge of nanoparticles.

6.2.2 Pulmonary deposition of ultrafine dusts

It is well known in industrial hygiene that a worker exposed to substances that may be airborne has three potential absorption routes: pulmonary absorption, cutaneous absorption and absorption by ingestion.

The lungs are the main route for dust to enter the human body. Dust deposits along the pulmonary tree vary considerably according to the granulometry of ultrafine dusts and their behaviour in air. Normally, for the coarser dusts encountered in the work environments, alveolar dust deposits are inversely proportional to particle size, reaching a maximum value of around 20% for 3-micrometre particles. This percentage gradually diminishes afterwards. This situation has led industrial hygienists and occupational health physicians to develop the reflex that the smaller the particle, the more deeply it is deposited in the lungs. Take note that the situation is completely different for nanoparticles!

Figure 5, taken from Witschger and Fabriès (2005) and reproduced with the authorization of the Institut National de Recherche Scientifique (INRS) in France, illustrates the deposition rate in the different pulmonary regions according to particle size. This figure clearly illustrates that no particle with an aerodynamic diameter of 1 nm, or 0.001 micrometre, reaches the alveoli, while 80% are deposited in the nose and pharynx. The other 20% are deposited in the tracheobronchial region. At this size, retention of inhaled nanoparticles is nearly 100%.

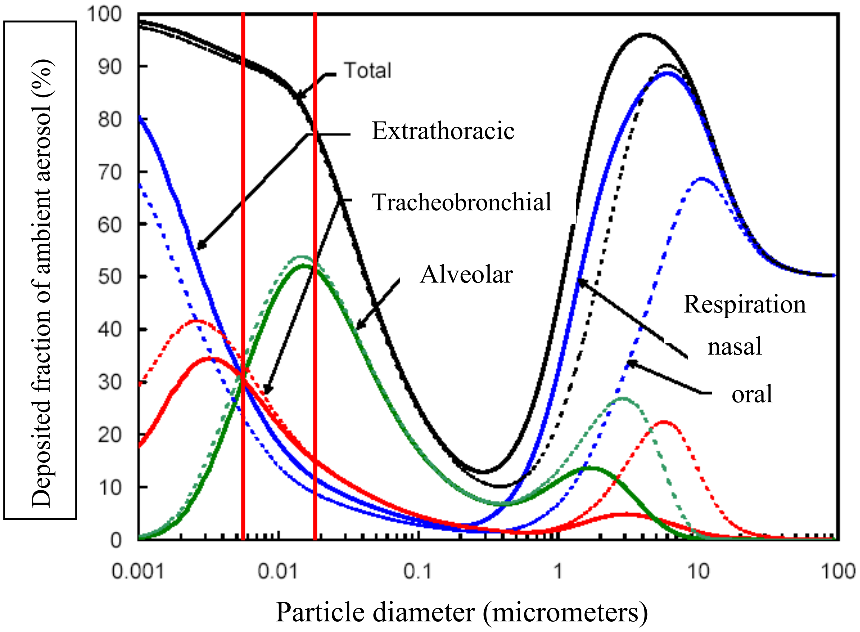


Figure 5 : Prediction of total and regional deposits of particles in the airway according to particle size (41). Reproduced with the authorization of INRS-France

By increasing the particle size to 5 nm (vertical line on the far left), 90% of all inhaled particles are retained in the lung and then are deposited relatively uniformly in the three regions. The total absorption of 20 nm particles (second vertical line to the right) decreases to no more than 80%

but more than 50% of the 20 nm particles are deposited in the alveoli. This means that 20% of the inhaled particles penetrate the lung but leave it upon exhaling. The particle granulometry thus has a major impact on the pulmonary deposition site (Witschger and Fabriès 2005; Oberdorster 2005b). In several nanoparticle manufacturing processes, the granulometry can also vary greatly according to the stage reached by production. To understand the behaviour of dusts and aggregation phenomena, it is recommended that readers consult the IRSST report (Ostiguy et al., 2006).

Given the major surface differences of each of the three pulmonary regions, even if the mass of 20 nm ultrafine particles deposited in the alveolar region represents more than 50% of the total, the dust concentration deposited per surface unit in the lung will be more than 100 times greater in the nasal region and more than 10 times greater in the tracheobronchial region (Oberdörster, 2005b). These differences in dust distribution in the lungs may have major consequences on the health effects of inhaled ultrafine particles and on the elimination mechanisms involved (Kim and Jaques, 2000; Schiller et al., 1988; Jacques and Kim, 2000; Daigle et al., 2003; Oberdörster, 2005a, 2005b; Zhang et al., 2005b).

6.2.3 Elimination of dusts deposited in the lungs

The human body has different defence mechanisms for eliminating these undesirable foreign objects. Two processes are involved: chemical dissolution for soluble particles and physical translocation, meaning transport from one location to another, for insoluble or low solubility particles. Soluble ultrafine dusts will act at the solubilization site and will not be discussed here, since the effects vary widely according to dust composition.

By translocation, the low solubility or insoluble particles deposited in the pulmonary tree are eliminated from the respiratory system. The coarsest particles, which normally are deposited in the upper sections of the lungs, primarily at the tracheobronchial level, are eliminated by the mucociliary elevator, where the tracheobronchial mucous membranes are covered with ciliated cells that form an elevator and push the mucus containing particles towards the digestive system. Normally this is an efficient mechanism that eliminates particles, even ultrafine particles, in less than 24 hours (Kreyling *et al*., 2002).

At the alveolar level, macrophages will take charge of insoluble particles with a phagocytosis mechanism, whereby the macrophages will surround the particles, digest them if they can and direct them solely to the mucociliary elevator for elimination. This process is relatively slow and has a half-life of over 100 days in humans (HSE 2004a, 2004b; Oberdörster, 2005b). However, the efficiency of phagocytosis largely depends on the particle's form and size. Several studies seem to show that the unagglomerated ultrafine particles deposited in the alveoli are not phagocyted efficiently by the macrophages. However, macrophages are very efficient in the one to three micrometre range, and thus for much coarser particles (Tabata and Ikada, 1988, Green *et al*., 1998). Pulmonary macrophages cannot efficiently take over fibres longer than 20 micrometres.

The inefficient takeover of ultrafine dusts by macrophages can lead to a substantial accumulation of particles if exposure continues and to a greater interaction of these particles with the alveolar epithelial cells. Studies have shown that some ultrafine particles can pass through the epithelium and reach the interstitial tissues (Oberdörster *et al.*, 1992, 2000; Kreyling and Scheuch, 2000). This phenomenon seems to be more significant for higher species, such as dogs and monkeys, than for rodents (Nikula *et al.*, 1997; Kreyling and Scheuch, 2000). Once the particles pass through the epithelium, a fraction can reach the lymphatic nodules by interstitial transport.

Two other mechanisms are now recognized for ultrafine particles of nanometric dimensions (Oberdörster, 2005a, 2005b). Ultrafine particles can penetrate the extrapulmonary organs via the bloodstream. Moreover, certain particles can be transported along the axons of the sensitive nerves to the central nervous system. These two mechanisms could play a major role in the development of certain cardiac or central nervous system diseases, but these phenomena have yet to be clearly demonstrated in humans. Katz *et al.* (1984) described the neuronal transport of 20 to 200 nm microspheres from the nose to the brain. The inhalation of 35 nm radiomarked carbon particles led to a significant accumulation in the olfactory bulb of rats seven days after exposure. Several studies showed that when rats are exposed to dusts or welding fumes containing manganese, a manganese fraction could cross the hematoencephalic barrier by circulating directly from the nose to the brain via the olfactory nerves, thus allowing manganese to accumulate in the brain. Such studies were also performed on various soluble metals and led to the same conclusions (Tjalve and Henriksson, 1999; Brenneman *et al.*, 2000; Dorman *et al.*, 2002; HSE 2004a, 2004b; Oberdörster *et al.*, 2004; Ostiguy *et al.*, 2003, 2005; Salehi, 2005).

6.2.4 Effects of inhaled ultrafine dusts

When particles are reactive or present in sufficient quantity, they can activate or destroy the macrophages or the epithelium and produce an inflammatory mechanism that is pathogenic to pulmonary function. In the event of high and repeated pulmonary dust exposure, the natural defence mechanisms may no longer be enough to do the job. In their model developed in 2003, Faux *et al.* explain how an overload of low solubility dusts can generate oxidizing free radicals, lead to an antioxidant deficit, create oxidative stress and produce inflammation. A whole series of reactions likely to lead to the development of occupational lung diseases are then triggered.

Since knowledge of pulmonary toxicity related to nanometric particles is limited, we will report the principal known toxic effects related to respirable or ultrafine particles of up to a few micrometres, i.e. up to over 1000 nm. We will then establish the knowledge level relating to nanometric particles so that we can draw general conclusions.

Dusts found in work environments, often around one micrometre in size, can accumulate in the lungs and lead to several occupational lung diseases, such as pneumoconiosis (asbestosis, silicosis…), smelter's fever, occupational asthma, berylliosis and lung cancer. Donaldson (2005) presents a review of the current knowledge in the field. On the pulmonary level, it clearly appears that toxicity is related to oxidative stress caused by the presence of transition metals, an organic fraction or deposited dusts with a very high specific surface. This oxidative stress can lead to inflammation of epithelial cells. The section on fullerenes noted that toxic effects of these new molecules are also related to an oxidative stress mechanism.

The most common lung diseases are pneumoconioses, which can be caused by fibrous or non-fibrous dusts and constitute an alteration of the pulmonary structure, resulting from dust accumulation in the lung. This excludes asthma, bronchitis and emphysema (Faux *et al.*, 2003).

Pneumoconiosis can vary greatly in severity, ranging from very mild to very severe. In mild cases, dust accumulation in the lungs only causes benign effects to the lung structure without harmful consequences. This is often the case, for example, with exposure to iron or tin dusts, which eventually can lead to siderosis or stannosis (HSE, 2004a, 2004b, 2004c). In more severe cases, as often occur following exposure to asbestos (asbestosis) and silica (silicosis), fibrotic changes in the lung lead to major deficiencies in terms of gaseous exchanges. Lung capacity then is greatly reduced and the disease can be fatal. In some cases, these substances, silica and asbestos, have led to the development of lung cancers. Exposure to asbestos fibres can also lead to the development of mesothelioma (HSE, 2004a, 2004b; Patty's, 1993).

Occupational asthma can also be caused by dusts or aerosols reaching the lungs. In the case of asthma, the lung becomes hypersensitive and subject to constriction, which obstructs the airway. The reaction is often allergic. Bronchitis is a bronchial inflammation which can also be due to dust accumulation in the bronchial region. This condition can also obstruct the airway, and bronchitis is characterized by a major secretion of mucus (HSE, 2004a, 2004b; Patty's, 1993). Emphysema, often related to cigarette smoking, but which can also result from dust exposure in the work environment, is characterized by the breaching of certain alveolar walls. The direct consequence is that gaseous exchange becomes more difficult, since the available surface for these exchanges is diminished.

What about the pulmonary toxicity of nanoparticles? The data presented in section 6.1 and the main literature reviews available all suggest, based on the body of knowledge developed regarding rats, that at equal mass, nanoparticles are more toxic than microparticles for the same product.

