

Nanoparticles: A Closer Look at the Risks to Human Health and the Environment

Perceptions and Precautionary Measures of Industry and Regulatory
Bodies in Europe

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"All research is useless, unless it is allied with internal research"
Gandhi

Abstract

Nanotechnology is a collective definition referring to every technology and science which operates on a nanoscale. Nanoparticles have different properties than larger particles and these properties can be utilized in a wide spectre of areas such as in medicine, information technologies, energy production and storage, materials, manufacturing and environmental applications.

Although nano-derived applications have great potentials, there are some concerns about the potential nanoparticles have to cause adverse effects on human health and the environment. The different properties that make nanoparticles so promising are at the same time properties that are likely to have impact on ecosystems and organisms.

This research maps out the current knowledge base of hazards and risks of nanoparticles to human health and the environment. Furthermore it investigates the perceptions that producers and regulatory bodies have of the risks and looks at the precautionary measures taken.

The main findings of this study are that nanoparticles may cause more toxic effects in the lungs than bigger particles and can translocate within the environment and the body. However, nanoparticles are likely to cause different impacts on human health, occupation health and the environment, depending on the size, shape and chemical composition of the nanoparticle. There is therefore great uncertainty about what the actual risks of nanoparticle to human health and the environment are. Both industry and regulatory bodies are aware of the potential risks of nanoparticles. The producers do not believe that nanoparticles represent a risk to the environment, but sees that nanoparticles can be more problematic in occupational settings. Producers therefore apply some precautionary measures to protect their workers, but limited for the protection of public health or environment. The issue of nanoparticles have a low priority among the regulatory bodies at the moment. The regulators are waiting for more scientific evidence and are therefore not taking any direct precautionary measures.

Executive Summary

Background for the Research

Nanotechnology is a collective definition referring to every technology and science which operates on a nanoscale and refers to the scientific principles and new properties that can be found and mastered when operating in this range. When we bring materials down to the nanoscale, the properties change and nanoparticles have other optical, magnetic or electrical properties than larger particles. These properties are and will be utilized in a wide spectre of areas as in medical applications, information technologies, energy production and storage, materials, manufacturing, instrumentation, environmental applications and security. There are few industries that will escape the influence of nanotechnology (DTI, 2002) and consequently will it also affect our daily life in the future. Some analyses estimate that the market for nanotechnology based products is currently around 2500 million Euro, but could rise to hundreds of billions of Euro by 2010 (EC, 2004a) and exceed trillions thereafter (DTI, 2002).

However, there are also some potential negative environmental and health aspects that may follow the nanotechnology. Engineered nanomaterials like the nanoparticles are so small that they can pass through the skin, lungs and intestinal tract with unknown effects to human health. From the point of intake can nanoparticles travel around in the body and reach for example the brain. The new engineered nanoparticles have novel properties not previously known and it is likely that those properties will cause impacts on ecosystems and organisms. There are currently no regulations that cover nanomaterials and there is no demand to do risk assessment of nanoparticles if the parent, bulk compound is already assessed. The published research on environmental risk assessments and toxicological studies of nanoparticles as such is therefore very limited.

Research Objective and Focus

The main objective of this thesis is to provide a basic understanding of the risks to human health and the environment involved when the smallest constituents of materials are brought down to the size of a few nanometers. As occupational settings are the areas were people get exposed to the materials first, it is important to take a closer look at the occupational health risks. Indications of risks in occupational settings are often an indicator that other risks will arise in other fields as well.

This thesis attempts to answer three research questions:

- 1. What is the current knowledge base of the risks of nanoparticles to human health and the environment?*
- 2. How are the hazards and risks of nanoparticles perceived among regulatory bodies and industry?*
- 3. What precautionary measures are taken to prevent harm?*

The research questions were approached by conducting a literature review of the published scientific knowledge base. This was supplemented by interviews of the different actors in the field, nanoparticle experts from academia and non-governmental organisations, producers, occupational health authorities and the European Commission. In total were 21 interviews conducted. The research focused on the three countries Germany, Switzerland and the UK.

Research Questions, Findings and Conclusions

The main findings of this thesis are structured as to answer the research questions.

Research Question 1: What is the current knowledge base of the risks of nanoparticles to human health and the environment?

The answers to this research question were found through literature review and interviews with academia and NGOs.

Nanoparticles cause more inflammation when inhaled and deposited in the lung than larger particles of the same material, which is believed to be caused by the increased surface area that follows a decrease in particle size. This theory is well established. Inhaled nanoparticles are able to translocate from the point of intake to secondary organs in the body. The effects nanoparticles cause in the secondary organs are not known. However, nanoparticles cause different levels of interaction with the biological system and have different mobility based on the size, shape and chemical composition. Therefore it is not possible to address the hazards and risks of nanoparticles in a general way, as each type nanoparticle need to have its own toxicity understood.

There are different types of nanoparticles that share the same physical property of size, but have different characteristics and engineered purpose. A categorisation was therefore developed and suggested separating nanoparticles into the following three categories: ultrafine particles, traditional nanoparticles and novel nanoparticles. The ultrafine particles are produced unintentionally as a by product in a process and are typically originated from combustion processes or food cooking. These particles can originate both from natural and anthropogenic sources. The traditional nanoparticles are produced in larger bulk quantities for already existing applications in the market. This category encompasses common engineered nanoparticles like carbon black, titanium dioxide and fumed silica and has generally been produced for decades especially in the chemical industry and the polymer industry. The novel nanoparticles are particles that are deliberately engineered to have properties only existing in the nano-range and specific characteristics in terms of size, shape and where those properties and characteristics are utilized to fill a specific function. These types of nanoparticles are, as of today, typically produced in small quantities, typically in the kg range. The different types of nanoparticles have different knowledge base and may have different impacts on public health, occupation health or environment. There are probably sub-groups of the population that have higher risks. Such groups include people with especially cardiovascular or respiratory diseases, children and elderly.

At present the occupational health risks due to inhalation of novel nanoparticles in the production phase seem to be the most potent risk. However, it is reasonable that in the future the most potent risks will be due to exposure from applications of nanoparticles, as occupational settings are easier controlled. As long as we don't know what the hazards are of nanoparticle exposure it is advisable to use precautionary measures that limits the exposure to workers and the environment as far as possible.

Research Question 2: How are the hazards and risks of nanoparticles perceived among regulatory bodies and industry?

The perceptions of the regulatory bodies and the industry were investigated through conducting interviews with the actors.

The producers seem to be updated on the recent studies, but it also seems like the producers do not believe the nanoparticles they produce themselves are problematic. The occupational regulations are not adequate at the moment for assessing nanoparticles, but the companies believe there should be regulations for nanoparticles. The producers further believe that the

nanoparticles do not represent a risk to the environment because of the measures they are taking, although nanoparticles are released into the environment during manufacture and through applications.

