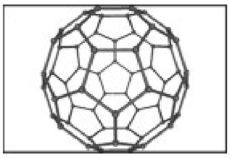
GreenFacts
Facts on Health and the Environment

Scientific Committees
on consumer products
on emerging and newly identified health risks
on health and environmental risks



Nanotechnologies

Source document:
SCENIHR (2006)

Summary & Details:
GreenFacts (2007)

Level 2 - Details on Nanotechnologies

The answers to these questions are a faithful summary of the scientific opinion produced in 2006 by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR): *"modified Opinion (after public consultation) on the appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies"*

The full publication is available at: http://copublications.greenfacts.org/en/nanotechnologies/
and at: http://ec.europa.eu/health/opinions2/en/nanotechnologies/

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- These answers are developed in more detail in Level 2.
- Level 3 consists of the Source document, the internationally recognised scientific opinion which is faithfully summarised in Level 2 and further in Level 1.

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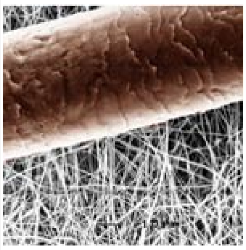
1. What is nanotechnology?

Nanotechnology refers to the branch of science and engineering devoted to designing, producing, and using structures, devices, and systems by manipulating atoms and molecules at nanoscale, i.e. having one or more dimensions of the order of 100 nanometres (100 millionth of a millimetre) or less.



A human hair is approximately 80 000 nm wide
Credit: eSpin Technologies, Inc.

In the natural world, there are many examples of structures with one or more nanometre dimensions, and many technologies have incidentally involved such nanostructures for many years, but only recently has it been possible to do it intentionally.

Many of the applications of nanotechnology involve new materials that have very different properties and new effects compared to the same materials made at larger sizes. This is due to the very high surface to volume ratio of nanoparticles compared to larger particles, and to effects that appear at that small scale but are not observed at larger scales.

The applications of nanotechnology can be very beneficial and have the potential to make a significant impact on society. Nanotechnology has already been embraced by industrial sectors, such as the information and communications sectors, but is also used in food technology, energy technology, as well as in some medical products and medicines. Nanomaterials may also offer new opportunities for the reduction of environmental pollution.

But these new materials may also present new health risks. Humans have developed mechanisms of protection against various environmental agents of different sizes. However, until recently, they had never been exposed to synthetic nanoparticles and their specific characteristics. Therefore the normal human defence mechanisms associated with, for example, immune and inflammatory systems may well not be able to respond adequately to these nanoparticles. In addition, nanoparticles may also disperse and persist in the environment, and therefore have an impact on the environment.

As far as health risks are concerned, there are two types of nanostructure to consider:

- those where the structure itself is a free particle, called free nanoparticles, which is the group of greater concern; and
- those where the nanostructure is an integral part of a larger object, for instance, materials with coatings composed of nanomaterials. However, as long as the nanoparticles are fixed to the carrier, there is no reason to suppose that they pose a greater risk for health or the environment than the larger scale materials.

2. What is the current state of nanoscience and nanotechnology?

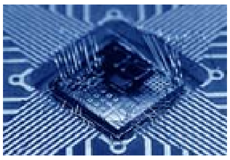
Current knowledge of science at the nanoscale comes from developments in disciplines such as chemistry, physics, life sciences, medicine and engineering. There are several areas in which nanoscale structures are under active development or already in practical use:

In **materials science**, nanoparticles allow for the making of products with mechanical properties very different from those of conventional materials and can also improve surfaces by adding new friction, wear or adhesion properties.

In **biology** and **medicine**, a greater understanding of the functioning of molecules and of the origin of diseases on the nanometre scale has lead to improvements in drug design and targeting. Nanomaterials are also being developed for analytical and instrumental applications, including tissue engineering and imaging.

A wide variety of nanoscale materials and coatings are already in use in **consumer products** such as cosmetics and sunscreens, fibres and textiles, dyes, and paints.

The constant drive towards miniaturization in **electronic engineering** has led to devices that are well within the nanometre range. Data storage devices based on nanostructures provide smaller, faster, and lower consumption systems.