One of the first studies illustrating this effect is by Ferin *et al.* (1992), focusing on TiO_2 particles. The researchers exposed rats to agglomerated TiO_2 nanoparticles, the elementary particles of which had a mean diameter of 21 nm with an agglomerate of 250 nm. They also exposed rats to 250 nm TiO_2 particles. Since the two fractions have the same granulometric characteristics due to aggregation of the nanoparticles, the researchers assumed that the dusts would be deposited in the same location in the rat's lung. The two fractions (nanometric and non-nanometric) induced inflammatory reactions at the alveolar and interstitial level. However, the reaction caused by the nanometric particles was much stronger (up to 43 times) and sustained than for the micrometric particles. The two products led to a pulmonary fibrosis, which was much more severe in the case of the nanometric fraction. Epithelial damage was reported for the nanometric fraction, but not for the coarser fraction. On a mass basis, clearance was about three times slower for the nanoparticles than for the microparticles. Although marked differences had been observed on a product mass basis, the results became comparable when the researchers instead considered the surface of the products. The smallest particles have a larger specific surface than the coarsest particles for the same mass, while the difference in reactivity seems to be related to this increased nanoparticle surface.

The conclusions of the Ferin *et al.* study (1992) were confirmed by several research teams on different products. This is particularly true for aluminium oxide, Al_2O_3 (Oberdörster *et al.*, 1990), metallic cobalt (Zhang *et al.*, 2000), titanium dioxide, TiO_2 (Borm *et al.*, 2000; Heinrich *et al.*, 1995; Lee *et al.*, 1985; Oberdörster *et al.*, 1992; Renwick *et al.*, 2004) and carbon black (Gallaher *et al.*, 2003; Gilmour *et al.*, 2004; Li *et al.*, 1996; Renwick *et al.*, 2004).

Driscoll (1996) reports that for different insoluble and non-cytotoxic particles, lung tumours were observed in rats when the total surface of the inhaled particles was greater than 2000 cm^2. Tran *et al*., (2000) suggested a limit value of 200 to 300 cm^2 before TiO_2 dusts of different granulometries cause pulmonary inflammation. In its review of current knowledge, HSE (2004a) also mentions that the physicochemical properties, the surface properties, and the catalytic properties with high potential for generating free radicals (Donaldson *et al*., 1996; Zang *et al*., 1998) are all factors that can contribute to the higher toxicity of nanoparticles compared to microparticles.

Zang *et al*., (1998) showed that metallic nickel nanoparticles caused a greater inflammation than metallic cobalt or TiO_2. Cobalt had a higher inflammatory potential than TiO_2. TiO_2 displayed a low capacity to form free radicals, while the two metals showed comparable potential. Another factor that could influence the toxicity of nanoparticles would be their capacity to deagglomerate in the lung. Thus, Oberdörster *et al*., (1992) showed a translocation of nanoparticles to the pulmonary interstice. This phenomenon was greater with TiO_2 nanoparticles compared to carbon black. The authors associated this difference with the relative facility of deagglomeration of nanoparticles in the lungs.

As already mentioned, surface treatments can totally alter the toxicity of nanoparticles, regardless of whether they are found in the lung in the form of unitary particles or agglomerates. Oberdörster (2001) also showed that surface treatment of TiO_2 nanoparticles substantially altered their toxicity. Several pharmacological studies aimed at the development of new drugs exploit this characteristic.

As described in the section on elimination of dust deposited in the lungs, certain nanoparticles can pass through the pulmonary barrier, become systemically available and cause effects elsewhere in the body. The toxicity of these nanoparticles circulating in various organs is not totally known (HSE, 2004a, 2004b, 2004c; Donaldson, 2005; Oberdörster 2005a, 2005b). Nonetheless, animal studies of ultrafine particles have shown pulmonary inflammation with pathological change and translocation of particles to extrapulmonary tissues.

Several studies suggest possible systemic effects of nanoparticles (HSE, 2004a, 2004b, 2004c; EPAQS, 2001; Ibald-Mulli *et al*., 2002; Donaldson 2005). According to some authors, the fine fractions of polluting particles, those in the nanometric field, would pass directly from the lung into the bloodstream, alter blood viscosity and thus be responsible for the effects observed (EPAQS 2001; MacNee *et al*., 2000).

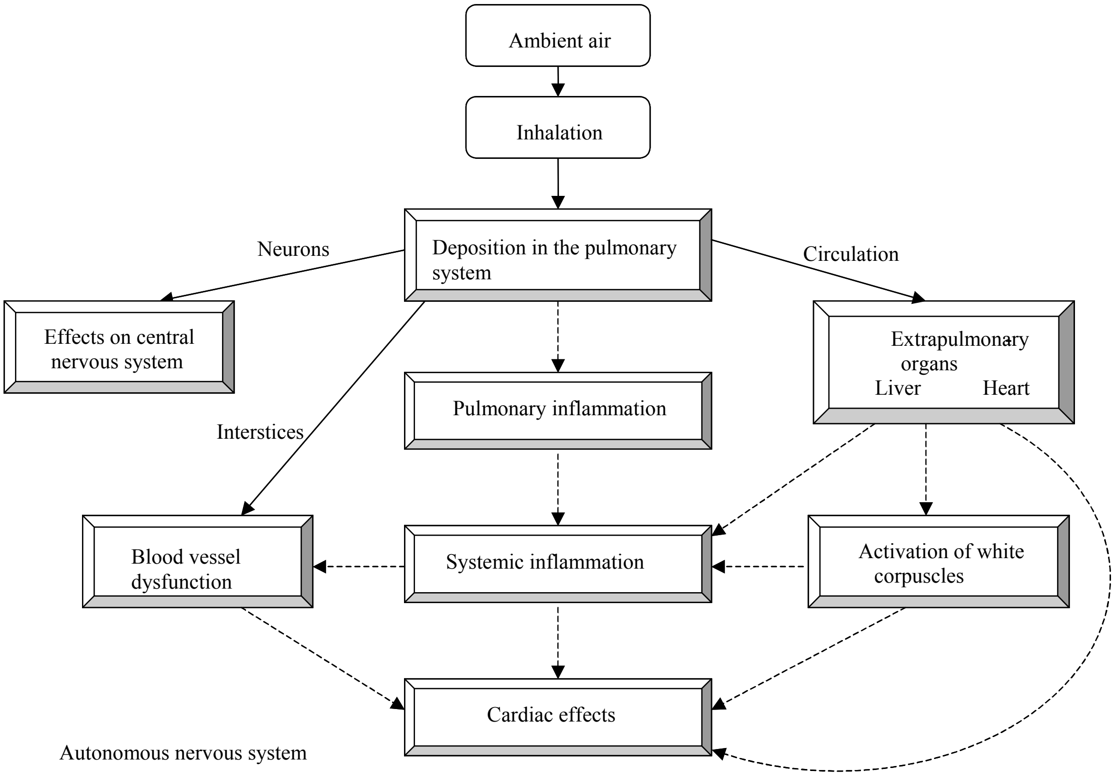
Other studies suggest that smelter's fever appearing after acute exposure would also be related to nanometric particles produced during smelting and welding operations and containing different metals, such as zinc or cadmium (Oberdörster *et al*., 1995).

The translocation of inhaled ultrafine particles into the bloodstream could affect the endothelial function and promote thrombosis and other circulatory system problems, including increased blood coagulation (Nemmar *et al*., 2002a; Elder *et al*., 2000, 2002, 2004; Zhou *et al*., 2003; Kreyling *et al*., 2002). This phenomenon has been shown in hamsters (Nemmar *et al*., 2002b, 2003) but the situation in humans remains ambiguous.

In humans, at the cardiovascular level, epidemiological studies and studies of volunteers have shown that the level of inhaled particles has direct effects on cardiovascular physiology, with alterations of health rhythm and arterial diameter. Moreover, several epidemiological studies (Wichmann *et al*., 2000; Peters *et al*., 1997, Penntinen *et al*., 2001, Pekkamen *et al*., 2002) identified a direct relationship between exposure to ultrafine dusts of nanometric dimensions and respiratory and cardiovascular effects. Several epidemiological studies have established significant relationships and shown that an increase in fine particle air pollution, originating mainly from vehicle emissions, led to a rise in mobility and mortality of more fragile populations with respiratory and cardiac problems (Bruske-Hohlfeld *et al.*, 2005). Controlled clinical studies in the laboratory have shown deposition of ultrafine dusts throughout the pulmonary tree, accompanied by cardiovascular problems (Daigle *et al*., 2003; Brown *et al*., 2002; Pietropaoli *et al*., 2005; Oberdörster, 2005a, 2005b). Studies of coal miners exposed to ultrafine dusts have proved the accumulation of such dusts in the liver and spleen (Donaldson, 2005). The accumulation was higher in miners displaying severe pulmonary problems, thus suggesting that damaged lungs or lungs with major deposits favour the passage of ultrafine particles into the circulatory system.

To summarize, ultrafine dusts of the same dimensions as nanoparticles enter the body mainly by inhalation and are deposited in the lungs; some of them can reach the brain directly via the olfactory nerves. The lungs do not necessarily succeed in eliminating these undesirable particles, which then cause pulmonary inflammation, potentially leading to the development of certain lung diseases. Moreover, some of these very fine dusts can pass through the various protective barriers of the lungs, reaching the circulatory system; they are then distributed to all parts of the body, where they can cause different kinds of damage. Oberdörster (2005b) summarizes the effects on the body of inhalation of ultrafine dusts of nanometric dimensions. The translocated particles can then become mediators, causing various effects on the body. Figure 6 summarizes the potential effects of inhaled ultrafine particles.

Figure 6 : Potential effects of inhaled ultrafine particles (Reproduced with permission of Dr. Gunter Oberdörster, 2005b



Translocation of particles: ⟶

Mediator: - - - - - - - - ->

6.2.5 Cutaneous absorption

The skin is composed of three distinct superimposed layers: the outer layer or epidermis, the dermis and the inner subcutaneous layer. The outer wall of the epidermis, the stratum corneum, is composed of dead skin cells piled on top of each other and bound together by keratin. This offers a barrier that is normally effective against penetration by dust, while the absorption speed of liquids varies according to their physicochemical properties. Thus, most studies that have focused on particles of micrometric dimensions have not found major problems resulting from cutaneous contact, except under conditions of local irritation, abrasion or sensitization to certain metals following solubilization on the skin surface (HSE, 2004a). Some recent studies have revealed some cutaneous penetration by ultrafine beryllium particles (NIOSH, 2003) and the formation of cutaneous nodules (Muller-Quernheim, 2003). Nonetheless, the studies conducted to date diverge and allow no conclusion on the cutaneous absorptive potential of nanoparticles.

Despite this lack of knowledge, some products containing nanoparticles are commercially available, such as certain lipsticks containing iron oxides and even sun creams containing TiO_2. For TiO_2, Lademann *et al*. (1999) showed that nanoparticles do not penetrate beyond the stratum corneum except in the hair, where the concentration was very low. These results were confirmed by Schultz *et al*. (2002). In their review of health risks, the HSE (2004a, 2004b) concluded that systemic toxicity resulting from cutaneous absorption of insoluble nanoparticles should not cause significant problems. However, there are no significant differences between nanometric particles and microparticles in terms of systemic effects following cutaneous exposure. The risk of solubilization of certain components of these particles and the toxic effects that may be associated with them are the same as for coarser particles.