The occupational health authorities are aware and updated on the potential risks of nanoparticles and see the need to assess nanoparticles on an individual basis. They are prepared to amend the existing regulations, but they are aware that today, this is not possible as it is not known whether the exposure levels should be set based on mass, volume, particle numbers or surface area. However, the risks of nanoparticles have not a high priority among the authorities today, as there are no clear indications whether the nanoparticles constitute a risk or not to human health.

The European Commission believes that the benefits of nanotechnology will outweigh the potential risks, but stresses that today, there are no identified risks of nanoparticles, only identified hazards.

Research Question 3: What precautionary measures are taken to prevent harm?

To find out what precautionary measures that are taken to prevent harm, interviews with regulatory bodies and producers of nanoparticles were conducted.

The companies are using engineering control in production which protects the products from contamination as well as the workers from the products. When the workers are handling the nanoparticles they apply the personal protective equipment normal for a chemical or dusty working environment like masks and gloves. However, today nanoparticles are often treated as dust in terms of precautionary measures, but the question is whether the precautionary measures applied by the producers need to take the uncertainties into account and address nanoparticles as in a worst case-scenario.

There are limited precautionary measures taken to protect public health and the environment from exposure to nanoparticles. Precautionary measures for these purposes seem today to have a very low priority.

The European Commission has a duplex role as they are both promoting nanotechnology, but at the same time has a legal obligation to protect the citizens and the environment. The EC is not taking any precautions of today and it is likely that questions of precautionary measures will be left fully to the individual member states. However, no direct precautionary measures have been taken by the occupational health authorities, but some countries like the UK are more active than other countries and have already established working groups and contact networks covering both industry and scientists on this issue.

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1 Introduction

1.1 Background

Nanotechnology is a collective definition referring to every technology and science which operates on a nanoscale and to the scientific principles and new properties that can be found and mastered when operating in this range. In this thesis we will use the following definition of nanotechnology, as defined by the Royal Society: *Nanotechnology is the design, characterisation, production and application of structures, devices and systems by controlling shape and size at nanometer scale* (The Royal Society & The Royal Academy of Engineering, 2004a). In the nanoscale, which is normally seen as going from 100 nm and down to just a few nanometers, the materials have properties that can be very different from those at a larger scale. The prefix ‘nano’ is derived from the Greek word for dwarf. A nanometer (nm) is one thousand millionth of a meter, 10^{-9} . To illustrate this, the size of a human hair is 80 000 nm wide and a virus is around 100 nm in diameter. About ten atoms in a line make up one nanometer.

There are two principal ways of manufacturing nanoscale materials; the top-down nanofabrication starts with a large structure and proceeds to make it smaller through successive cuttings while the bottom-up nanofabrication starts with individual atoms and builds them up to a nanostructure. When we bring constituents of materials down to the nanoscale, the properties change. Some materials used for electrical insulations can become conductive and other materials can become transparent or soluble. For example gold nanoparticles have a different colour, melting point and chemical properties, due to the nature of the interactions among the atoms that make up the gold, as compared to a nugget of gold. Nano gold does not look like bulk gold, the nanoscale particles can be orange, purple, red or greenish depending on the size of the particle (Ratner & Ratner, 2003). All these new properties that open up when bringing the material down in scale is of great interest for the industry and society as it enables new applications and products.

Nanotechnology is considered by some to be the next industrial revolution and is believed to cause enormous impacts on the society, economy and life in general in the future (Hett, 2004). The fields in which the nanotechnology is and will be used reaches over a wide spectre of areas as in medicine, information technologies, biotechnologies, energy production and storage, material technologies, manufacturing, instrumentation, environmental applications and security. There are few industries that will escape the influence of nanotechnology (DTI, 2002) and consequently will it also affect our daily life in the future. However, it is important to understand that nanotechnology as such is not an industry, but an enabling technology that, combined with other technologies, has the potential to impact most other industries in various ways.

Some analysis estimate that the market for nanotechnology based products is currently around 2500 million Euro, but could rise to hundreds of billions of Euro by 2010 (EC, 2004a) and exceed trillions thereafter (DTI, 2002).

The many promising application areas of nanotechnology have boosted the public funding for research and development rapidly. This year the publicly funded initiatives are estimated by the European Commission to be over 3000 million Euro while the private investments are calculated to be close to 2000 million Euro, implying a total global R&D investment in nanotechnology of around 5000 million Euro (EC, 2004a). There are big research and

development programs taking place all over the world, but with USA, Japan and Western Europe in leading roles.

There are also some potential negative environmental and health aspects that may follow the nanotechnology. Engineered nanomaterials can penetrate the skin, lungs and intestinal tract with unknown effects to human health as nanoparticles can travel around in the body and reach for example the brain (G. Oberdorster et al., 2004b). The new engineered nanoparticles have novel properties not previously known and it is likely that they exactly because of the novel properties will cause impacts on ecosystems and organisms. As an example, a study led by Eva Oberdörster found that a type of buckyball - a carbon nanoparticle that shows promise for electronic and pharmaceutical uses - can cause brain damage in fish (E. Oberdorster, 2004). Nanoparticles can cause other effects if they react with other substances or even carry other substances into organisms, soil or groundwater.

The debate on nanotechnology has already been going on for years and the opinions are diverse. *"Its most extreme supporters claim that nanotechnology can rebuild the human body from within and effectively abolish death, while its enemies fear that instead, it could do away with life, by turning the surface of the Earth into an uninhabitable grey mess."* (Wood, Jones, & Geldart, 2003) As with any new technology development it is clear that we have both benefits and risks. One of the leading global reinsurance companies, SwissRe, considers nanotechnology as an emerging risk that challenges the insurance industry because of the high level of uncertainty in terms of potential nanotoxicity or nanopollution, the ubiquitous presence of nanoproducts in the near future (across industry sectors, companies and countries) and the possibility of long latent, unforeseen claims (EC, 2004b).

There are currently no regulations that cover nanomaterials and there is no demand to do risk assessment of nanoparticles as such, if the parent, bulk compound is already assessed. When risk assessments are conducted on for example chemicals, one of the biggest uncertainties lies in the exposure assessment. This is no exception for nanoparticles where the uncertainties are probably even higher, because it is not fully known which properties nanoparticles have and what the future applications will be. The published research on environmental risk assessments of nanoparticles is very limited; a preceding review found none and additionally there are limited toxicological studies, because it is not easy to obtain financing as sponsors are primarily interested in scientific progress or valuable patents (Hett, 2004). This imposes a challenge in the research phase, as the background literature is of predictive nature. Additionally, as nanoparticles can have such widely different applications and forms of hazards and risks, the limited literature available is published in very different journals categorized under a wide area of topics which makes it difficult to get an overview of the relevant literature. This is time consuming and also an expressed problem for producers, researchers and authorities.