The smallest components of a computer chip are on a nanoscale.
Credit: NanoPrism Technologies, Inc.

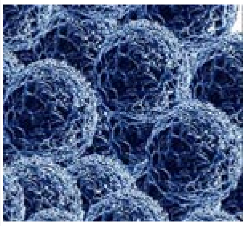
Optical devices have also benefited from this trend and new types of microscopes have been invented, that can produce images of atomic and molecular processes at surfaces.

3. What are the physical and chemical properties of nanoparticles?

Nanoparticles often have unique physical and chemical properties. For example, the electronic, optical, and chemical properties of nanoparticles may be very different from those of each component in the bulk. At the nanoscale, materials behave very differently compared to larger scales and it is still very difficult to predict the physical and chemical properties of particles of such a very small size.

The principal parameters of nanoparticles are their shape, size, surface characteristics and inner structure. Nanoparticles can be encountered as aerosols (solids or liquids in air), suspensions (solids in liquids) or as emulsions (liquids in liquids). In the presence of certain chemicals, properties of nanoparticles may be modified.

The composition of a specific nanoparticle can be very complex, depending on what interactions it has had with other chemicals or particles and on its lifetime. The chemical processes taking place on the surfaces of nanoparticles are also very complicated and remain largely unknown.


Nanoparticles can group together
Credit: NanoPrism Technologies, Inc.

Nanoparticles have different ways of interacting with each other. They can remain free or group together depending on the attractive or repulsive interaction forces between them. These interactions remain difficult to characterize. Nanoparticles suspended in gas tend to stick to each other more readily than in liquids.

4. How are nanoparticles formed?

Free nanoparticles are formed through either the breaking down of larger particles or by controlled assembly processes.

Natural phenomena and many human industrial and domestic activities, such as cooking, manufacturing or road and air transport release nanoparticles into the atmosphere.

In recent years, nanoparticles intentionally engineered for advanced technologies and consumer products have become a new source of exposure. At present it is not clear just how significantly human exposure to these engineered nanoparticles has increased, be it in the workplace, or through the use of nanotechnology-based products.

There are two approaches for the manufacturing of nanomaterials:

- The "**top-down**" approach involves the breaking down of large pieces of material to generate the required nanostructures from them. This method is particularly

suitable for making interconnected and integrated structures such as in electronic circuitry.
- In the "**bottom-up**" approach, single atoms and molecules are assembled into larger nanostructures. This is a very powerful method of creating identical structures with atomic precision, although to date, the man-made materials generated in this way are still much simpler than nature's complex structures.

4.1 How do nanoparticles form in the liquid phase?

Man-made nanoparticles engineered to have the desired size, chemical composition, and surface and charge properties can be produced in the liquid phase mainly through controlled chemical reactions. It is also possible to control conditions at which individual atoms and molecules assemble themselves into the required structure.

Naturally occurring processes that generate nanoparticles in the liquid phase include erosion and chemical disintegration of organic materials (such as plant or microorganism debris) or geological materials (such as clay).

4.2 How do nanoparticles form in the gas phase?

The main route of **bottom-up** formation of nanoparticles in the gas phase is by a chemical reaction whereby gases are converted into tiny liquid droplets, followed by condensation and growth. Such reactions that generate nanoparticles occur naturally in the atmosphere, in volcanic plumes, and in human activities such as cooking, welding or smelting, and polymer manufacture.

Recently, this type of formation of nanoparticles in the gas phase has become an important pathway for the industrial production of nanoparticle powders of metals, oxides, semiconductors, polymers and various forms of carbon, which may be in the form of spheres, wires, needles, tubes, or other shapes.

The **top-down** formation of nanoparticles through disintegration of larger particles is severely limited in the gas phase since nanoparticles tend to stick to each other very strongly.

4.3 What are the sources of airborne nanoparticles?

In ambient air, the number of nanoparticles can be surprisingly similar in urban and rural areas, with as much as one million to one hundred million nanoparticles per litre of air depending on conditions.

In rural areas, nanoparticles are the product of chemical reactions involving compounds emitted by living organisms or by human activities such as wood burning.