6.2.6 Absorption by ingestion

Ingested particles smaller than 20 µm (20,000 nm) can pass through the intestinal barrier and enter the bloodstream (Gatti and Rivasi, 2002). Hillyer and Albrecht (2001), according to a series of biopharmacological research studies, which indicate that latex, polystyrene and prophylactic polyglycolic acid particles ranging from 50 nm to 20 µm are mainly absorbed by the Peyer's patches of the small intestine, without significant translocation to non-lymphoid intestinal tissues. Intestinal absorption would be related to the particle size, with the smallest being more readily absorbed. Polarity is also a significant factor, since hydrophobic particles are captured in preference to hydrophilic particles. Translocation can be increased if inert particles are coupled with proteins, such as lectin or invasin.

6.2.7 Comments on the contribution of the use of nanomaterials in biopharmacology

The potential applications of nanomaterials in the biomedical and pharmacological field are very numerous and this field is growing rapidly (Buxton *et al*., 2003). Nanoparticles used in medicine have the feature of allowing great absorption by the cells, which makes them useful as pharmacological vectors or colourings in target cellular compartments or organs (Orive *et al.*, 2004). The types of nanoparticles used are dendrimers, ceramic nanoparticles, nanocapsules or nanospheres, liposomes, micelles, and hybrid nanodevices. The preferred targets, in particular, are the smooth muscle cells, neoplasic cells, inflammation mediators, proteins released during viral inflammation and cellular organelles, such as mitochondrias. Other nanomaterials can be used as biosensors, diagnostic markers, in the medical imaging sector. A nanomaterial can exercise combined pharmacological actions (e.g., diagnostic and therapeutic). Another major field of application is tissue regeneration, as well as grafts and implants, due to the ability of certain nanomaterials to act as matrices conducive to cellular growth, in particular.

We mention these applications without going into detail, because the scientific literature regarding them is too abundant and this subject is beyond the scope of this report. Although the pharmaceutical industry's goals are related to medical applications, this field of research reveals the variety of possible behaviours of nanoparticles *in vivo*. The implications of *in vitro* or *in vivo* studies performed on abnormal cells are currently difficult to interpret regarding healthy cells. However, this is worth noting, because industrial production or industrial use of these nanomaterials is likely to pose a potential risk to the workers who handle them, depending on the conditions of exposure. The effects of such exposure are difficult to predict because the workers' exposure routes probably would not be the same as when these substances are administered for therapeutic or diagnostic purposes. However, due to the great absorption and distribution potential of nanomaterials, it is possible that inhalation, for example, could generate intravascular circulation of certain nanomaterials and eventually produce cellular effects similar to those contemplated by medicine, which might or might not be desirable.

6.2.8 Quantitative assessment of the risk of exposure to nanoparticles

The international experts assembled by the European Commission are unanimous that the potential deleterious effect of nanoparticles cannot be predicted from the toxicity of bulk materials of the same chemical composition but of greater size (European Commission, 2004b). The risk assessment cannot be established precisely, since the dose-response relationships are insufficiently known. For most of the particles that can become airborne and breathed in, the primary concern is the potential damage to the respiratory system, which represents the most likely absorption route in the work environment. The solubility of the particles directly affects their toxicity and the way they must be assessed or analyzed. In the presence of soluble particles, the entire mass deposited in the pulmonary air passages will quickly become available by dissolution in the biological fluids. This mechanism is well known for particles of larger dimensions. It is the same for nanoparticles. For soluble particles, the assessment of the total mass concentration of these particles thus will become a good indicator of their toxicity.

However, insoluble or low solubility particles will retain their form and expose their surface to the host organism. It then becomes important to document the specific toxicity of these insoluble or low solubility nanoparticles. In the absence of adequate knowledge, attention should also be paid to the cutaneous system and the possibility of ingestion of nanoparticles, particularly by adopting strictly hygienic safety measures.

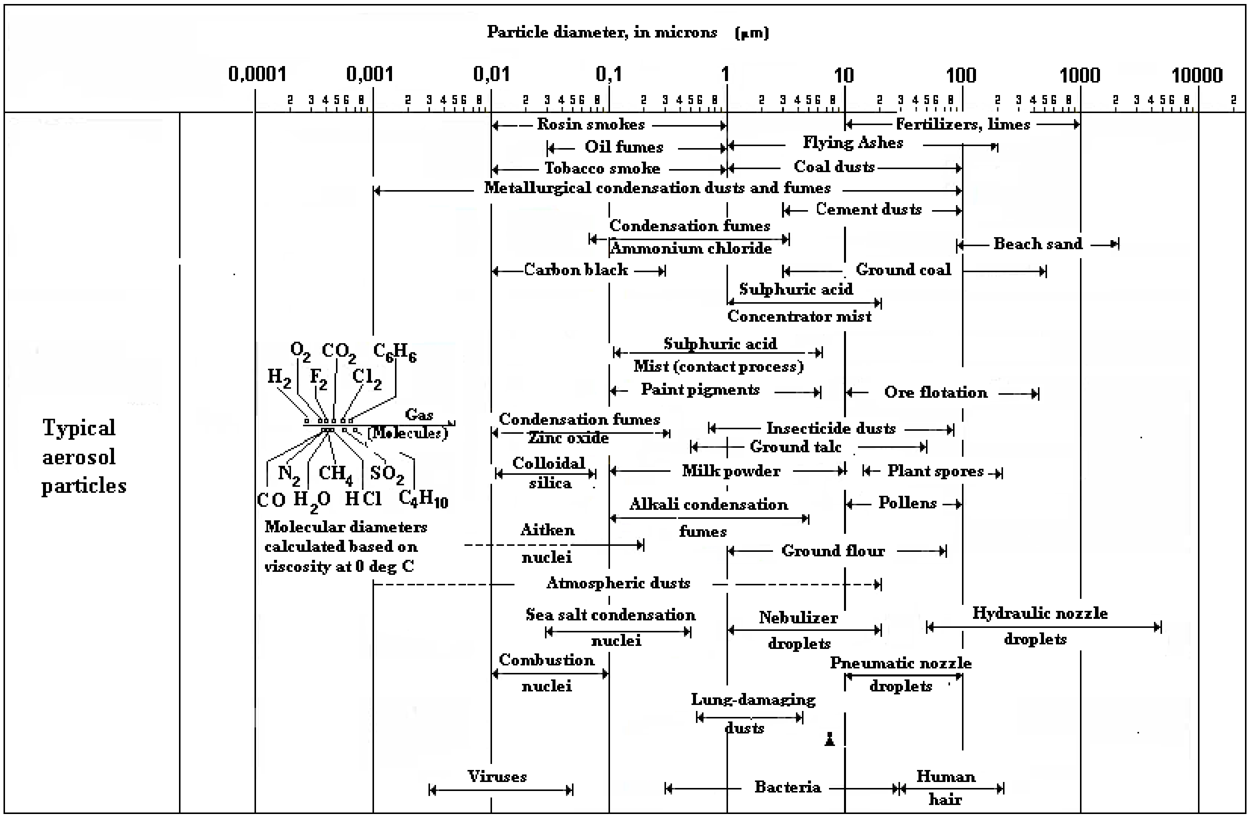
To assess the potential human health effects of nanoparticles, it is important to develop knowledge that can provide answers to several questions. Specifically, it is essential to document how nanoparticles are absorbed into the human body by several routes (pulmonary, cutaneous and gastrointestinal), how nanoparticles are distributed in the body (blood, lymphatic system), the organs in which nanoparticles tend to accumulate significantly (lungs, brain, kidneys, liver…), and how nanoparticles are metabolized and then eliminated (Durrenberger, 2004).

7. NANOMATERIALS, THEIR BEHAVIOUR AND THEIR AIRBORNE DETECTION

7.1 Definition

As already mentioned, there is no unanimity on the dimensions of nanoparticles and several authors differentiate nanoparticles from ultrafine particles. The current definition defines nanoparticles as particles with at least one dimension smaller than 100 nm or 0.1 µm, and with different properties than particles of larger diameters made of the same material (The Royal Society, 2004a, 2004b; Brouwer *et al.* 2004; Ji *et al.* 1999; Jacobson and Seinfeld, 2004). Figure 7 compares the diameters of certain aerosols of interest in industrial hygiene.

Figure 7: Dimensions of typical aerosol particles



As already mentioned, two major factors contribute to the changes of properties observed for nanoparticles compared to bigger materials: a much greater relative surface area per unit of mass and a predominance of quantal effects. The first factor is responsible for changes in reactivity while the second, observed for particles of a few dozen nm, explains the changes in optical, electrical and magnetic properties. 5% of the atoms of 30 nm particles are surface atoms, compared to 20% for 10 nm particles and 50% for 3 nm particles. The hygienist's challenge will be to assess occupational exposure adequately.

7.2 Formation and behaviour of nanometric or ultrafine particles

The size of particles formed by a process primarily depends on their formation mechanism. Different mechanisms are responsible for formation of nanoparticles or ultrafine particles. The principal mechanisms are nucleation, evaporation, precipitation and attrition. These nanoparticle formation mechanisms and the principal industrial processes involved have already been described in section 5.2.

When particles are very fine and can be described as nanoparticles, the diffusion forces become significant and explain their behaviours, which are similar to the behaviour of a gas or a vapour. This differentiates them from coarser particles, for which inertial forces tend to dominate. Particle size absolutely must be considered in the interpretation and establishment of occupational exposure control methods.

A major forum reviewed the current state of scientific knowledge of aerosols of nanometric dimensions (Friedlander and Pui, 2003). It concludes that nanoparticles can display unpredictable mechanical, optical, biochemical and catalytic properties. Studies are continuing to characterize their formation and behaviour (Friedlander and Pui, 2003). Nonetheless, it is now possible to describe the principal behaviours of airborne nanoparticles, once nucleation has occurred (Aitken *et al*., 2004, Friedlander and Pui, 2003).

7.2.1 Diffusion

Diffusion of aerosol particles is the net transport of these particles in the presence of a difference in concentration. Diffusion always occurs from the highest concentration to the lowest. If we exclude convection, diffusion is the principal mode of transport of particles smaller than 100 nm. The speed at which particles diffuse is determined by their coefficient of diffusion, which is inversely proportional to their size. Nano-scaled particles will diffuse much faster than micro-scaled particles. Thus, nanoparticles will not stay localized in the zone near a leak in the work environment. They will diffuse rapidly and may end up far away from a source, potentially exposing many individuals located a long distance from the leak.

7.2.2 Coagulation and agglomeration

Because of diffusion and Brownian motion, aerosol particles will be subjected to a multitude of collisions, which will lead to their agglomeration or coagulation and an increase in their diameter. The speed at which the particles agglomerate will depend on their numerical concentration and mobility. The mobility of particles is inversely proportional to their diameter. Coagulation of very small particles will quickly lead to the formation of larger particles in lower concentration, which will persist longer because their mobility is reduced. Particles from 1 nm to 100 nm formed by nucleation tend to agglomerate quickly to form larger diameter particles. When they reach a size of around 100 nm, they grow at a slower pace, up to 2000 nm. This slowed growth zone, between 100 and 2000 nm, is called accumulation mode.

The primary aerosol particles that come into contact will adhere to each other to form aggregates, which are held together strongly by ionic/covalent bonds. Aggregates can bond to each other to form agglomerates. These aggregates tend to adhere to each other because of Van der Waals forces that only act over short distances, electrostatic forces present in the particles and adhesion forces related to the liquids adsorbed to their surface. Coagulation is thermal when caused by Brownian motion. It is kinetic when caused by an external force, such as gravity, electrical forces or aerodynamic effects. Van der Waals forces are weak forces that hold aggregates together (Friedlander and Pui, 2003). Murr *et al.* (2004) clearly showed that airborne particles were mainly aggregates of aerodynamic diameters ranging from a few nanometres to several micrometres.