This thesis therefore attempts to give an overview of the most recent knowledge about the hazards and the potential risks of nanoparticles. There are already applications on the market based on nanotechnology and there are more to come. As there are so many uncertainties and limited knowledge, there are few risk assessments done so far. However, when there are so many uncertainties it is generally accepted that more precautions are taken. This thesis will therefore investigate the perceptions that producers of these nanoparticles have, regarding the potential risks to human health and the environment and further see how these perceptions correspond with the regulatory bodies. Finally it will investigate what precautions are taken.

1.2 Objectives

The objective of this thesis is to provide a basic understanding of the risks to human health and the environment involved in technologies that brings materials down to the size of nanometers and how we currently are handling these risks. To meet this objective the following three research questions were investigated:

1. *What is the current knowledge base of the risks of nanoparticles to human health and the environment?*
2. *How are the hazards and risks of nanoparticles perceived among regulatory bodies and industry?*
3. *What precautionary measures are taken to prevent harm?*

1.3 Scope and limitations

There are several interesting countries involved in the development of nanotechnology, but this thesis focuses on Switzerland, the United Kingdom (UK) and Germany as they are, by a great margin, the biggest actors in Europe, according to the NanoInvestor database¹. These three countries are therefore believed to be also at the research forefront when it comes to development of nanotechnology in Europe. By choosing these countries for investigating perceptions and the knowledge level of hazards and risks of nanoparticles among producers and authorities, it is believed that it will provide a just representation of the dominating perceptions in Europe.

As occupational settings are the areas where people get exposed to the materials first, it is important to take a closer look at the occupational health risks. Indications of risks in occupational settings are often an indicator that other risks will arise in other fields as well. The thesis therefore focuses on the precautionary measures producers take in the production phase to protect the workers and the environment and how producers perceive the risks of nanoparticles in general.

Nanotechnology encompasses a wide variety of technologies and applications and there are several authorities that are involved with the hazards and risks of nanotechnology, but this thesis focuses on the occupational health authorities in the selected countries.

1.4 Methodology

To find out what the current knowledge base is regarding if nanoparticles in general represent a risk to human health and the environment, literature reviews and expert interviews were conducted. The literature review consisted of studies done on the effects of nanoparticles on human health and the environment. The literature was found from Internet searches². Literature was also collected from conferences, found through suggestions by people in this field and also given by people working in this field.

¹ According to the database of NanoInvestorNews (August 2004) there are currently 932 companies involved in nanotechnology world-wide (NanoInvestorNews, 2004b). It is believed that this database probably gives the most updated and comprehensive overview. The report 'Nanoparticles: An occupational hygiene review' estimates that 44% of nanotechnology companies are involved in activities where nanoparticle exposure could occur (Aitken, Creely, & Tran, 2004). This means that around 35 companies are involved in activities with potential exposure in Germany, 18 in the UK and 14 in Switzerland, based on the statistics from the NanoInvestorNews database (NanoInvestorNews, 2004a).

² The searches were conducted with Google and the online databases PubMed, NanoInvestorNews, Web of Science, NEBIS, ELIN and ScienceDirect using the keywords: 'nanotechnology' + 'environment', 'sustainability', 'risks', 'applications',

The information collection through interviews was divided into three sections: interviews with independent experts and one Non-Governmental Organisation (NGO), interviews with representatives of occupational health and safety agencies and nanoparticles producer representatives with expertise in occupational health and safety and environmental issues. The interviewed experts of nanoparticles and the NGO were identified from the reviewed literature as key authors, the participations list of conferences and workshops in the field and also from suggestions of people working in this field through a “snowballing” technique. The interviews were conducted by phone during June, July and August 2004, using a structured questionnaire, see Appendix II, but additional follow up questions were also made when appropriate. In total, 21 interviews were conducted.

To find out the knowledge base and perceptions of nanoparticle producers towards hazards and risks of nanoparticles in an occupation setting and the precautionary measures taken, nanoparticle producers were interviewed by phone and/or through written surveys, displayed in Appendix III. The questions were the same for both interviewing methods. There is currently no overview of nanoparticle producers in the EU. The selection of nanoparticle producers was therefore done through literature review of nanoparticle products, from participation-lists in workshops and conferences and from suggestions by experts and other people working in the field of nanoparticle research and development. From these different sources, the producers that were most often suggested or figuring either in terms of research forefront or in terms of quantity of nanomaterials produced were approached. The selection of nanoparticle producers was based on both the opinion of the contacted people and the literature review in combination providing a good indication of the most relevant actors from both groups of nanoparticle producers. There was in total 13 companies approached and six of those chose to participate.

To find out the knowledge base, perceptions and the precautionary measures taken by occupational health authorities and the European Commission (EC) regarding the hazards and risks of nanoparticles, interviews were conducted with these organisations. The representatives from the occupational health authorities in the respective countries and the EC were chosen by the authorities themselves as a response of a direct request to their main office of an interview about nanoparticle risks. The interviews with the occupation health authorities were conducted by phone, using a structured questionnaire, displayed in Appendix IV. The interviews all followed the same structure, but there were also additional questions made when appropriate. The interview with the EC-representative followed a loose structure where the following topics were discussed: ‘the kind of hazards and risks of concern to human health and environment’, ‘how the EC works with these issues’ and ‘precautionary measures, regulations and actions planned in the future’. The transcript of the interview is displayed in Appendix V.

All the results of the interviews were transcribed and processed into a suitable form, before presented in Chapter 3, 4 and 5. Together with the literature review, the results from the interviews were analysed and used as the basis for discussions and recommendations.

‘medicine’ (also in different combinations); *‘nanotubes’* OR *‘carbon nanotubes’* + *‘properties’*, *‘applications’*, *‘asbestos’*, *‘toxicity’* (also in different combinations); *‘nanoparticles’* OR *‘nanomaterials’*, OR *‘nano*’* OR *‘*particles’* OR *‘ultrafine particles’*+ *‘environment’*, *‘health’*, *‘impacts’*, *‘effects’*, *‘translocation’*, *‘human’*, and *‘impacts, lung’*, *‘blood’* (also in different combinations); *‘Risk communication’*; *‘risk perception’* + *‘technologies’*. Additionally the Journals *‘Nanotechnology’* and *‘The Journal of Nanoparticle Research’* were searched. The references cited in the literatures were also explored.

1.5 Outline

Chapter 1: Introduction. This chapter gives an introduction to the topic and why the thesis was written. It describes how the research was carried out, the methodology used, the focus areas and the limitations of the thesis

Chapter 2: Nanoparticles. In this chapter, the different uses of the term ‘nanoparticles’ are explained. It also gives a general introduction to what nanoparticles are and also an introduction to the different kind of applications that nanoparticles are and can be used in.

Chapter 3: Hazards and risks of nanoparticles to human health and the environment. In this chapter, the knowledge base regarding hazards and potential risks of nanoparticles is investigated. This chapter is based on literature reviews and interviews with experts from academia and NGO.