In urban areas, the primary sources of nanoparticles are diesel engines or cars with defective or cold catalytic converters. Particularly, high-speed road traffic produces high numbers of nanoparticles of very small size.


In urban areas, most nanoparticles come from diesel engines or cars with defective or cold catalytic converters

In some workplaces, airborne nanoparticles may represent a potential health risk. It is unlikely that nanoparticles would be released during manufacture because processes that generate them are often performed in closed chambers. Instead, exposure to nanoparticles is more likely to happen after the manufacturing process itself, or as a result of leaks arising from improper sealing. It is important to bear in mind that smaller nanoparticles remain airborne for longer periods of time than larger particles.

5. What are the uses of nanoparticles in consumer products?

Nanoparticles can contribute to stronger, lighter, cleaner and "smarter" surfaces and systems. They are already being used in the manufacture of scratchproof eyeglasses, crack-resistant paints, anti-graffiti coatings for walls, transparent sunscreens, stain-repellent fabrics, self-cleaning windows and ceramic coatings for solar cells.

Nanotechnology can be used to increase the safety of **cars**. Nanoparticles can improve adhesion of tyres to the road, reducing the stopping distance in wet conditions. In addition, the stiffness of the car body can also be improved by use of nanoparticle-strengthened steels. Moreover, ultra-thin transparent coatings can be applied to displays or panes to avoid glare or condensation, and in the future it may be possible to produce transparent car body parts to improve all-round vision.


Nanoparticles can increase tire adhesion to the road

Nanotechnology can be applied in the processing of **food**. In addition, food packaging – and, as a result, food safety – can be improved through nanomaterials placing anti-microbial agents on coated films and modifying gas permeability as required for different products.

Nanomaterials are also being used in **biology** and **medicine** in a wide variety of ways. Examples include products for drug delivery and gene therapy, tissue engineering, DNA probes and nanoscale "biochips".

6. What are potential harmful effects of nanoparticles?

6.1 Can nanoparticles interact with living organisms?

Nanoparticles, can have the same dimensions as biological molecules such as proteins.

In living systems, they may immediately adsorb onto their surface some of the large molecules they encounter as they enter the tissues and fluids of the body.

This ability of nanoparticles to have molecules "sticking" to their surface depends on the surface characteristics of the particles and can be relevant for drug delivery uses. Indeed, it is possible to deliver a drug directly to a specific cell in the body by designing the surface of a nanoparticle so that it adsorbs specifically onto the surface of the target cell.

But the interaction with living systems is also affected by the dimensions of the nanoparticles. For instance, nanoparticles no bigger than a few nanometres may reach well inside biomolecules, which is not possible for larger nanoparticles. Nanoparticles may cross cell membranes. It has been reported that inhaled nanoparticles can reach the blood and may reach other target sites such as the liver, heart or blood cells.

Key factors in the interaction with living structures include nanoparticle dose, the ability of nanoparticles to spread within the body, as well as their solubility. Some nanoparticles dissolve easily and their effects on living organisms are the same as the effects of the chemical they are made of. However, other nanoparticles do not degrade or dissolve readily.

Instead, they may accumulate in biological systems and persist for a long time, which makes such nanoparticles of particular concern.

There remain many unknown details about the interaction of nanoparticles and biological systems and more information on the response of living organisms to the presence of nanoparticles of varying size, shape, chemical composition and surface characteristics is needed to understand and categorize the toxicity of nanoparticles.

6.2 Which characteristics of nanoparticles are relevant for health effects?

Studies specifically dealing with the toxicity of nanoparticles have only appeared recently and are still scarce. Most of the information available comes from studies on inhaled nanoparticles and from pharmaceutical studies in which nanomaterials are used, among other things to improve drug delivery.