7.2.3 Gravitational sedimentation

Gravitational sedimentation is the phenomenon whereby particles fall into a medium under the effect of gravity. Sedimentation speed increases with particle diameter and depends on several factors, particularly the viscosity of the medium in which it occurs. Sedimentation of very small particles is slower than for large particles. Gravitational sedimentation thus cannot be considered an efficient mechanism for elimination of small particles, particularly nanoparticles.

7.2.4 Resuspension

Resuspension of particles from powder is extremely complex. Several factors can influence this process, particularly size, form, electrostatic particle charge and ambient humidity. The forces responsible for the particles' adhesion to each other are also responsible for the particles' adhesion to the surfaces. The smaller the particles, the more difficult they will be to detach and resuspend. Most nanoparticles, once they are attached, i.e., aggregated or agglomerated in powder form, will not be easy to separate or suspend in the air of the work environment.

7.3 Detection of nanoparticles

The quantitative determination of exposure to nanoparticles currently poses a major challenge, because every environment already contains airborne particles in suspension. Through this mixture of dusts of different granulometries and various compositions, the content and characterization of nanoparticles must be determined. In industrial hygiene, airborne dust quantities are normally determined in units of mass per volume for most dusts, except in the case of fibres, which are counted. These different ways of evaluating airborne dusts account for parameters improved the definition of the correlation between the health impairment risk and the exposure level.

The current data (see Chapter 6) strongly suggest that the health risks related to nanoparticles instead are correlated to the specific surface of the nanoparticles. It then becomes important, in some cases, to evaluate the concentration by number of particles and by surface area (Brouwer *et al.*, 2004). The worker's exposure measurements normally are taken in the respiratory zone. However, they can be deducted from fixed station sampling, but very cautiously, because the literature has reported major variations of numerical concentration granulometry, even for short distances (Brouwer *et al.*, 2004). These authors conclude that personnel workstation concentrations are normally higher than the environmental concentrations (Brouwer *et al.*, 2004).

Because of the rapid major variances in particulate concentration observed for nanoparticles and ultrafine particles, the direct reading devices used must react quickly. Unfortunately, no device is currently adapted to sample such particles in the respiratory zone. The existing devices capable of detecting nanoparticles and ultrafine particles are bulky and not conducive to sampling in the work environment, even at fixed stations. Major developments will be required to determine the precise occupational exposure on a routine basis with user-friendly, robust and affordable instruments (Friedlander and Pui, 2003).

Nanoparticles can be detected by electrostatic methods, by condensation on particles to grow them until they are measurable optically, or by other methods. Electrostatic methods require that the particles be charged and are not very sensitive, while condensation on particles is the only means allowing detection of neutral aerosol particles, which are too small to be measured by the optical method. The existing devices using condensation techniques can cover a wide range of diameters and concentrations.

The devices using the detection methods described above are often used with other devices, such as electrical mobility analyzers acting as preselectors. Combining these two types of devices obtains the granulometries or fine structures of ultrafine aerosols.

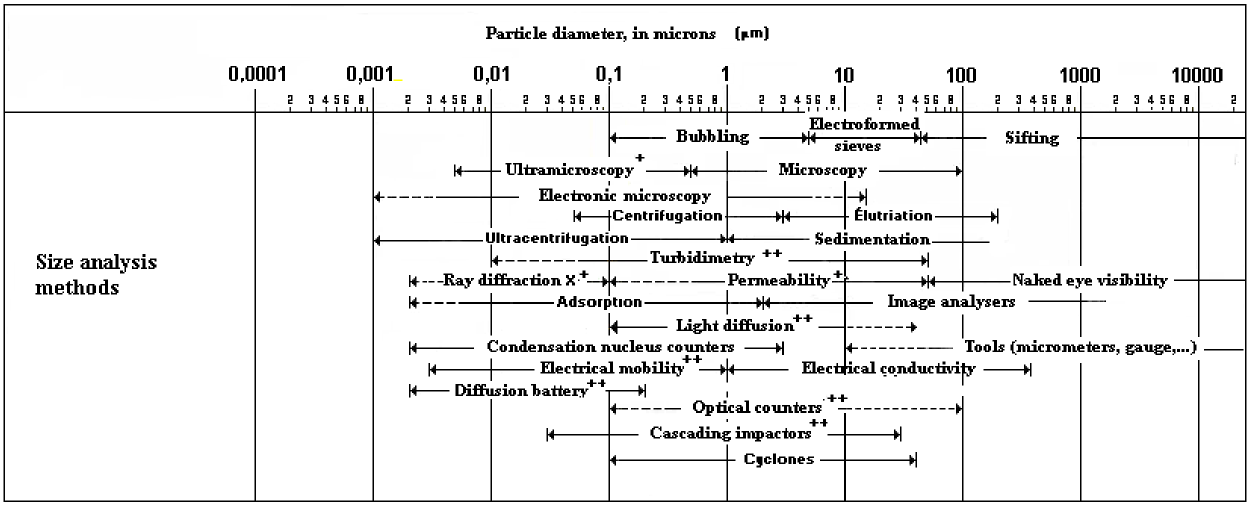
Most of the devices used for nanoparticle detection cannot discriminate between nanoparticle agglomerates or single particles. This is why they are limitative in terms of assessment of aerosol toxicity, because it has been shown that nanoparticle agglomerates can have increased toxicity compared to solid particles of the same size (Oberdörster *et al*., 1994).

7.3.1 Devices for direct measurement of concentration

Different devices and techniques allow measurement of certain parameters of particles in suspension in a liquid or gaseous medium. These parameters generally are the particulate concentration by mass, surface or number present in a certain liquid or gaseous volume. Some devices or techniques also make it possible to obtain the granulometric structure of these suspensions, that is, obtain these parameters for the different particle sizes present. Figure 8 briefly illustrates some of these devices or techniques and their range of applicability.

The following sections briefly describe the relevant nanoparticle detection techniques. Although described here, most of these techniques show serious limitations and require improved sensitivity and finer particle detection capacity. Moreover, continuous measurements would be desirable in most situations. Finally, we should note that it is difficult to calibrate these instruments, due to the unavailability of well-characterized reference standards (Friedlander and Pui, 2003). Thus, photometric optical techniques are excluded because they are applicable only for particles of diameters greater than 100 nm.

Figure 8: Techniques available for determination of size analysis



\+ Gives the mean diameter of the particles but not the granulometric distribution
++ Granulometric distribution

7.3.2 Diffusion batteries

Diffusion batteries are used as preselectors for detection devices, such as condensation nucleus counters (CNC). They use the well-known phenomenon of the increase in particle diffusion capacity in inverse proportion to the decrease in particle diameter. Small particles passing through a sieve will interact with it more due to surface attraction forces and will be deposited more quickly on the neighbouring walls than coarse particles. The batteries use this phenomenon to separate the particles by granulometry brackets. This separation technique can be used for particles ranging from 2 nm to 200 nm (Hinds, 1982) but is most often applied for particles smaller than 100 nm (McMurray, 2000a). Granulometric resolution is limited (Willeke, 1993), which explains why the devices described above, using electrostatic classification, are preferred to diffusion batteries. TSI is the only manufacturer to offer such a device with its model 3040/3041.

7.3.3 Condensation nucleus counters (CNC)

Condensation nucleus counters (CNC) serve to measure the numerical concentrations of particles. They are also called condensation particle counters (CPC) or Aitken nucleus counters (ANC). This technique is applicable to the detection of particles ranging from 2 nm to 3000 nm (Brouwer *et al.*, 2004; McMurray, 2000b). Their generally slow response time means that the number of concentration peaks is underestimated. However, their integrated values remain reliable (Shi *et al.*, 2001). Table 2 lists some commercially available devices and their range of use.

Table 2 : Commercial condensation nucleus counter

Manufacturer	Device	Analytical range (nm)
BGI	Pollack counter	>2.8 (1)
Environmental One	Rich 200	
Gardner	CNC	>3.8 (1)
TSI	CPC 3007 (in real time)	10 to >1000
TSI	CPC 3022	> 6 (2)
TSI	UCPC 3025	> 3 (2)
TSI	P-Trak 8525 (in real time)	20 to > 1000
TSI	CNC, model 3760	> 14 (1)
MET	CNC, model 1100	> 10 (1)
KAN	CNC, model 3851	> 10 (1)
ACT	CNC, model 5000	> 50 (1)

1. Willeke and Baron, 1993

2. Aalto, 2004

7.3.4 Electrical mobility analysers

Devices using electrical mobility make it possible to classify particles or deposit them on surfaces. They use the drift of a charged particle in an electrical field to classify or deposit it. Electrical aerosol analyzers (EAA) and differential mobility analyzers (DMA) classify particles. Electrostatic precipitators (ESP) allow deposition for subsequent laboratory analysis, by microscopy, for example. Apart from electrostatic precipitators, these devices must be used in series with different detection devices to determine the granulometry of an ultrafine or nanofine aerosol. Thus, an electrostatic precipitator or an electrical aerosol sampler (EAS) must be combined with an electrometer, while a differential mobility analyzer (DMA) must be used with a condensation nucleus counter or an electrometer to obtain a granulometry. All these devices require precisely controlled sampling of the aerosol to be analyzed before the mobility analyses and their conversion into granulometry measurements. These techniques are difficult to apply for particles smaller than 10 nm because these particles are difficult to charge. The scanning mobility particle sizer (SMPS) and the differential mobility particle sizer (DMPS) are very bulky and barely portable. However, they rank among the best devices available for analysis of particles between 5 and 800 nm (Brouwer *et al.*, 2004) or between 8 and 200 nm (McMurray, 2000a). The SMPS is an EAA combined with a CNC, while the DMPS is a DMA connected in series with a CNC. The main devices and techniques and their range of application are listed in Table 3.

Table 3 : Main electrical mobility analysers

Manufacturer	Device or technique	Analytical range (nm)
	SMPS	5 to 800 (1)
In-Tox Products	ESP (with an electrometer)	> 30 (2)
Hauke KG	Hauke-Aeras (SAAS 3/150)	3 to 150 (2)
University of Vienna	EMS VIE-06 (requires a CNC)	
TSI	SMPS model 3071	10 to 350 (3)
	MAS	< 100
TSI	EAS model 3100	< 500
TSI	DMPS model 3092	10 to 1000 (4)
TSI	DMPS model 3932	10 to 1000 (2)

[1] Brouwer *et al.*, 2004 [2] Willeke and Baron, 1993
[3] Shi *et al.*, 1999 [4] Vincent, 1995

7.3.5 Cascading impactors

Impactors allow separation of aerosol particles into different granulometry brackets. Each granulometry bracket is associated with a stage of the impactor, on which a collection substrate or a detection element is placed. Impactors offer the advantage of allowing subsequent analysis of particles on the collection substrates and gravimetric determinations. In general, the most common impactors have a range of use between 50 and 30,000 nm (Willeke, 1993).

A wide range of impactors exist but some have been developed specifically for ultrafine particles. They have a lower detection limit. Among them, the micro-orifice uniform deposition impactor (MOUDI), model 110 can classify particles from diameters of 56 nm to 15000 nm while the nano-MOUDI allows three-stage collection of 32, 18 and 10 nm nanoparticles. Table 4 presents some commercial impactors usable for nanoparticles.