Chapter 4: Perceptions and precautionary measures of producers of nanoparticles. This chapter investigates how producers of nanoparticles look upon the risks and what precautionary measures they take. The chapter is based on interviews with companies producing nanoparticles.

Chapter 5: Perceptions of regulatory bodies. This chapter investigates the perceptions of the regulatory bodies especially focusing on occupation health risks. The chapter is divided in two main parts where one part is investigating how the EC look upon the risks of nanoparticles and a second part investigates how occupational health authorities perceive the risks of nanoparticles. The information in both parts is based on interviews.

Chapter 6: Discussion. In this chapter a categorisation of nanoparticles is discussed and suggested. The uncertainties, hazards and risks of nanoparticles are also discussed and the implications on the precautionary measures for producers and authorities are analysed. Finally, the nanotechnology development and public debate is compared to the biotechnology development and debate where the similarities are analysed and lessons learned from the biotechnology debate is presented.

Chapter 7: Conclusion. This chapter concludes the research. It returns to the research questions and answers them. Suggestions on precautionary measures or actions for producers and authorities are made as well as focal points for further research.

2 Nanoparticles

Particles play in general a dominant role in many industrial processes and natural phenomena. 60% of the products made by major chemical companies such as Dupont, Dow or ICI are either made as particles or involve significant particle technology in their manufacture (PTL, 2004). Furthermore particle science and engineering is central to the environment (air pollution, climate change, green house effect), energy utilization (fossil fuel combustion, turbine combustion, fly ash) and medicine (virus and bacteria transport, medicine delivery, allergies) (PTL, 2004).

Nano-sized materials are naturally present from forest fires and volcanoes, but are also generated unintentionally from anthropogenic sources as a by-product of combustion and deliberately as manufactured nanomaterials. Nanoparticles have been used for centuries. The coloured glass that we see in many old cathedrals from the middle age was made of gold nanosized clusters that created different colour depending on the size of the nanoparticles. The most prominent example of engineered nanoparticulate material is carbon black which has been around us for decades in applications like printing inks, toners, coatings, plastics, paper, tires and building products. However, carbon black would for many be excluded from the nanoparticle category, as nanotechnology is about deliberately and knowingly exploiting the nanoscale nature of materials (Holister, Weener, Vas, & Harper, 2003).

Two of the major factors why nanoparticles have different properties (optical, electrical, magnetic, chemical and mechanical) than bulk material are because in this size-range quantum effects start to predominate and the surface area to volume ratio is increased (Holister et al., 2003). The increase in the surface-area-to-volume ratio is a gradual progression as the particles get smaller which leads to that atoms on the outside of the particle will increasingly begin to dominate the ones inside the particle. This changes the individual properties of the particle and how it interacts with other materials in the surroundings. The increase of relative surface area makes them very interesting for the industry, as high surface area is a critical factor in for instance efficient catalysis and in structures like electrodes. This can improve the performance of products like batteries, but also reduce resource usage in catalytical processes and hence decrease the amount of waste. The large surface area also increases the mixing with other materials in the surrounding and is especially beneficial in intermixed materials like composites.

Once particles become small enough they start to exhibit quantum mechanical behaviour. Classical mechanics can explain the relation between theory and observation for large objects. However, only quantum mechanics can explain the behaviour of objects as small as electrons. Quantum mechanics describes the matter and radiation taking quantization³ into account.

Nanoparticle are currently made out of a very wide variety of materials, the most common is ceramics, which can be split into metal oxide ceramics, such as titanium, zinc, aluminium and iron oxides, and silicate nanoparticles (silicates, or silicon oxides are also ceramics), generally in the form of nanoscale flakes of clay (Holister et al., 2003). Silicate nanoparticles, as any nanoparticles, can be mixed into polymers. Pure metal nanoparticles can mix together into a solid composite at lower temperatures than for larger particles, which can improve coatings

³ Quantum theory states that all energy exists in very small separate packets, which are handed around from one owner to the next. An individual packet of energy is called a 'quantum' (Avison, 1989).

and make the coatings easier to create, harder and more durable. The formation of coatings and bulk materials at lower temperature reduces the manufacturing costs compared to their non-nano counterparts. Metal oxide ceramic, metal and silicate nanoparticles are the majority of nanoparticles that have existing applications.

2.1 Promising application fields

Nanotechnology often brings together different disciplines and this interdisciplinary approach is expected to contribute to innovations that might solve many of today's challenges in the society. A selection of the applications involving nanoparticles that exist or show promises are presented here.

Nanotechnology is already being used in commercial applications for bulk products, such as sunscreens with increased transparency and cosmetics containing nanoparticles with the ability to target deeper into the body. The cosmetic companies have been active in using nanotechnology to improve their existing products and e.g. L'Oreal holds a very high number of nanotechnology patents (Wood et al., 2003). Also nanoparticles as fillers have been introduced in the composite materials with an enormous market. The nanoparticles change the material's properties as e.g. metal gets harder, ceramics get softer and mixtures like alloys may get harder up to a point where they get softer again. By introducing clay nanoparticles it is possible to make the materials stronger, lighter, more durable and often transparent. These have especially potentials in aerospace industry, packaging and in the car industry where they already have been introduced in the GM Motors Safari and Chevrolet Astro vans (Wood et al., 2003). Other short-term uses includes solar energy collection (photovoltaics), medical diagnostic tools and sensors, flexible display technologies and e-paper, glues, paints and lubricants, various optical components, and new forms of computer memories and electronic circuit boards (Twist, 2004).

There are smart textiles developed with the help of nanotechnology and in the long run textiles are expected to be able to change their physical properties according to the surrounding conditions, or even monitor vital signals (Holister, 2002). The introduction of nanoparticles in textiles can make it possible to produce very light and durable textiles with resistance against water, stains and wrinkling.

Medical applications are one of the fields with the biggest expectations regarding human welfare. With the development of new materials and a combination of nanotechnology and biotechnology it could be possible to make artificial organs and implants through cell growth which could repair damaged nerve cells, replace damaged skin, tissue or bone (Wood et al., 2003). Furthermore in the synergy of information technology and medicine there are expectations to e.g. diagnosis instruments for personal health monitoring providing ultra-fine precision and quick response time to the diagnosis tests. Another application field in medicine is drug-delivery where research is especially intensive on the possibility of manipulating nanoparticles to deliver drugs because nanoparticles can have a better solubility and absorption potential than bigger particles. The nanoparticles can carry the drug and perhaps release it in fine-tuned doses over a long time period to a targeted area, reducing the side-effects of the traditional drugs.

There are also future environmental applications developed with the help of nanotechnology. For example carbon nanotubes show promises as a storage medium for hydrogen giving new possibilities for renewable energy. Other applications researched are nanoparticles as bioremediation. Biological organisms that are used to clean up soil pollution face the

problem that in the soil most pollutants are not bioavailable, but locked up within pores in the soil structure. By using nanoparticles it may be possible to deliberately mobilize pollutants in a controlled manner so that they become bioavailable and ensuring that clean-up organisms are not killed by a rapid release.