The characteristics of nanoparticles that are relevant for health effects are:

- **Size** – In addition to being able to cross cell membranes, reach the blood and various organs because of their very small size, nanoparticles of any material have a much greater surface to volume ratio (i.e. the surface area compared to the volume) than larger particles of that same material. Therefore, relatively more molecules of the chemical are present on the surface. This may be one of the reasons why nanoparticles are generally more toxic than larger particles of the same composition.
- **Chemical composition and surface characteristics** – The toxicity of nanoparticles depends on their chemical composition, but also on the composition of any chemicals adsorbed onto their surfaces. However, the surfaces of nanoparticles can be modified to make them less harmful to health.
- **Shape** – Although there is little definitive evidence, the health effects of nanoparticles are likely to depend also on their shape. A significant example is nanotubes, which may be of a few nanometres in diameter but with a length that could be several micrometres. A recent study showed a high toxicity of carbon nanotubes which seemed to produce harmful effects by an entirely new mechanism, different from the normal model of toxic dusts.

6.3 How can inhaled nanoparticles affect health?

Particulate matter present in air pollution, especially from traffic emissions, is known to affect human health, although it is not clear exactly how. Epidemiological studies on ambient air pollution have not proved conclusively that nanoparticles are more harmful than larger particles, but these studies may not be well suited to demonstrate such differences.

Inhaled particulate matter can be deposited throughout the human respiratory tract, and an important fraction of inhaled nanoparticles deposit in the lungs. Nanoparticles can potentially move from the lungs to other organs such as the brain, the liver, the spleen and possibly the foetus in pregnant women. Data on these pathways is extremely limited but the actual number of particles that move from one organ to another can be considerable, depending on exposure time. Even within the nanoscale, size is important and small nanoparticles have been shown to be more able to reach secondary organs than larger ones.

Another potential route of inhaled nanoparticles within the body is the olfactory nerve; nanoparticles may cross the mucous membrane inside the nose and then reach the brain through the olfactory nerve. Out of three human studies, only one showed a passage of inhaled nanoparticles into the bloodstream.

Materials which by themselves are not very harmful could be toxic if they are inhaled in the form of nanoparticles.

The effects of inhaled nanoparticles in the body may include lung inflammation and heart problems. Studies in humans show that breathing in diesel soot causes a general inflammatory response and alters the system that regulates the involuntary functions in the cardiovascular system, such as control of heart rate.

The pulmonary injury and inflammation resulting from the inhalation of nanosize urban particulate matter appears to be due to the oxidative stress that these particles cause in the cells.

6.4 What are the health implications of nanoparticles used as drug carriers?

Nanoparticles can be used for drug delivery purposes, either as the drug itself or as the drug carrier. The product can be administered orally, applied onto the skin, or injected.

The objective of drug delivery with nanoparticles is either to get more of the drug to the target cells or to reduce the harmful effects of the free drug on other organs, or both. Nanoparticles used in this way have to circulate long distances evading the protection mechanisms of the body. To achieve this, nanoparticles are conceived to stick to cell membranes, get inside specific cells in the body or in tumours, and pass through cells. The surfaces of nanoparticles are sometimes also modified to avoid being recognized and eliminated by the immune system.

With dermal administration, it was found that particle size was less important than the total charge in terms of permeation through the skin. For instance, only negatively charged particles were found to overcome the skin barrier and only when concentration of charge was high enough.

Nanoparticles may be used effectively to deliver genes to cells, to treat cancer, as well as in vaccination .

The use of nanoparticles as drug carriers may reduce the toxicity of the incorporated drug but it is sometimes difficult to distinguish the toxicity of the drug from that of the nanoparticle. Toxicity of gold nanoparticles, for instance, has been shown at high concentrations. In addition, nanoparticles trapped in the liver can affect the function of this organ.

Nanoparticles have the potential to cross the blood brain barrier, which makes them extremely useful as a way to deliver drugs directly to the brain. On the other hand, this is also a major drawback because nanoparticles used to carry drugs may be toxic to the brain.

6.5 How should harmful effects of nanoparticles be assessed?

Traditionally, doses are measured in terms of mass because the harmful effects of any substance depend on the mass of the substance to which the individual is exposed. However, for nanoparticles it is more reasonable to measure doses also in terms of number of particles and their surface area because these parameters further determine the interactions of nanoparticles with biological systems.

Several hypotheses were proposed for the adverse health effects of nanoparticles as part of ambient air pollution. These hypotheses address nanoparticle characteristics, their distribution, and their effects on organ systems, including effects on immune and inflammatory systems.