Table 4 : Some commercial impactors usable for nanoparticles

Manufacturer	Device	Analytical range (nm)
Atmospheric Technology	Low pressure impactor	50-4000 (1)
Andersen Samplers Inc	Low pressure impactor	80-35000 (1)
Hauke KG	Berner impactor	63-16700 (1)
MSP corporation	MOUDI	56-18000 (1)
MSP corporation	Nano-MOUDI	10 - 32
PIXE International Corp.	Orifice impactor (model 1L-CI)	60-16000 (1)
Dekati	Electrical low pressure impactor (instantaneous measurements)	7- 10 000

[1] Willeke and Baron, 1993

7.3.6 Direct surface measurement devices

No instrument is fully adapted to personal or fixed station surface measurements for aerosols. The epiphaniometer is the only instrument developed for nanoparticles and specifically for this type of measurement. It can provide the total surface measurement of particles between 10 and 1000 nm. This instrument is bulky and has the disadvantage of using radioactive source, which complicates and restricts its use in the work environment. However, an aerosol's specific surface can be measured from an aerosol's granulometric distribution by assuming a specific geometry of the particles (Brouwer *et al.*, 2004).

Surface measurements can also be performed from samples collected by the Brunauer Emmett Teller (BET) adsorption method, using nitrogen or CO_2. This technique allows measurement of all the inner surfaces of the pores. It thus gives a better estimate of the total surface presented by an aerosol than the measurement based on SEM or TEM electron microscopy (Brouwer *et al.*, 2004). However, this method requires the use of large sample quantities and does not allow nanoparticles to be differentiated from other particles (Brouwer *et al.*, 2004). The few commercially available devices are presented in Table 5.

Table 5 : Particle surface determination devices

Manufacturer	Device	Analytical range
Micromeritics Instruments Co	FlowSorb III 2305/2310 (B.E.T.)	> 0.01 m^2/g
Paul Scherrer Institute	Epiphaniometer[4]	0.003 $\mu m^2/cm^3$
Ecochem	Standard Particulate Monitor LQ1-DC	

[4] Gaggeler *et al.*, 1989.

There is consensus on the current limitations of industrial hygiene measuring instruments and the need to develop new instruments adapted to nanoparticle specificities, as well as the absence of reference standard nanoparticles that can be used to calibrate instruments. Simultaneously, the availability of nanomaterials will allow development of new measuring tools applicable to a wide range of environmental situations, in the work environment, in the medical field, etc. (National Science and Technology Council, 2003).

8. EXPOSURE CONTROL

Risk assessment is an essential preliminary step to determine what control level must be implemented to limit emissions in the air or water and prevent a toxic substance from affecting certain target organs in workers. Thus, the control measures must be proportional to the risk (Roberge *et al*., 2004). However, in the absence of adequate knowledge of the toxicity and behaviour of airborne nanoparticles, strict control measures should be put in place to minimize the risk to workers of pulmonary and cutaneous absorption.

With nanoparticles that can become airborne and inhalable, there may be a potential for occupational exposure, whether in production, use, equipment maintenance, recycling or waste disposal. This section discusses the general principles of control of worker exposure to these products. It is the user's responsibility to decide what means should be applied, depending on the risk assessment in particular situations. Special attention must be paid to nanoparticles that involve substantial or unknown health risks and have little or no solubility. The control level must be adjusted according to the severity or uncertainties of the documented risk.

Before discussing how to eliminate or at least reduce and control the risks, it must be remembered that protection of worker health and safety is imperative for corporate development. It is essential that the senior management of every establishment make OSH an action priority, especially since the federal Bill C-45 now holds corporate executives criminally responsible if they fail in their responsibility or act negligently regarding their obligation to protect their workers' health and physical integrity (Department of Justice, 2005). Quebec also has an Act respecting occupational health and safety and various regulations that must be followed. The employer controls the management and supervision of the employees, equipment and work methods. The employer thus has an obligation to adopt all reasonable means to ensure that its employees work in safety. When required, the development and implementation of a prevention program specific to the company will have to cover various aspects. Among these aspects, risk identification, information and training for workers and the various exposure control strategies are essential. Continuous employee information and training is an essential step in establishing and maintaining preventive measures and good work methods.

8.1 Risk assessment

A classical step-by-step approach to health and safety management involves the following components:

- Identifying the danger;
- Assessing the risk;
- Preventing and controlling the risk;
- Evaluating the effectiveness of the control measures.

Risk assessment assumes a good knowledge of the identity and toxicity of the products and the exposure levels at the various workstations. In the case of nanoparticles, the sections on health risks and occupational exposure have clarified the serious lack of knowledge in these two fields essential to the assessment of danger or risk. Nonetheless, we find that the toxicity of nanoparticles probably can be better correlated to the total surface area of particles than to their total mass. As already discussed in detail in Chapter 6, the preliminary results suggest that nanoparticles of identical mass show greater toxicity than larger particles with the same chemical composition.

Given the multiple unknown factors at present, it appears preferable, as a precaution, to minimize occupational exposure in order to prevent the risk of overexposure and the development of occupational diseases. These precautions are essential, even if the only industrial hygiene study available gives reason to believe that, in most manufacturing situations; airborne carbon nanofibres will mainly be found in agglomerated form in relatively low concentrations. Moreover, regarding safety, clouds of nanoparticles that are organic, metallic or composed of any combustible substance have major explosive potential. Since this is mainly related to the extensive reaction surface areas present in nanoparticles, the explosive potential must always be considered (Pritchard, 2004). The quantity of airborne nanoparticle dusts must be minimized to reduce these various risks.

The most effective way to minimize nanoparticle exposure is to implement effective control strategies, taking into account the differences between nanoparticles and larger particles. These control strategies may include many factors, which will be examined and selected according to their adaptability to the specific situation studied (Roberge *et al.*, 2004).

8.2 Risk and nanoparticle-control strategies

In general, there are three main approaches to risk and exposure control: engineering techniques, administrative means and individual protective equipment. These complementary approaches should be considered starting with the design stage of an industrial process (Ménard, 2004). To minimize the workers' exposure risks, special attention must be paid to the installations, processes, equipment activities and workstations during design. The designer is responsible for recognizing the risk factors specific to the processes and production modes and then anticipating how to eliminate or at least reduce these risk factors. The designer must also design and recommend control measures and ensure that the measures implemented are effective (Ménard, 2004).

Nanoparticle behaviour varies greatly depending on the dimensions and degree of agglomeration. Airborne, non-agglomerated nanoparticles behave much like gases, thus allowing rapid diffusion over long distances. They can subsist in the air for a long time before sedimentation, particularly if their atmospheric concentration is low. For example, 50% of 0.5 nm particles at a concentration of one g/m^3 will be agglomerated after 0.4 microseconds (HSE, 2004). If the nanoparticle measures five nm and the concentration is reduced to one mg/m^3, the time required for 50% of the particles to agglomerate will be 0.12 second. However, if the concentration of 20 nm particles is one ng/m^3, the time will be 44 days.

In case of a production systems leak, diffusion favours environmental dispersion of nanoparticles. For this reason, the engineering control systems intended to present or limit the emission or accumulation of airborne nanoparticles in the work environment, such as enclosure and ventilation, must be designed according to the gaseous and particulate properties of the nanoparticles.

8.2.1 Engineering techniques

- Design

Design is the first and most determining stage in the organization of a business. The design stage occurs when it is necessary to produce the building plans and plan the production and installation of various procurements, production, warehousing, shipping and other systems. In addition to taking into account the regulatory requirements and production imperatives, safe layouts must be designed to eliminate situations involving risks for the process and for the workers.

- Substitution of products, processes and equipment

One of the main risk control approaches that first comes to mind is substitution to replace relatively toxic products with products that are less toxic. Similarly, the most effective risk control methods are process changes, for example from dry processes to wet processes; substitution of equipment involving fewer toxic products; and avoidance, reduction and better control of emissions (Bégin and Gérin, 2002; Gérin and Bégin, 2004). Obsolete equipment that generates contaminants should be replaced.

- Isolation and enclosure

In a number of processes and workstations, chemical handling must be isolated to reduce worker exposure. Some risky operations are then performed by isolating the source in separate, ventilated rooms equipped with a system that avoids any possibility of contamination of other workplaces. Isolation of the process by establishment of closed-circuit processes, physical isolation of risky processes and enclosure allow more effective emission control in open processes, while facilitating treatment of environmental emissions, when necessary. 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 (Ménard, 2004).

The main control method for nanoparticle production is enclosure of the process. The principal advantage is to minimize the airborne release of nanoparticles in the work environment during production. In case of a leak, the nanoparticles will escape just as easily as a gas and will quickly disperse everywhere in the plant. However, as the process progresses, the particles agglomerate and airborne dispersion becomes more difficult. Nonetheless, inhalation exposure to these aggregates is always possible during nanoparticle recovery, bagging and maintenance and cleaning operations. Materials such as carbon black, silica fumes, nanometric TiO_2, metals and nanometric metallic oxides normally are produced in closed circuit processes.

- Ventilation

In some processes, it is impossible to avoid airborne release of pollutants. Source capture of these pollutants is then the method of choice to prevent airborne propagation of these products in the work environment and being breathed in by workers, while contaminating all the work areas (Turcotte *et al.*, 2004). General ventilation, by dilution in the work environment, can draw the contaminants outward. This approach is often ineffective and, in some situations, recirculation of a fraction of the air may be prohibited by the regulations in force.

To ensure a new air supply for some processes, a fraction of the air used in the collection and filtration systems must also be evacuated. This evacuated air will have to go through several filtration stages and 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.

Reduction by source capture remains one of the most effective measures in operations not performed in closed circuits, such as mixing, recover, bagging or weighing of products. Source capture is commonly used in welding, cutting and spray metallization processes, among others (Roberge *et al.*, 2004). These processes, which have been known for many years, generate a significant number of particles of nanometric dimensions. However, this equipment's performance is closely linked to the quality and efficiency of design and maintenance, and often of work methods. The efficiency of new ventilation systems should always be evaluated to ascertain their performance level. For nanoparticles, the specifications and quality of these systems should be similar to those used for gases and vapours. The scientific literature review was unable to identify studies that evaluated the performance of equipment normally used in nanoparticle applications; still, a well-designed system should perform very well, provided the aspiration system intake is correctly positioned and an adequate capture speed is maintained continuously (Mark, 2005a). However, there is frequent documentation of significant exposure levels in carbon black production, because this equipment is not designed or maintained adequately (Aitken *et al.*, 2004).

Cleaning operations should also use a vacuum cleaner with a high-efficiency filtration system. Before performing maintenance on equipment, it should also be vacuum cleaned.

- Air recirculation and filtration

Filtration of air recirculated or discharged into the atmosphere plays a major role in control of exposure to airborne particles. Nanoparticles can be filtered efficiently with a High Efficiency Particulate Arrester (HEPA). Particles much smaller than filter mesh are captured by various mechanisms, such as diffusion, interception, impaction and gravitational sedimentation, as well as electrostatic forces. Brownian diffusion, which is caused by collisions between air and nanoparticles, creates random motion of nanoparticles, increasing the probability that nanoparticles will hit the filter (Lee and Mukund, 2001). This is the leading mechanism for efficient nanoparticle filtration (Mark, 2005a). All these mechanisms ensure that efficient separation can be achieved, even with very small diameter particles. When these particles adhere to the filter fibres, they are arrested efficiently by Van der Waals forces. The efficiency of HEPA filters is determined by the conventional method (Department of Energy, 1998) with medium-sized particles 0.3 µm in diameter. Efficiency must exceed 99.97%. Given the dimensions and physical properties of nanoparticles, an approved HEPA filter should have filtration efficiency greater than 99.97%. Aitken *et al.* (2004) report that the efficiency of HEPA filters could decrease for nanoparticles of less than two nm, but the efficiency of such filters still needs to be quantified.