The development of doing things smaller, lighter and faster than before has already been going on for many years. This enhanced precision could enable existing products and processes to be more effective, hence require less raw materials and energy. This is especially true in the field of IT, electronic and energy industry, as can be seen in Figure 1, but also in the military, space and security fields has nanotechnology high application potentials. .

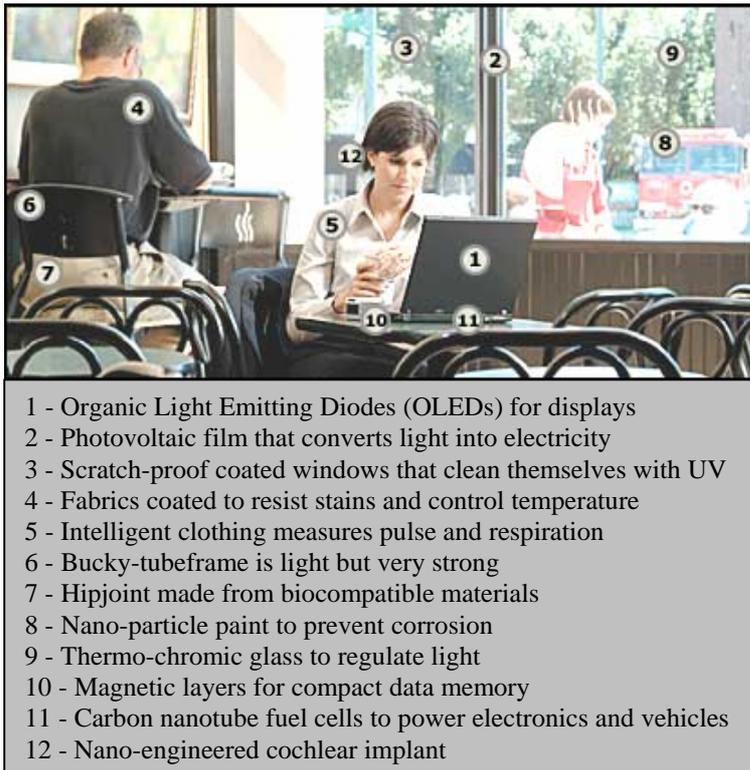


Figure 1: Potential uses of Nanotechnologies (Twist, 2004).

2.2 The nomenclature ‘nanoparticles’

This thesis uses the most widely-accepted definition of nanoparticles, where nanoparticles are less than 100 nanometers in at least one of their dimension (Holister et al., 2003). However, nanoparticles are in general materials that have dimensions in the nanoscale in at least two dimensions, encompassing particles as well as fibrous material and tubes, but excluding materials which are nano-sized in only one dimension, such as coatings, films and multilayers. Under this umbrella term, there are several types of particles which only have the similarity of their small size. In this thesis as well as in the common language people in general are using the term ‘nanoparticles’ as a collective term. However it is important to notice that it can be used for quite different particles. The following section tries to give an overview of the most common types of nanoparticles that is used under this term.

Nanoparticles are often also used for the term ‘ultrafine particles’ that are produced either naturally in volcanoes or forest fires, or from anthropological sources as by-products and can

originate from combustion soot, welding fumes, food cooking and diesel exhaust. These airborne particles may be created as by-products in processes.

The term nanoparticles is also used for a range of particles produced in established technologies and products that has been around us for decades. These particles include among others carbon black, fumed silica, titanium dioxide, polystyrene B, and have long traditions of production in for example the chemical industry and the plastic industry. These particles are typically produced in large quantities and have less defined size and shape.

Nanoparticles also encompasses a range of new engineered materials in the nano-range that have because of their size, new novel properties, that are deliberately explored and used in applications. It is these types of materials which are representing the 'true' nanotechnology development. These particles are engineered to have a relatively precise size and shape. There are several types of these new nanomaterials like the quantum dots, fullerenes and nanotubes.

Quantum dots are particles that work under the laws of quantum mechanics that cannot be explained by the classical mechanics and electromagnetic theory. Quantum dots are often fabricated in semiconductor material. The size and shape can be precisely controlled and a quantum dot may have certain number of electrons. Quantum dots show among other potential within the information technology.

The first fullerene discovered was the buckyball in 1985. Fullerenes are carbon molecules formed as large hollow closed-caged clusters and have several special properties that were not found in any other compound before. Carbon nanotubes can be seen as the nearly one-dimensional form of fullerenes as shown in Figure 2. The nanotubes are typically a few nanometers in diameter, but can be several micrometers long. These nanotubes show highly promising potentials as they often are described as having one hundred times the tensile strength of steel, thermal conductivity better than all but the purest copper, and electrical conductivity similar to or better than copper, but with the ability to carry much higher currents. (Holister, Harper, & Vas, 2004) There are very different nanotubes with different properties and shape: long, short, single-walled, multi-walled, open, close, with different types of spiral structure etc.

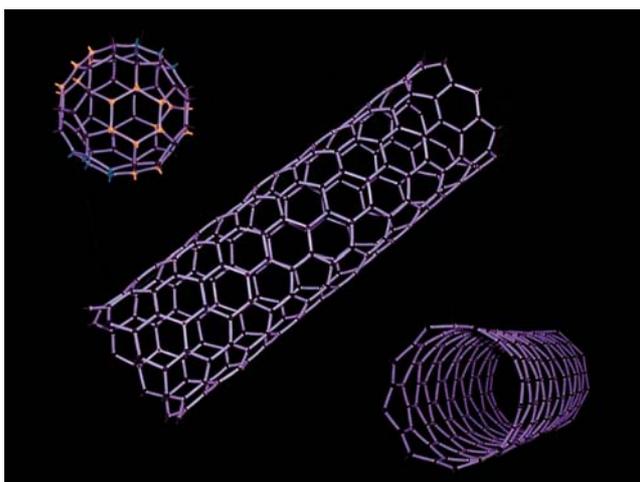


Figure 2: Model of a buckyball (fullerene) and carbon nanotubes (NCCR, 2004)

3 Hazards and risks of nanoparticles to human health and the environment

There are many concerns regarding the possible impacts on human health and the environment that can arise when the smaller constituencies of materials are brought down to the nanoscale. Although these impacts may not be any different from those that can be caused by chemicals, it is not possible today to anticipate the impacts based solely on the chemical composition as such. This chapter aims to give an overview of the most updated knowledge of the impacts nanoparticles can have on human health and the environment.

3.1 Defining hazard and risk

The terms ‘hazard’ and ‘risk’ is frequently occurring in this thesis. To fully understand the characteristics of both the hazard and the risk, the distinction between hazard and risk must be clearly understood.