However, some of these hypotheses may be of limited or no relevance for engineered nanoparticles. For instance, the adhesion of toxic substances onto the surface of nanoparticles may be of less relevance for production and handling facilities of large volumes of engineered nanoparticles compared to the particles in ambient air.

In addition, drawing conclusions from tests on healthy animal models may be unsuitable as some of the effects of nanoparticles may only be a risk for susceptible organisms and predisposed individuals, but not to healthy people. For instance, age, respiratory tract problems and other pollutants can modify the pulmonary inflammation and oxidative stress induced by nanoparticles.

Because of the specific characteristics of nanoparticles, conventional toxicity tests may not be enough to detect all their possible harmful effects. Therefore, a series of specific tests was proposed to assess the toxicity of nanoparticles used in drug delivery systems. One mechanism of toxicity of nanoparticles is likely to be the induction of oxidative stress in cells and organs. Testing for interaction of nanoparticles with proteins and various cell types should be considered as part of the toxicological evaluation.

With the exception of airborne particles delivered to the lung, information on the behaviour of nanoparticles in the body including distribution, accumulation, metabolism, and organ specific toxicity is still minimal.

6.6 What are the effects of nanoparticles on the environment?

There are almost no publications on the effects of engineered nanoparticles on animals and plants in the environment.

However, a number studies have examined the uptake and effects of nanoparticles at a cellular level to evaluate their impact on humans; it can reasonably be assumed that the conclusions of these studies may be extrapolated to other species, but more research is needed to confirm this assumption. Moreover, careful examination and interpretation of existing data and careful planning of new research is required to establish the true impact of nanoparticles on the environment, and the differences with larger, conventional forms of the substances.

Persistent insoluble nanoparticles may cause problems in the environment that are much greater than those revealed by human health assessments.

7. How can exposure to nanoparticles be measured?

7.1 How can nanoparticles be detected and their specific properties measured?

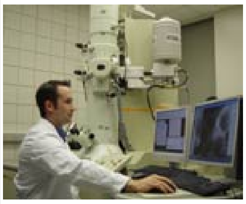
Methods are required that reliably detect nanoparticles and measure their physico-chemical properties in air, water, soil, and consumer products, the media in which humans and ecosystems are exposed to nanoparticles. To assess the risk of nanoparticles, additional tools are required that detect them in cells, fluids, or plant tissues.

Detecting nanoparticles is complex, both in gases and in liquids. Indeed, nanoparticles are so small that they cannot be detected by optical microscopes. In addition, chemical analysis of individual nanoparticles in gases and liquids was for a long time impossible due to their low mass. Only recently have methods become available for this purpose, so that even surface coatings may now be detected.

The prominent role of nanoparticles in areas of current interest such as climate and health research has favoured the development of technologies capable of detecting nanoparticles suspended in gas. Currently available instruments can detect particles as small as 3 nm, while new developments may reach the 1 nm limit. While the instruments used are not themselves size selective, they can be coupled with other instruments covering specific size ranges, for instance the low nanometre size range. Recently developed alternative procedures involving the use of a mass spectrometer allowed for very precise measuring of the chemical compositions of nanoparticles of specific sizes **inside a gas**.

In liquids, commercially available instruments can detect nanoparticles down to the 3 nm limit. However, most of the techniques to measure nanoparticles in liquids imply complicated sample preparation for analysis.

Electron microscopy is the usual method to study particle size, shape and structure in liquids and can currently detect particles below 10 nm. When equipped with a specific spectrometer, chemical composition can also be determined, at least for large nanoparticles.


A scientist operating an electron microscope
Credit: Thames-Rawlins Polymer Research

7.2 How can exposure to airborne nanoparticles be assessed?

Most people are routinely exposed to particles in ambient air, mainly from diesel fumes. Burning fuels produces a vast number of nanoparticles which are initially only about 10 nm in diameter but rapidly join together to form larger groups of up to 100 nm that may remain in the air for days or weeks. The air in a normal room can contain 10 000 to 20 000 nanoparticles/cm^3 while concentration in urban streets can be 100 000 nanoparticles/cm^3.