- Administrative means

Administrative means of control constitute an additional approach when the other methods have not achieved the expected control levels. Administrative means of control must never substitute for engineering techniques, which must always be performed according to standard practices. In some situations, engineering measures are not sufficiently advanced technically, and must be held up for a while before they are implemented; in other situations, they cannot be implemented due to their prohibitive costs. In these situations, reduction of work periods, modification of work practices, personal hygiene measures, housekeeping and preventive maintenance constitute other ways of limiting the occupational exposure risks.

Reduction of work periods mainly applies in a context of work under stressful conditions in a hot environment or in situations where risks cannot be controlled by engineering techniques. In some situations, work practices can be modified to reduce the risks. For example, work near high-temperature furnaces is conducive to heat stroke, and work periods should be adjusted to minimize the risk for workers. In addition, the use of water can reduce dust emissions during certain processes or at some dry material drop-off or transfer points (Ménard, 2004).

Personal hygiene is important. The presence of washbasins and showers in the workplace allows decontamination of areas of the skin exposed to dust. If there is potential for toxic product spatters or spills, the emergency shower is an indispensable tool to respond as quickly as needed. Clothing must be cleaned safely and air jets totally prohibited. In the presence of highly toxic products, double lockers avoid any risk of contamination outside the work areas. Soiled clothing must not be taken home and smoking and drinking in the workplace must be banned, except in areas reserved for this purpose; these areas must be clean and have equipment that will facilitate effective cleaning of workers so that they can avoid ingesting toxic products. In the specific context of work with nanoparticles, the administrative means to be applied depend on the products involved and the work to be performed.

Work area maintenance, including removal of dust deposited on the floors and work surfaces, must be performed regularly to avoid any (i) accumulation (ii) risk of atmospheric resuspension or (iii) explosion, should the dusts be explosive, as in the case of certain metallic powders. The dusts must be sucked up with a vacuum cleaner equipped with a high-efficiency filter; this is particularly important in the case of nanoparticles. Building design must take into account dusts with explosive potential and, when they are, equipment must be blastproof. All equipment should be cleaned thoroughly and padlocked, as needed, before it undergoes maintenance. Preventive maintenance of equipment minimizes the risks of unscheduled interruption of production while assuring safer operations. All spills must be cleaned up immediately, using a safe procedure established on the basis of the risk involved. A good example of a workplace maintenance and decontamination methodology is provided in the best-practices guide for working with beryllium (Dion and Perrault, 2004).

- Personal protection

Personal protective equipment is normally used as a last resort, and only when all others means of control have been implemented without being able to protect the worker adequately.

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- Respiratory protection

In situations where it is necessary to wear respiratory protection, the Quebec Regulation respecting occupational health and safety (2001) makes it mandatory to develop and implement a respiratory protection system.

The individual airway protection equipment used in locations where nanomaterials are produced in the form of dust must be particularly efficient. Wearing a full-face mask with high-performance filters (over 99.97% efficient) is recommended). Masks are used primarily in maintenance work on production machines after they have been decontaminated. The main problem with respiratory protection is related more to mask seal efficiency, comfort and maintenance than to its filtration performance.

Intermediate protection is assured by using a PAPR (powered air-purifying respirator), which includes high-efficiency filtration and a pump supplying a full-face mask. The air current generated on the wearer's face increases the level of protection while 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 high-efficiency dust filters are insufficient, air-line respirators or self-contained breathing apparatus are necessary. A complete guide to respirator selection and use, produced by the IRSST, is available on the following Web sites: www.irsst.qc.ca/fr/_publicationirsst_673.html and www.prot.resp.csst.qc.ca.

- Skin protection

The development of new knowledge in industrial hygiene is increasing our awareness of the importance of taking into account cutaneous absorption in aggregate exposure risk assessment. The nature of industrial nanoparticle synthesis processes is such that there is a strong probability of cutaneous exposure. The product recovery and packaging stages, and general maintenance of workplaces and equipment, all provide opportunities for contact with the skin. The products that make up nanoparticles can penetrate the skin by dissolution. However, it seems that even certain insoluble products that make up nanoparticles could penetrate the epidermis and possibly end up in the bloodstream, where they can travel throughout the body. Chapter 6 on health risks revealed the very limited state of current knowledge in this field. As a precaution, it is preferable to introduce controls to minimize cutaneous exposure.

Schneider *et al.* (1999, 2000) proved that there are many factors that contribute to the inefficiency of skin protection equipment. The main factors limiting this equipment's efficiency include, notably: (i) direct penetration of solid material or permeation of a liquid through the materials making up the equipment, and (ii) the transfer of substances through direct contact between the equipment surfaces and the skin. Penetration of the equipment by nanoparticles is likely to be even greater than by larger particles, for which tests have shown a high penetration rate. Maintenance of skin protection equipment is also an important aspect to consider. Given the context, and as a precaution, it would be desirable, when possible, to use disposable clothing, which normally provides excellent skin protection. For example, the use of Tyvek® hooded coveralls, aprons and shoe covers may provide good skin protection, though the information currently available cannot guarantee absolute effectiveness. The same principle applies to gloves, which are available in a wide range of sizes and resistances to various chemicals, cuts and perforations. The real effectiveness of such skin protection equipment cannot be determined from the literature; however, because of the small diameters of nanoparticles, there is a strong probability that the various kinds of skin protection equipment have very limited effectiveness.

Since the list of existing means of control is relatively long, readers interested in more information should consult an industrial hygienist or refer to recent manuals on industrial hygiene, processes, chemical engineering or ventilation. The brief discussion in this chapter has covered only a few means of control that seem the most relevant.

9. PREVENTION

Prevention and sound work practices are essential in occupational health and safety. The production of nanoparticles may involve various kinds of risks. Consequently, we recommend in the strongest terms that the management and employees of each company give priority to preparing a prevention program designed specifically for the company. A guide to best practices in the field of nanomaterials (publication expected in 2006) will provide much information applicable to nanotechnologies. The guide for preventing exposure to lead (Turcot *et al*. 2003) and the guide to best practices in working with beryllium (Dion and Perrault, 2004) are other examples of guides that set forth the principle points for consideration in a prevention program designed specifically for dust.

In developing the prevention program, the company director must, among other things, clearly identify the responsibilities of various individuals in the company and make sure that senior management gets involved (see Chapter 9). Likewise, all research teams and laboratories must get involved. In Quebec, the CSST, the joint sector-based associations, the prevention mutuals, the *Agences de développement de réseaux locaux de services de santé et de services sociaux* (the development agencies of the local health and social services networks) and the *centres locaux de santé et de services sociaux* (CLSC, local health and social services centres) are other organizations that can help develop prevention programs.

Current toxicity data on the effects of the new nanoparticles on humans is limited. However, several studies demonstrate certain toxic effects of nanoparticles on animals. The behaviour of these particles in the air, water or soil, as well as their potential for build-up in the food chain are not yet very well known. Until their effects on the environment and humans are adequately documented, strict prevention measures should be taken as a precaution to limit their release into the work/occupational environment and the environment outside the company.

The most important risks to consider in the work environment are those related to the toxicity of substances, including controlling exposure (discussed in the previous chapter) to catalytic effects and to the risk of fire or explosion (Pritchard, 2004). Indeed, many chemical processes are catalyzed by small quantities of substances; the efficiency of the catalysis is generally a function of the surface area of the catalytic agent. However, nanomaterials have large surface areas; this favours their catalytic activity and may result in rapid – or even violent or explosive -- reactions. Taking into account the processes that have already been introduced, risk of asphyxiation is possible in processes using large quantities of inert gases. There is also risk of electrocution related to the use of high-voltage and strong-current processes (Shakesheff, 2005).

9.1 The risk of explosion

Pritchard (2004) reviewed the literature to determine the risk of explosion linked to nanoparticles. He concluded that the literature has not yet documented this phenomenon. We are obliged therefore to extrapolate the knowledge available with regard to fine and ultra-fine powders. The author concludes that extrapolating the behaviour of nanoparticles based on observation of the behaviour of larger particles is not feasible given the important changes in the physical and chemical properties of particles measuring less than 100 nm. With large-diameter particles, the general propensity toward violent explosion and the ease of ignition increase as the size of the particles decreases. Indeed, due to their very fine granulometry, the reactivity of the dust increases together with its parameters of explosibility. The finer the dust, the greater the rise in pressure and the lower the ignition energy. On the other hand, for several types of dust this tendency is less pronounced and reaches equilibrium when the dust attains a diameter of a few dozen micrometres. Normally, the energy required to detonate dust is greater than that required for a gas. In sum, the risk of nanoparticles exploding is potentially high (Pritchard, 2004).

9.2 Fire control and prevention

Fire prevention should take into account existing regulations, especially electrical requirements. Considering the very low granulometry and very long settling time of nanoparticles, electrical equipment should be protected from the dust. In certain cases, it should even be vapourproof. In addition, further precautions should be taken regarding the operation temperature of electrical equipment and increased risks of auto-ignition of nanoparticles.

To date, fire control has not been documented in the available literature. However, the same principles applying to pulverulent materials in general should be considered in the case of nanoparticles, with particular care taken in the case of easily oxidizable metallic dust.

The selection of an extinguishing agent must consider the compatibility or incompatibility of the material with water. Metallic dust reacts with water to form, among other things, hydrogen, which ignites very easily and deflagrates. Chemical powders are available to extinguish metallic dust powders. During the attack to extinguish metallic dust powders, care must 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 may prove necessary to use controlled-atmosphere production and storage processes (carbon dioxide, nitrogen or inert gas).

9.3 Storage

Nanoparticle storage has special characteristics stemming from the different granulometric characteristics and reactivity of the particles. The fine granulometry of the materials may result in long settling times and re-dispersion. Reservoirs must 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.

Storing nanoparticles also involves special protection to conserve the products. 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. To avoid oxidation, or even explosion in the case of certain metals, nanoparticles often need to be protected. Depending on the product to be stored, a variety of preventive procedures will avert deterioration of the product and risk of fire or explosion. Possible solutions include storage in inert gas or in anhydrous conditions. In other conditions, it may be possible to surround the nanoparticles in a protective layer of salts or various polymers. These layers can be discarded before using the product.

9.4 Other aspects of prevention

Several other aspects could be considered, but will not be described here because they are highly specific to the product being utilized, synthesized or handled, as well as to the processes being applied. In addition, the literature provides no information on specific measures to apply in the case of nanoparticles. We are thinking, for example, of preventive measures that need to be developed and implemented for asphyxia, electrocution, accidental spills and discharge, as well as for waste disposal, emergency protective equipment, first aid and health surveillance.

10. REGULATION AND RECOMMENDATIONS

10.1 Essential ethical rules

The potential risks, which are currently impossible to quantify, involving toxicity or the release of nanoparticles should prompt us to act responsibly and take all necessary precautions. At the international level, the UN has thus stipulated that binding rules of use for nanotechnologies must be established and adopted to avoid possible abuses (for example in respect for privacy or perverse military uses).