The term ‘hazard’ can be defined in many ways. This thesis uses the definition by the United States (U.S.) Environmental Protection Agency (EPA) which defines ‘hazard’ as *the inherent toxicity of a compound* (USEPA, 2004). For example, a chemical substance that has the property of being toxic, and therefore dangerous, is hazardous. An exposure to a hazardous substance will consequently lead to an adverse health effect or even death for the individual. Hence, the hazard may be thought of as the consequence of an event occurring, such as the consequence for an individual being exposed to a toxic or hazardous substance.

The definition of ‘risk’ that is used in this thesis is, as defined by the U.S. EPA, as following: *A measure of the probability that damage to life, health, property, and/or the environment will occur as a result of a given hazard* (USEPA, 2004). If the probability of an event occurring is high and the consequences are significant, the risk is considered to be high. However, human health risks are considered to be high, if the hazard or consequence is adverse health effects, even though the probability of occurrence is low, for example a nuclear power accident. It is therefore important to consider both the frequency of the event and the degree of severity of the consequences, if the event were to take place.

Usually a schematic distinction is made between two categories of risks, “known risks” on the one hand and “hypothetical risks” on the other, to which correspond two different public policies (Perret, Audétat, Petriccione, Joseph, & Kaufmann, 2004). When the relation between a cause and an effect is established, we talk of *known* or *identified risks*. The responsibility of such risk can generally be attributed. When the causal relation is established, prevention can be applied. When the relation between a cause and a damage is not well established, we talk of *hypothetical* or *potential risks*. In these cases, we don’t know whether there is a danger, the importance of the damage or the probability of occurrence, all being still in the realms of hypotheses. This situation is best characterised by a general state of suspicion in which people gather indications and hypotheses on dangers that are not yet objectively established and it is generally admitted that a precautionary approach can be applied (Perret et al., 2004).

This distinction between hazard and risk is important as we can identify that a substance can cause harm – that it is hazardous, but the likelihood that this will happen – the risk, is the

fact that determines how cautious we should be and what preventative or precautionary measures we should take.

3.2 Literature review

As nanoparticles are used in so many different technologies and exists in so many different settings, the literature is also spread in many different journals. There are no special journals where researchers publish their work that is relevant for assessing the hazards and risks to nanoparticles. To find for the relevant information is both time consuming and challenging. This chapter therefore summarizes the most important published works to find out what the scientific knowledge base is.

3.2.1 Inhalation of nanoparticles

The most elementary property that nanoparticles have is the size. Small sized particles have an increase both in number and in relative surface area compared to particles of a bigger size, but with the same mass. If comparing bigger particles with e.g. a mass concentration $10 \mu\text{g}/\text{m}^3$ with nanoparticles of the same mass concentration, there seems to be a correlation between a decrease in particle size and an increase in toxicity. This is a well established hypothesis when it comes to lung toxicity, where it is shown that ultrafine particles made of low-soluble, low-toxicity materials causes a stronger defence reaction in the lung tissue of rats than finer respirable particles made from the same material (Donaldson et al., 2002; G. Oberdorster, 2001; Zhang et al., 2003). It is important to notice that the lung toxicity knowledge of the effects of fine particles compared to nanoparticles is primarily based on studies of three types of particles; titanium dioxide, carbon black and diesel particles (Warheit, 2004). This defence reaction that is called inflammation is a sign of tissue injury, infection or irritation which leads to swelling, redness, heat and pain at the affected area. An immune response is then normally stimulated where usually a healing process is gradually followed. However, a persistent or high inflammatory response may damage the cell layer at the surface of the tissue and other cells (such as macrophages used for particle clearance of the lungs), which can result in tissue damage and loss of function (Borm & Kreyling, 2004). If we take the example of nickel, it is shown that indicators of lung injury were greater with ultrafine nickel (20 nm) than standard nickel (5 μm) (Zhang et al., 2003) suggesting that ultrafine particles have a much more toxic effect than finer particles of the same material. However, the mechanisms behind are poorly understood.

There are theories that are trying to explain the mechanisms behind the increased toxicity of ultrafine particles. The most well established theory is that it has to do with the increased surface area and/or combination with the increasing number of particles (Warheit, 2004) . The increase in particle surface area is believed linked to lung cancer, lung fibrosis and inflammation in the lung. Air pollution research on bigger particles has established clear links with the increase of particulate matter in the air and the number of hospital admission rates (Chan-Yeung, 2000). There are a considerable body of epidemiological studies suggesting that an increase in ambient particle concentration is related to increase in mortality and diseases in the exposed population. The strongest associations are seen for respiratory and cardiac deaths, particularly among the elderly and particulate air pollution is also associated with asthma exacerbations, increased respiratory symptoms, decreased lung function and increased medication use (Utell & Frampton, 2000). However it is not established what causes this yet, but a theory is that the increase in particle concentration in the air may overload the lungs and the phagocytes that are responsible for eliminating those particles.

This overloading of the lungs causes inflammation of the surrounding tissue, also known as oxidative stress.

The nanoparticles that are free and can become airborne to form an aerosol is perceived as the most potentially hazardous type of nanoparticles, according to a contribution to a EC-workshop in 2004 by professor Jos Put at DSM Research. If the nanoparticles are inhaled, they can have possible adverse effects. These effects are related to the enormously enhanced surface to mass ratio. All properties related to surfaces: adsorption, reactivity, catalytic activity, etc. will multiply the factor (EC, 2004b).

As already mentioned, there are a lot of concerns of nanoparticles, but nobody knows yet if they can be biodegradable. Particles that disappear within 1 to 2 weeks will probably not cause many problems, according to Paul Borm of the Center for Expertise in Life Sciences, Hogeschool Zuyd, the problems start when you use insoluble particles like carbon black, gold and so on (Walgate, 2004). According to Borm and Kreyling two third of inhaled fibres that are less than 20 μm are not cleared out of the lungs, which means that the fibers will bioaccumulate in the lungs unless they are biodegradable or cleared out by other mechanisms than macrophages clearing that transport particles from the lower parts of the lung (Borm & Kreyling, 2004). To make nanoparticles biodegradable will therefore prevent many problems.

3.2.2 Absorption through the skin

There are many consumer products containing nanoparticles already in the market that are applied to the skin. There are nanoparticles in cosmetics, suntan lotion and baby products that regulate and improve the moisture, odor or color. Up till today, there is no clear evidence whether nanoparticles can be absorbed through the skin, but the studies that are done are highly debated by scientists as the examination methods are of various characters. For example some studies are not based on living samples of skin which makes them only of limited relevance (Hett, 2004). It is also unknown how susceptible damaged skin is to nanoparticles. On the other hand there is some evidence that dermal exposure to nanoparticles may lead to direct penetration into top layer of the skin and possibly beyond into the blood stream (Aitken et al., 2004). Considering the wide variety of products already on the market, this needs to be found out urgently.