Exposure is low in terms of mass but significant in terms of numbers of particles. Every hour individuals breathe millions of nanoparticles, and it is estimated that at least half of these reach the lungs. However, it is not known what proportion of these are engineered nanoparticles.

Collecting samples of nanoparticles is a challenging task for several reasons. First, the collection must represent the real exposure at the site in question. Secondly, separation of nanoparticles from larger particles can only be achieved under certain conditions. Thirdly, it is necessary to collect huge volumes of air in order to obtain a mass that is large enough for some analyses. In addition, it is important to distinguish between existing ambient particles and engineered nanoparticles.

It is the number of particles, their size, and their surface characteristics that are determinant for interactions with living systems.

There is no clear opinion on which parameter(s) – mass, number of particles and/or surface area – should be measured as a most appropriate measure of assessing exposure. The available portable instrumentation for nanoparticle exposure is inadequate and new sampling techniques and strategies for assessing exposure at the workplace and in the environment should be elaborated. Also, the possibility of establishing Occupational Exposure Limits for chemicals in the form of nanoparticles should be considered.

7.3 In what ways are humans exposed to nanoparticles?

Inhalation is the primary route of human exposure to nanoparticles. The different compartments of the human respiratory tract (nose, larynx, airways, lungs) all act as a filter for nanoparticles. The smaller the particle, the more likely its chance to reach the lung.

Motor vehicle emissions are the most significant source of nanoparticles in urban areas. Today, nanoparticles generated by the combustion of fossil fuels constitute the most important source of human-induced nanoparticles.

Engineered nanoparticles are likely to enter **the environment** either during the manufacture of nanomaterials or through the use and disposal of such products containing nanoparticles, including personal care products such as cosmetics and sunscreens. Currently, very little is known about the behaviour of these particles in the environment.

Exposure to nanoparticles at **the workplace** may occur in research and development facilities in the nanotechnology sector, in chemical and pharmaceutical companies, in facilities where paints, cement, and other products involving powder handling are manufactured, and during processes where nanoparticles are by-products such as in baking, welding and polymer processing. However, data on occupational exposure is scarce.

Potential **dermal exposure** concerns mostly cosmetic or pharmaceutical skin preparations that use nanoparticles. Although, in theory, these products could harm the area of skin where the product was applied or be adbsorbed through the skin, travel in the bloodstream and possibly harm other parts of the body, there is no scientific evidence of this as yet. But there is very little data on this route of exposure.

Ingested nanoparticles can move from the gut to other parts of the body through different mechanisms. Their ability to cross the lining of the intestine depends on their size and electrical charge. Once again, there is very little information on potential exposure through the digestive system.

8. Are current risk assessment methodologies for nanoparticles adequate?

Chemicals in their nanoparticle form have properties that are completely different from their larger physical forms and may therefore interact differently with and in biological systems. As a result, it is necessary to assess the risks arising from any nanoparticle that will potentially come in contact with humans, other species or the environment, even if the toxicology of the chemicals that make up the nanoparticle is well known.

Because of the restricted range of nanoparticle types whose biological properties have been studied to date, it is uncertain whether or not the current limited evidence on the behaviour in biological systems is representative of nanoparticles in general.

The traditional risk assessment methodology – which consists of exposure assessment, hazard identification, hazard characterization and finally risk characterization – has not yet been applied to nanoparticles. At the moment, there are no official guidelines on what is an appropriate testing procedure. The commercial manufacture of nanoparticles is relatively new and there is very little data available on their effects on human populations or on the environment.

More specifically, risk assessment of nanoparticles may need to address:

- Worker safety during the manufacture of nanoparticles.

- Safety of consumers using products that contain nanoparticles.
- Safety of local human populations due to release of nanoparticles from manufacturing and /or processing facilities.
- The impact on the environment and on the potential for human re-exposure through the environment.
- The environmental and human health risks involved in the disposal or recycling of nanomaterials.

More safety requirements are expected for new or emerging technologies than for tried and tested technologies. If these expectations are not met, the public may come to fear or even reject products based in nanotechnology.