In Quebec, the *Commission de l'éthique de la science et de la technologie*, (a science and technology ethics committee), which comes under provincial jurisdiction, is currently examining all ethical aspects related to nanotechnologies and nanomaterials. In France, a working group on nanotechnologies was set up within the *Comité Consultatif National d'Éthique* (CCNE, a national consultative ethics committee). England's Royal Society and the Royal Academy of Engineering (2004a) and the Netherlands' (Levert, 2004) *Académie des arts et des sciences des Pays-Bas* (Levelt, 2004; an arts and sciences academy) are among the numerous organizations emphasizing the importance of dealing with ethical issues in the field of nanoparticles. The United States, the EEC and many Asian countries have also raised this ethical concern.

10.2 Regulation in Europe and in the nations of Europe

Regulation in Europe regarding nanoparticles is based on existing laws and regulations for chemicals. Nanoparticles in chemicals must meet the requirements of the REACH program (Registration, Evaluation and Authorisation of Chemicals). The European Union adopted this regulatory framework in October 2003. The principal objective of the new program is to ensure a greater level of protection for human health and the environment, while allowing internal markets for innovation and competition in the chemical industry to function effectively. By contrast, a report of the Royal Society and of the Royal Academy of Engineering (2003) proposes that every existing substance produced in the form of nanoparticles be considered a new substance; as such, they propose, every new nanoparticle should be tested to determine its toxicity before being used. Thus, the report recommends that the use of nanoparticles in cosmetics should be conditional upon approval by the Scientific Advisory Committee of the European Community. This committee has already approved adding TiO_2 nanoparticles to sun creams but has not given similar approval for zinc oxide.

The European commitment to safeguard the production, marketing, transport and use of new materials involves manufacturers. The manufacturer must determine the properties and potential exposure resulting from the production and use of nanomaterials. The European Nanobusiness Association is an organization whose mission is to promote the professional development in Europe of nanotechnology industry and trade. The association's activities include writing standards, keeping the public informed, analyzing legislation and providing expert evidence for political leaders and decision makers. Several other organizations in the pharmaceutical field and the agroprocessing industry have been set up and are evaluating the impact of introducing new products (European Nanotechnology Gateway, 2004).

In Germany, the government created the Office of Technology Assessment (TAB) with the mandate of generating ideas to guide the government in research and development in the field. This involves the application of existing laws and regulations to the field of nanotechnology (air pollution, chemicals, labour code, pharmaceutical and medicinal product legislation, food and preservatives, new products, etc.), rather than the development of new ones. Pressure groups, too, are active in various areas of public opinion.

In the **United Kingdom,** the government mandated the Royal Society and the Royal Academy to carry out an independent study on developments in nanotechnology. The study is supposed to examine the impact of nanotechnologies on the emergence of new health and safety problems, the environment, ethics and society. It is also supposed to emphasize and demystify a new sector: public information. The Medicine and Healthcare Products Regulatory Agency was set up, subsequent to the merger of two other organizations, to monitor the development of new products for pharmaceutical and medical use, including nanomaterials.

In the **Netherlands,** the pressure group Foundation Nature and Environment was set up to inform people of the damage to health -- as demonstrated in animals -- of certain nanomaterials. Other pressure groups (Friends of the Earth Netherlands, Zuid-Hollandse Milieufederatie) are also active in this field and receive funding from the government to carry out their activities (Lorrain and Raoul, 2003).

10.3 Asia-Pacific Area

In this region, Japan is the leader in nanotechnology development by virtue of its economic and commercial position. It alone wields more than half of the total capital budget for research and development in this region of the world. The highly variable economic situation of various Asian countries greatly affects administrative measures they take to protect workers and the public. For example, the policies of poorer nations such as India, Pakistan, Sri Lanka and Nepal are less strict than those of more developed nations, such as Japan, Taiwan and Singapore, in the areas of environmental protection and protection of the populace as a whole (Lorrain and Raoul, 2003). This major economic and social difference will have a noticeable impact on the ethics and control measures applied to nanomaterial research and production. Nanotechnologies can provide enormous benefits to populations, but they may also have potentially devastating effects if, from the outset, countries do not address the problems associated with nanotechnology development.

10.4 North America

There is little regulation in North America applying specifically to nanoparticles. OSHA in the United States, the Government of Canada (federal) and various provincial organizations in Canada already regulate several substances based on their chemical composition. Certain provinces refer to the TLV Booklet of the ACGIH for information on chemical contaminants. Certain regulatory bodies, such as the EPA and OSHA expect to make changes. These are outlined in the section on the United States (Feigenbaum *et al.*, 2004).

10.4.1 The United States of America

In the US, federal regulation mechanisms are in place to assess and regulate the occupational setting and the environmental and health risks of materials and new technologies. Regulatory amendments must now consider nanotechnologies. Studies are underway to determine how materials used in nanotechnologies differ from conventional materials in terms of their impact on public health and the environment. In terms of occupational health, Americans employ standards specified by NIOSH (National Institute for Occupational Safety and Health), OSHA (Occupational Safety and Health Administration), ACGIH (American Conference of Governmental Industrial Hygienists) and the FDA (Food and Drug Administration). They select protective equipment on the basis of criteria established by OSHA, NIOSH and ASTM. Since August 2003, an interagency group has been in place to assess the potential impacts of nanoparticles on health and the environment. Its mandate consists in providing a special communication link, identifying the issues that require either individual or interagency action, examining the production and use of nanomaterials, developing a best practices guide for occupational settings (NIOSH) and working with the academic community and industry to develop a nomenclature for nanomaterials. It does not approve or certify consumer products (excluding food and medicine). This is a huge challenge because it is possible for a chemical product to take different forms (such as diamond, nanotube, graphite, carbon black, fullerene, carbon nanofoam); in certain materials, the only variation is granulometric (TiO_2) (Feigenbaum *et al.*, 2004).

In addition to its responsibility for monitoring air and water pollution and managing waste, the Environmental Protection Agency (EPA) has the authority to regulate nanosubstances through the Toxic Substances Control Act (TSCA). This is an atypical type of regulation since it covers aspects of manufacturing, transport and the damage caused by new products derived from nanotechnology development. Using this legislation, EPA can require that the health effects on workers and potentially exposed populations be established for all new substances. Manufacturers can be required to disclose the start-up of operations for new products and to provide all information pertaining to their safe use.

In the long term, the EPA could put the use of nanomaterials on a par with the start-up of operations for new chemical products, applying all the precautionary and preventive measures required by existing regulations and laws to ensure safe use. A 90-day period of notice would then be required to allow the EPA to review all necessary information on these new chemical products and their new uses that may have implications for health, safety and the environment. Following this review, the EPA could require the implementation of special measures designed to ensure appropriate methods of control (Feigenbaum *et al.*, 2004).

The Occupational Safety and Health Administration (OSHA) has a variety of standards that are applicable to nanotechnology. For example, manufacturers of nanosubstances are required to make available Material Safety Data Sheets describing the properties of these materials, their impact on health and the preventive measures required. If the control techniques are inadequate, respiratory protective equipment must be provided to workers. Lastly, an OSHA moral responsibility clause requires employers to keep work environments free from known dangers.

The White House Office of Science and Technology Policy is planning to mandate a group on the development of voluntary standards for nanotechnologies. OSHA could eventually distribute these standards. The nanotechnology industry must be proactive in the development and application of scientific techniques for risk assessment and efficient methods of control to provide adequate protection for the public,

The existing regulatory network will be modified if necessary. Here are a few examples of regulations applicable to nanoparticles and nanostructures that could be modified (Teague, 2004). The EPA manages several of these involving the environment (air, water and soil). They are the Toxic Substances Control Act (TSCA) of 1976, which regulates 75,000 chemical products, the Clean Air Act for Particulate Matter < 10 µm, the Clean Air Act for Particulate Matter < 2,5 µm, as well as the Waste Disposal Acts.

In occupational environments, OSHA applies a regulation based on Permissible Exposure Limits (PEL), the threshold limit values for chemical substances regulated in the United States. The National Institute of Occupational Safety and Health (NIOSH) recommends threshold limit values, known as the Recommended Exposure Limits (REL), which do not have the force of law. The American Conference of Governmental Industrial Hygienists (ACGIH) is adopting a similar approach with its Threshold Limit Values (TLVs). For personal protective equipment, OSHA is applying the regulations for personal protective equipment to reduce exposures; NIOSH is evaluating and approving equipment and the American Society for Testing and Materials, (ASTM) is establishing protective equipment (Feigenbaum *et al.*, 2004).

In terms of food and drugs, the FDA intends to modify certain regulations and have new ones adopted, including “Nanoparticles for drugs to be metabolized in human body, to be used as diagnostics or therapeutic medical devices (such as quantum dots)” as well as “Nanostructured particles/substances to be incorporated into food” (Feigenbaum *et al.*, 2004).

10.4.2 Canada

To our knowledge, Canada and its provinces have not yet adopted laws or regulations dealing specifically with nanoparticles.

10.4.3 Quebec

In Quebec, application of the *Loi sur la santé et la sécurité du travail* (LSST, Act respecting occupational health and safety) as well as the *Règlement sur la santé et la sécurité du travail* (RSST, Regulation respecting occupational health and safety) cover the general requirements for developing company prevention programs and controlling contaminants in the occupational setting. Several chemical products making up nanomaterials have already been set out in Appendix I, which specifies the standards for chemical contaminants. This regulation does not take into account the granulometry of particles or the possibility of variable toxicity based on this granulometry. Particle shape and granulometry can have a significant impact on the degree of absorption of a product and, consequently, on its toxicity. Toxicological studies will occasionally be required to determine safe levels for new forms of products. The RSST does not consider these aspects.

Quebec is a member the Workplace Hazardous Materials Information System (WHMIS), a Canadian system that requires suppliers to label chemical products, and provide material safety data sheets describing the various products, the principal characteristics of these products, their health risks and the required associated protective measures. Employers must make the data sheets available and train their employees. Several other provincial or federal laws, such as those involving the transportation of hazardous material, may apply to nanoparticles just as they apply to other chemical products. However, to our knowledge, no law deals specifically with nanoparticles.

11. THE MAIN ACTORS IN QUEBEC

Quebec is highly involved in nanotechnology research and is the only Canadian province to have developed an overall strategy to promote the development and commercial production of nanotechnologies. NanoQuebec plays a major role in planning and structuring nanotechnology. It is a non-profit organization co-financed by the Government of Quebec (via the *ministère du Développement économique, de l'Innovation et de l'Exportation*, the *ministère des Affaires municipales et des Régions* and *Valorisation-Recherche Quebec*) and the Government of Canada (via Canada Economic Development for Quebec Regions). Its objective is to create critical masses of researchers and the synergy required for improving the research and status of nanotechnologies. It bases its approach on consultation and networking, that is, getting the various actors in the field of nanotechnology to interact (companies, researchers, governments, manufacturers and financiers). All of its initiatives are geared toward eventual business and industrial applications.

Due to its ongoing concern for ethics, occupational safety and health and the environment, NanoQuebec has created a Web portal providing information to educate the general population about nanotechnology:http://nanoquebec.ca/nanoquebec_w/site/index.jsp.