3.2.3 Absorption through the intestinal tract

Nanoparticles that are swallowed will sooner or later end up in the intestinal tract. A very important consideration is what happens with food containing nanoparticles. Will they remain in the intestinal tract or will they move on into the body? The two tasks of the intestine is to take up nutrition while protecting the body from unwanted substances in the food. It is not known whether nanoparticles is regarded as an 'unwanted substance' and excreted or it will be absorbed. According to a report by the SwissRe can particles of under some 300 nm reach the bloodstream, while particles that are smaller than 100 nm are also absorbed in various tissues and organs (Hett, 2004). As a general rule, the smaller the particles are, the more of them are absorbed and the deeper into the body they can go.

3.2.4 The translocation of nanoparticles in the body

What will happen to nanoparticles that enters the body involuntary through the lungs or the digestive system or deliberately for medical purposes? Normally will foreign substances that

enter the bloodstream be absorbed by special cells called phagocytes, which remove the foreign substance from the bloodstream. However, everything smaller than about 200 nm, is no longer specifically absorbed by these phagocytes, but by cells that are not actually “designed” for this function (Hett, 2004). This can mean that nanoparticles, once entered the body can travel freely in the blood and through the body.

Additionally small size means increased mobility. Nanoparticles diffuse more easily than solid particles and behave more like gas molecules in the air and like large molecules in solutions, being less subject to sedimentation than bigger particles. This may have implications also for the movement of nanoparticles in tissue. Whether nanoparticles enter and transfer within the body to different organs can have a significance importance for the impacts of nanoparticles on human health and in the environment.

Inhaled ultrafine particles are depending on the particle size, deposited in the nose region, and upper and lower level of the respiratory system. A recent study concluded that the central nerve system and the brain can be targeted by airborne solid ultrafine particles and that the most likely mechanism is from deposits in the nose region (G. Oberdorster et al., 2004a). The study furthermore concluded that the nose region could provide a portal of entry into the central nerve system for solid ultrafine particles, circumventing the tight blood-brain barrier, but the potential effects on the central nerve system needs to be determined by further studies. The blood-brain barrier represents an insurmountable obstacle for a large number of drugs, including antibiotics, antineoplastic agents, and a variety of central nervous system-active drugs, especially neuropeptides and scientists have successfully transported drugs through this barrier of drug delivery to the brain by using nanoparticles (Kreuter, 2001). If nanoparticles designed for drug-delivery can target the brain it is also likely that other nanoparticles can do the same.

There are a number of studies done that supports the hypothesis that ultrafine particles are able to translocate from the lung into the systemic circulation and reach organs like the liver in animals (Kreyling et al., 2002; Nemmar et al., 2001; G. Oberdorster et al., 2002; Takenaka et al., 2004; Takenaka et al., 2001). However the amount of particles that translocate into the blood and organs differed among the studies (Nemmar, Hoylaerts, Hoet, & Nemery, 2004) and therefore this hypothesis needs additional detailed and differentiated consideration.

The large surface of nanoparticles also means that it can be able to bind, absorb and carry compounds such as drugs, probes and proteins (Borm & Kreyling, 2004), but also other substances like metals or toxic substances. This increasing reactivity with other substances can have consequences both for human health and the environment.

3.2.5 Novel properties, different toxicity

The novel properties are exactly what are making novel nanoparticles of such interest for the industry and society. However the properties which make the nanoparticles interesting are also believed to change the toxicity of the material. Single-walled carbon nanotubes (SWCNT) have a very broad commercial application potential due to their superior mechanical and electrical properties, but are very light and can become airborne. In a study by (Lam, James, McCluskey, & Hunter, 2004) SWCNTs were induced into lungs of mice. The results showed that if carbon nanotubes reach the lungs, they are much more toxic than carbon black and can be more toxic than quartz, which is considered a serious occupational health hazard in chronic inhalation exposures. Another study showed that SWCNTs induced in rats caused inflammation and does not appear to follow the normal paradigm of toxic

dusts such as quartz and silica suggesting a potentially new mechanism of pulmonary toxicity and injury by SWCNTs (Warheit et al., 2004). The ability of SWCNTs to cause lung damage may be consistent with their unique physiochemical properties which impart to them enhanced structural properties, but may also make them more persistent in biological and ecological systems (Dreher, 2004).

In current practice SWCNTs are classified as a new form of graphite on material safety data sheets provided by manufacturers of these nanoparticles. As the two studies showed, the exposure limits for graphite-based material may not be adequate for setting a safe exposure level for SWCNTs and it is a question whether SWCNTs should have different exposure limits than bigger graphite material.

3.2.6 Chemical composition and coating

In addition, another consideration is the toxicity of the material the nanoparticles consists of. (Zhang et al., 1998) showed in a rat study that the different materials nickel, cobalt and titanium dioxide give dramatically different inflammatory responses in the lung. Nickel was more toxic than cobalt with titanium dioxide giving the least toxic effect. It further showed that the substances had different ability to create free radical activity. This difference in free-radical-generation activity therefore could underlie the difference in inflammation that these three ultrafine particle types induced. Free radicals are atoms that possess an “unsatisfactory” number of electrons and the atoms either snatch or force electrons on the neighbouring atoms. In this way the original free radicals optimize their own structure, but transform other atoms into free radicals, triggering a chain reaction. This process is completely natural in healthy cells, but when this process is reinforced by external factors they can harm cell walls and these radicals can initiate a chain reaction causing effects in the entire body. The effect of free radicals is not known and debated as the harm caused by radicals presumably depends on how frequently and on what scale such reactions occur in the body (Hett, 2004).

The surface coating of the material is also believed to have influence on the pulmonary⁴ toxicity of the particle. Warheit et al. have studied different commercial formulations of the surface coatings on titanium dioxide particles and found that one surface coating demonstrated more toxicity than the other coatings (Warheit, Reed, & Webb, 2003). The absence, presence or composition of surface coatings is therefore complicating the toxicity of nanoparticles. However, it is unknown how long safety coatings stay on the particles. The likelihood of coating breakdown has been shown in cell culture systems, where quantum dots were initially rendered non-toxic with coatings, but if the quantum dots were either exposed to air or ultraviolet radiation for as little as 30 min, they became very destructive to living cells (Derfus, Chan, & Bhatia, 2004).

3.2.7 Environment

In the environment, natural enzymes can change the surface properties of nanoparticles so the nanoparticles become colloids. In colloidal solutions nanoparticles remain mobile because they do not form conglomeration and are not deposited. According to a report by SwissRe, one of the leading global reinsurers, nanoparticles with colloidal characteristics ideal to carry toxic material, such as water-repelling pollutants and heavy metals (Hett, 2004), over long distances and could potentially pollute aquifers. As they tend to be more reactive, due

⁴ Pulmonary – Of or relating to the lungs (Oxford, 1999)

to the size, they may react with other substances in the environment and lead to new and possible toxic compounds. If the roots of plants were to absorb nanoparticles, the nanoparticles could enter the food-chains. The SwissRe report posed the question whether the nanoparticles could then also leak into the drinking water and be directly taken up by humans (Hett, 2004). However, the high reactivity also means that they react much faster with the surroundings and may be neutralized before causing harm. On the other hand, pollutants binding to a nanotube might neutralize pollutants and reduce the harm they normally would cause (Kleiner & Hogan, 2003).