8.1 What considerations should the risk assessment take into account?

In terms of general exposure and health risks to humans, it is important for any risk assessment methodology to consider that:

- Humans can be exposed to nanoparticles not only through inhalation, but also through ingestion, dermal contact, and injection or implantation.
- Exposure dose should not only be measured in terms of mass, but also in terms of total surface area, number of particles, or their combination .
- Nanoparticles may be able to go through cell membranes and have the potential to reach the cells of several organs, including the brain. This ability of nanoparticles to get inside biological systems may cause unique adverse effects never previously observed for chemicals in larger physical forms.
- The toxicity of nanoparticles and their ability to pass through cell membranes may either increase gradually as particle size decreases, or increase suddenly below a certain particle size. Nanoparticles may have a greater toxicity or, perhaps, a different toxicity compared to larger particles of the same substance.
- Nanoparticles may have the potential for bioaccumulation in humans and possibly in other species and in the environment.
- Nanoparticles in ambient air will probably be widely dispersed – unless they react with other components in the air – but they may distribute and persist in the environment differently from larger particles. The potential problems associated with nanoparticles that persist in the environment may be considerable.
- Some individuals, including people with severe chronic respiratory and heart diseases, are much more sensitive to the adverse effects of certain nanoparticles from ambient air pollution than the general public and potentially to other types of airborne nanoparticles.

8.2 What factors of exposure do risk assessment methodologies need to specify?

Risk assessment can be applied either to a chemical in nanoparticle form or to the product in which these nanoparticles are incorporated.

It is important for the purpose of assessing the risk of a chemical in nanoparticle form or of the product where such nanoparticles are incorporated to specify clearly the following factors:

- The physical and chemical properties of these nanoparticles or products, the amount that will be produced, the expected uses, the proposed routes for their disposal or recycling at the end of their useful lives, as well as their solubility, bioaccumulation and biodegradability.

- The likely human or environmental exposure in different situations of use, including normal and intensive use, misuses, and accidents.
- The detailed examination of human exposure, including how the nanoparticle enters the body and moves inside it, as well as the potential for accumulation in the body after repeated exposure.
- The detailed examination of environmental exposure, including the amount, distribution, and persistence of nanoparticles in the environment, as well as the potential for bioaccumulation in different species. Attention should be given to those nanoparticles that are designed to be deliberately released into the environment (for example agents used to clean up chemical spillages) and the waste products of nanotechnology.

If the above processes and characteristics of the nanoparticle are similar to those of the chemical at larger, conventional scale, the risk assessment could require fewer data.

8.3 How should risks and hazards related to nanoparticles be addressed?

The ability of nanoparticles to cause hazards can be mainly due to:

- a) the toxicological properties of the chemical composing the core of the nanoparticle; or
- b) their greater reactivity caused by their relatively large surface area compared to their volume ; or
- c) their potential to adsorb other chemicals of concern onto their surfaces; or
- d) any combination of these three factors.

In the case of a), the nanoparticles are expected to have properties similar to those of the same chemicals in larger, conventional forms, unless the distribution of the nanoparticles in the body or in the environment is very different.

In the case of b) and c), nanoparticles will have toxic effects different from those of the same chemical in larger physical forms. In addition, in the case of c), the potential for the release of these adsorbed chemicals of concern will need to be addressed.

To identify the hazards related to nanoparticles made up of well known chemicals, a testing method to determine whether or not the nanoparticle form will cause significantly different adverse effects is needed.

No conclusions applicable to all nanoparticle-based products can be drawn at this stage regarding risks and hazards. Therefore, each product and process involving nanoparticles must be considered separately when assessing the safety of workers involved in its manufacture, the safety of consumers and of the public living near manufacturing or processing facilities, the environmental impact, and the human health and environmental risks involved in the disposal or recycling of the nanoparticle products.

When suitable hazard information is lacking, particular care is needed regarding nanoparticles which are likely to be highly persistent in humans and in environmental species.

At present there is no reliable information on the effect of the simultaneous exposure to multiple forms of nanoparticles, or on the interaction between nanoparticles and other agents. Therefore, risks should be assessed on a case-by-case basis.