NanoQuebec has already made several national and international partnership agreements to improve Quebec's strategic position internationally. It maintains close partnerships with Quebec's principal universities working in the field of nanotechnology (Université de Sherbrooke, Université Laval, École Polytechnique, McGill University, Concordia, École de technologie supérieure, Institut national de recherche scientifique, Université de Montréal) and several CEGEPS. Quebec has a well-developed network of university-based research, with over 50 tightly networked research groups involved in the field. While the field has about forty companies, some of which are in the start-up phase, research and teaching currently account for the largest share in Quebec of persons potentially exposed to nanoparticles. In total, it is estimated that over 2000 persons in Quebec currently work in teaching or the manufacturing of nanoparticles. It is highly likely that this number will increase rapidly.

Several other organizations in Quebec are interested in nanotechnologies. Although it is impossible to draw up an exhaustive list here, it is worth noting that Cirano recently published an assessment of nanotechnologies (Feigenbaum *et al.*, 2004) and that the *Commission de l'éthique de la science et de la technologie* is currently studying all ethical aspects related to the production and use of these new materials.

In terms of occupational health and safety, the IRSST (*Institut de recherche en santé et en sécurité du travail du Quebec*) and the CSST (*Commission de la santé et de la sécurité du travail du Quebec*) are currently developing an area of expertise in this field to evaluate existing knowledge in terms of risks involving occupational health and safety. This will allow preventive intervention in companies to avoid an increase in occupational disease and accidents. To respond to specific, mutual concerns raised by their various partners, the IRSST and NanoQuebec have decided to jointly publish a guide to best practices in the work/occupational environment. They expect to publish it in 2006. Although NanoQuebec is in close contact with all parties involved in the production of nanoparticles, the extent to which Quebec uses nanomaterials – either locally produced or imported -- is not currently known.

12. POTENTIAL RESEARCH AVENUES

Nanoparticle research is a field teeming with excitement. To date, work in this field has dealt primarily with technological developments oriented toward the production of new materials with unique characteristics, but whose health and environmental impacts have been only partially established. Research on the potential health and environmental impacts of nanoparticles is barely underway, and on several levels there is a flagrant lack of scientific knowledge. Risk management is always more effective when it is based on comprehensive risk assessment. Currently, in-depth risk assessment is impossible to carry out due to a lack of essential information. We are therefore obliged to fall back on the implementation of a precautionary approach.

Needs that cannot be ignored in the development of new knowledge in occupational health and safety include future research designed to do the following (Aitken *et al*., 2004; Friedlander and Pui, 2003; Royal Society and Royal Academy of Engineering, 2003; Commission des Communautés européennes, 2004; Durrenberger, 2004; Mark, 2005a, 2005b):

- make an inventory of nanoparticles, and classify and categorize them by type, volume and application; accurate reference materials must be made available (dimensions, concentrations, compositions, morphology, structure);
- develop new methods for toxicological studies so as to be able to study a wide variety of these products within a reasonable time and at a reasonable cost;
- subsequent to pulmonary absorption by or cutaneous application in animals, determine the toxicity, bioaccumulation, biodegradation, biopersistance and localization in various organs of different types of carbon nanofibres of different grades and containing various metals, quantum wells and other nanoparticles. Conduct toxico-kinetic and pharmaco-kinetic studies, examining both acute and chronic toxic effects, and determine the action mechanisms of the nanoparticles. For substances showing toxicity, it is essential to determine the physical parameter most closely associated with the toxicities measured. This means that the product mass, the number of particles or the specific surface area; the distribution and biological fate of nanoparticles that have penetrated the organism, as well as their impact on target organs, must be established; in addition, dose-response relationships must be differentiated with a view to establishing occupational safety thresholds;
- develop risk-assessment and risk-management models based on the products under study, the processes involved and the work situations encountered;
- develop new tools accompanied by adapted strategies allowing researchers to specifically measure worker and researcher exposure to nanoparticles and nanotubes, as related to the measurement parameter most closely adapted to the toxicity of the products. Due to a lack of equipment, it is currently impossible to determine the specific surface area of particles in the air at individual workstations in occupational environments. The new equipment must facilitate improved description of aerosols, especially by measuring the concentration (expressed in specific surface area), particle size (granulometric) distribution and composition, and be able to distinguish between nanoparticles and other airborne

contaminants; nanoparticle description will be facilitated if there are comparative agents (reference materials) available.

- document and describe occupational exposure in various work environments and for various synthesis and use processes. Since there is a lack of equipment, the literature provides almost no information on occupational exposure. In addition, nanoparticles tend to agglomerate; this factor should be taken into account in assessing toxicity, developing measuring tools and assessing worker exposure. Exposure must be documented during the following steps: manufacturing, use, recycling, disposal and when there are spills or accidents;
- as production and use of nanoparticles increase, carry out epidemiological studies in occupational environments. These studies must involve both the producers and users of these products;
- measure the effectiveness of collective and individual protective devices. It is assumed, though not proved, that filtration with a high efficiency particulate air (HEPA) filter will be efficient. At the same time, skin protections require the development of equipment and adapted strategies whose performance will have to be assessed;
- assess the efficiency of conventional methods and determine the best approaches to cleaning contaminated surfaces. In addition, the state of the settled nanoparticle, its granulometry, its adhesion to the collecting (or absorbing) surface, the ease with which it can be dislodged from a surface and the best cleaning and decontamination strategies should be investigated;
- study the explosiveness of nanoparticles and the most effective storage, transport and implementation methods;
- assess the ethical issues related to occupational health and safety.

Lastly, access to new scientific knowledge will improve assessment of the risks of exposure to nanoparticles and management of these risks. Meanwhile, access to this information combined with the general principles of industrial hygiene described above form the basis of sound risk management.

13. CONCLUSION

Nanotechnologies and nanoparticles represent a promising and fast-growing field. This is principally because a nanodimensional substance can have physical and chemical properties that are different from those of the same substance with larger dimensions. Indeed, current technological developments in this field are attempting to take advantage of these unique properties. Even when nanoparticles have the same chemical composition as their more voluminous counterparts, they may often be considered new substances. This raises a major challenge for occupational health and safety. Given the lack of information, how does one assess the risk associated with these new products and prevent occupational disease and new, safety-related problems?

The colossal R&D investments in all industrialized countries will inevitably lead to major discoveries whose applications will, in the not too distant future, irremediably affect our everyday lives. In spite of the fact that their short-term effects are not known, many products are already available for consumption (cosmetics, paints for automobiles, waterproofing, textiles, etc.). The number and diversity of exposed workers will increase over the next few years. It is possible to introduce prevention and control measures promoting occupational health and safety at the very beginning of the conception and implementation stages of various processes. Consequently, these measures, if taken right away, can constitute an important asset for the field of nanotechnology. However, a major challenge remains since current knowledge concerning health risks in this field is very fragmentary.

Certain nanotechnology applications will entail few new occupational health and safety risks. One such field is electronics, where miniaturization is advancing rapidly and is now being measured nanometrically. By contrast, free nanoparticles in the air are cause for concern due to their potentially negative impact on occupational health and safety, their accumulation in the environment and their enrichment via the food chain. These could have long-term risks for the health of populations. Although current knowledge on the toxicity of nanoparticles and the potential level of worker exposure is very limited, preliminary results in most of the important studies reveal significant biological activity and adverse effects. In the short term, it will be almost impossible to acquire adequate knowledge of the risk associated with every type of nanoparticle. This is due not only to the proliferation of new nanoparticles but also to the modifications made to their surfaces; for these modifications greatly affect the surface properties of nanoparticles and possibly their biological reactivity and toxicity as well.

Given that it is currently impossible to carry out precise, quantitative risk assessment for every type of particle, it is important to develop a precautionary approach, using strategies based on prevention, sound practices and risk control that can thwart the spread of occupational disease. In the area of industrial hygiene, initiatives must be taken as soon as possible, using the best available measuring tools -- in spite of these tool’s limitations -- to estimate levels of occupational exposure. In view of the rapid advances in knowledge in occupational health and safety, it would seem important to update our assessment of knowledge in this field as soon as possible.

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15. SOME WEBSITES OF INTEREST

ftp://ftp.cordis.lu/pub/nanotechnology/docs/eurotech_nanoreferences.pdf

http://www.ccinfoweb.ccohs.ca/bibliographic/search.html

http://europa.eu.int/comm/research/era/pdf/nanoexpertgroupreport.pdf

http://icon.rice.edu/

http://investors.swissre.com/INTERNET/pwsfilpr.nsf/vwFilebyIDKEYLu/ULUR-5YNGET/$FILE/Publ04_Nanotech_en.pdf

http://nanostructures.phys.polymtl.ca/galerie.html (galerie d'images nano)

http://nanotech-now.com/images-sites.htm

http://www.academie-technologies.fr/pdf/NANOTEC.pdf

http://www.admiroutes.asso.fr/larevue/2004/51/Nanotech_Leloup.pdf

http://www.azonano.com

http://www.ccst.us/ccst/pubs/nano/biblio.html

http://www.cirano.qc.ca/pdf/publication/2004s-44.pdf (site consulté le 3 octobre 2004).

http://www.convergingtechnologies.org/articles/NYLJ.Convergence2.11-2003.doc

http://www.cordis.lu/nmp/home.html

http://www.dmoz.org/Science/Technology/Nanotechnology/

http://www.dti.gov.uk/nanotechnology

http://www.epa.gov/

http://www.foresight.org

http://www.greenpeace.org.uk/contentlookup.cfm?CFID=2768333&CFTOKEN=24046737&IncludeRaw=search3&mode=Text

http://www.his.com/~dionychus/nano/nanoindex.html

http://www.imp.cnrs.fr/utilisateurs/guillard/page2.html

http://www.industrie.gouv.fr/energie/matieres/textes/ecomine_note_oct02.htm

http://www.infochembio.ethz.ch/links/en/werkstoffe_nanoroehr.html

http://www.inex.org.uk

http://www.ipt.arc.nasa.gov/gallery.html (galerie de photos)

http://www.irsst.qc.ca

http://www.itsf.org/brochure-f/nano.html

http://www.mdeie.gouv.qc.ca/page/web/portail/scienceTechnologie/service.prt?svcid=PAGE_GENERIQUE_CATEGORIES40&iddoc=42648

http://www.mssmat.ecp.fr/physique/themes/nanostructures/fr/structures.html

http://www.nano.gov

http://www.nano.org.uk

http://www.nanoforum.de/

http://www.nanoinvestors.com

http://www.nanomedicine.com/NMI.htm

http://www.nanomicro.recherche.gouv.fr/fr/menu_vulgarisation.shtml

http://www.nanonet.de

http://nanoquebec.ca/nanoquebec_w/site/index.jsp

http://www.nanoreference.com/

http://www.nanotec.org.uk

http://www.nanotech-now.com/multimedia.htm (galerie d'images nano)

http://www.nanotechnologies.qc.ca/projets/nanotubes/?language=fr

http://www.nbtc.cornell.edu

http://www.nint.ca

http://www.nsf.gov

http://www.pa.msu.edu/cmp/csc/nanotube.html

http://www.phys.polymtl.ca/nanostructures/galerie.html

http://www.salsgiver.com/people/forrest/nanotechnology.html

http://www.smalltimes.com/document_display.cfm?document_id=5236

http://www.spirtech.com/flv/nano/

http://www.transfert.net/a9204

http://www.tsi.com

http://www.wtec.org/loyola/nano/societalimpact/nanosi.pdf

http://www.zyvex.com/nano

http://www2.envmed.rochester.edu/envmed/PMC/anrep02/rep02_intro.html

http://www2.envmed.rochester.edu/envmed/PMC/anrep02/rep02_C2.html