8.4 What should be done to improve the risk assessment of nanoparticles?

In order to produce detailed guidelines for the risk assessment of nanoparticles, critical **gaps in knowledge** need to be filled. For instance, it would require:

- new techniques for the measurement of exposure levels in humans and in the environment from the routine use of nanoparticle-based products.
- protocols to assess the release of nanoparticles from various products and production processes.
- to determine whether it is possible to extrapolate from the toxicology of non-nanosize materials to nanoparticles of the same substance, and between nanoparticles of different size ranges.
- information on the health of workers involved in the manufacture and processing of nanoparticles.
- information on the behaviour of nanoparticles in the environment and their effects on various species.
- data on current and past exposure of humans and the environment to nanoparticles.

The confidential nature of much of the research on nanoparticles calls for international cooperation on identifying and resolving gaps in knowledge. Cooperation with industry is also necessary.

Regulations for chemicals are currently based on tonnage, which may have to be reviewed as there are many more nanoparticles to the tonne than is the case for larger particles. Also, for the purpose of hazard warning labels, the nanoparticle form of each chemical should have its own identification. In addition, new workplace exposure standards need to be developed for nanoparticles that are different from those for dusts. Similarly, classification and labeling for human health and the environment may need to be reconsidered

Other needed developments include a harmonized terminology for the physical characteristics of nanoparticles and their general properties, standardized testing methodologies, available reference materials for the measuring of adverse effects, and a clear and widely acceptable framework to weight up the benefits and risks of nanotechnology.

9. Conclusion – Are existing methodologies to assess the potential human health and environmental risks associated with products of nanotechnology appropriate?

To the question: "***Are existing methodologies appropriate to assess potential and plausible risks associated with different kinds of nanotechnologies and processes associated with nanosized materials as well as the engineered and adventitious products of nanotechnologies?***", the SCENIHR is of the opinion that:

- Although the existing methods are appropriate to assess many of the hazards associated with the products and processes involving nanoparticles, they **may not be sufficient** to address all the hazards.
- More specifically, the mode of delivery of the nanoparticle to the test system should adequately reflect the exposure scenarios. Additional tests may be needed.
- Expressing the dose of exposure in terms of mass alone is not sufficient; it also needs to be expressed in terms of total surface area, number of particles, or a combination of the two.
- Also, the existing methods used for environmental exposure assessment are not necessarily appropriate.
- Therefore, the current risk assessment procedures require modification for nanoparticles.

To the question: "***If existing methodologies are not appropriate to assess the hypothetical and potential risks associated with certain kinds of nanotechnologies and their engineered and adventitious products, how should existing methodologies be adapted and/or completed?'"***", the SCENIHR is of the opinion that:

Existing methodologies need to be modified or new ones developed so that they are able:

- to determine the physical and chemical properties of nanoparticles routinely.
- to measure the representative exposure to free nanoparticles in air, soil, water...
- to better assess the potential hazard of nanoparticles, including whether or not they can exacerbate pre-existing medical conditions.
- to better detect the movement of nanoparticles inside living systems.

More specifically, these methodologies need to provide information on how nanoparticles distribute in human tissues and in the environment.

To the question: "***In general terms, what are the major gaps in knowledge necessary to underpin risk assessment in the areas of concern?'"***", the SCENIHR is of the opinion that:

The major gaps in knowledge that need to be filled to allow for satisfactory risk assessments for humans and ecosystems to be performed include:

- the mechanisms and the rate at which nanoparticles are released from products and processes.
- the actual levels of exposure to nanoparticles, both for humans and the environment.
- the extent to which it is possible to calculate the toxicology of nanoparticles from the knowledge on the same chemicals in larger physical forms.
- the movement of nanoparticles inside the body, the effects that nanoparticles cause at cellular level, and how target organs respond to different doses of nanoparticles.
- the exposure and related health effects of workers involved in the production and processing of nanoparticles.
- the behaviour of nanoparticles in the environment, how they are distributed, if they persist in it, and whether they accumulate in different species, including micro-organisms.
- the effects of nanoparticles on various environmental species.