Mark Wiesner of Rice University said on the annual meeting of the American Chemical Society 2004 that he has found through a preliminary research, that nanoparticles don't flow uniformly in water, they have widely varying behaviour. This may have implications on the assessment of nanoparticles in the environment as the behaviour of nanoparticles in groundwater or water treatment plants have to be assessed on an individual basis. This discovery also suggest limited roles for some nanoparticles in pollution treatment, environmental remediation, since they gum up before flowing very far (Bridges, 2004).

In the long term it is a possibility for a wide exposure of the entire ecosystem to engineered nanomaterials through the water and soil. One of the prominent environmental nano-researchers, Vicky Colvin, anticipates that if engineered nanomaterials applications develop as projected, the increasing concentrations of nanomaterials in groundwater and soil may present the most significant exposure avenues for assessing environmental risk (Colvin, 2003). She further believes that even though it is difficult to create water-soluble nanostructures, some nanomaterials can form a stable colloidal species in water from both a powder and an organic solution and hence enter groundwater.

One type of nanomaterials, the fullerenes are lipophilic and localize into lipid-rich regions such as cell membranes in living organisms, and being redox active and they therefore have the potential to be toxic. A study by Eva Oberdorster showed that fullerenes can induce oxidative stress in the brain of fish (E. Oberdorster, 2004). This is the first study done with new nanomaterials showing that nanomaterials can damage aquatic organisms. Further studies that evaluate the potential toxicity of manufactured nanomaterials, especially related with respect to translocation in the brain are needed.

3.2.8 Summary of the literature review

The literature review indicates that there might be a correlation between a decrease in particle size and an increase in toxicity. This probably has something to do with the increased surface area and/or with the increasing number of particles. It is known from studies that an increase in ambient particle concentration is related to an increase in mortality and diseases in the exposed population. Therefore are free nanoparticles that can become airborne perceived as the most potentially hazardous type of nanoparticles. Another consideration is chemical composition of the nanoparticles as studies show that different materials give dramatically different inflammatory responses in the lung. The surface coating of the material is also believed to have influence on the toxicity of the particle. To make nanoparticles biodegradable will therefore prevent many problems.

As a general rule, the smaller the particles are, the more of them are absorbed and the deeper into the body they can penetrate (Hett, 2004). Nanoparticles once entered the body may travel freely in the blood and through the body and reach organs like the liver or the brain.

There are nanoparticles in cosmetics, suntan lotion and baby products that regulate and improve the moisture, odour or colour, but up till today, there is no clear evidence whether nanoparticles can be absorbed through the skin

The novel properties are exactly what is making novel nanoparticles of such interest for the industry and society. However the properties which make the nanoparticles interesting are also believed to change the toxicity of the material.

If the roots of plants were to absorb nanoparticles, the nanoparticles could enter the food-chains. Nanoparticles with colloidal characteristics may be ideal to carry toxic material, such as water-repelling pollutants and heavy metals. As nanoparticles tend to be more reactive, due to the size, they may react with other substances in the environment and lead to new and possible toxic compounds. In the long run it is a possibility for a wide exposure of the entire ecosystem to engineered nanomaterials through the water and soil.

One observation is that only a limited amount of the published work is based on industrial research. It is more likely to believe that also the industry is doing research than that they don't know or do anything. The industry hence has a marginal contribution to the 'public' knowledge base.

3.3 Interview results of academia and NGOs

The research on the hazards of nanoparticles is still very limited. There is a lot of ongoing research which has not yet been published and it is therefore necessary to conduct interviews with experts in the field in order to get the most updated knowledge. This chapter is based on the results from interviews conducted with nanoparticle experts across Europe and in the U.S. The experts were located through the literature review as key authors, key speakers at conferences, or from suggestions of people working in the field through a "snowballing" technique. Twelve interviews were conducted with nanoparticles experts who are frequently consulted by national bodies and media, as well as by the European Commission. The range of expertise goes from lung toxicology (Donaldson, Riediker, Sauvain, Stone), toxicology (Borm, Krug, Kreyling), ecotoxicology (Oberdorster) and cellular toxicology (Curtis, Powell) to more general expertise in environmental (Thomas) and human impacts (Henshaw) of nanoparticles. The experts are presented in Appendix I.

3.3.1 About the hazards

What is known about the hazards of nanoparticles comes mainly from animal studies, where inhalation tests show clearly that smaller aerosol particles are more toxic than their larger counterparts of the same mass concentration. The interviewed experts agree that nanoparticles are more toxic than bigger particles of the same material. Inhalation of nanoparticles can cause lung effects and systemic effects as nanoparticles can penetrate deep into the lungs.

The majority of the interviewed experts says air pollution studies show that airborne particles in general are a concern for humans, as well as for organisms in the environment. This is because the particles are seen as the cause of mortality and diseases from air pollution. As nanoparticles have been proved in studies to be more toxic than the bigger particles, the majority of the interviewed experts believes that the nanoparticles are the main cause of the health effects. However, this is questioned by Powell who says "*...It is true that robust epidemiological studies suggest that there is a correlation between exposure to airborne particles and mortality.*"

It is also true that in experiments where scientists have used high doses of ultrafine particles they have seen greater effects than when they have used similar doses of fine or coarse particles, meaning higher toxicity of ultrafine particles. Many scientists therefore conclude that the fraction in air that is responsible for the increase in mortality is the ultrafine particles. But I think this is jumping the gun. The animal experiments induce reactive oxygen driven tissue damage, i.e. direct toxicity due to acute overload. I think the human effects that we are seeing from - exposure to particles in the atmosphere do not represent acute overload and toxicity but are due to immune activation and I believe then you must have active phagocytosis⁵. I therefore think that the main culprits are not the ultrafine particles, but the fine particles.”

The major theory, supported by all the interviewed experts, why nanoparticles has an increased toxicity compared to bigger particles, is because nanoparticles have a larger surface area than bigger particles of the same mass. This enhanced surface area is according to Stone, important in driving the production of reactive oxygen species⁶ and free radicals that stimulate and damage cells, drives inflammation and causes the disease changes. According to Borm, it seems like it is the surface area that drives diseases like lung cancer, lung fibrosis and inflammation in the lung. The mass of the particles seems like important in this perspective. For the lung effects it seems to exist a threshold level for the particle surface area. If this level is exceeded, health effects seem to be induced. In addition to the effects of the enhanced surface area, Curtis sees the fact that nanoparticles are taken up by the cells and phagocytised as the most dangerous with nanoparticles. This is because the nanoparticles that are taken up by the cells are left behind in the cells if the cells cannot destroy them. The cells need a way to deal with nanoparticles, either dissolve or render the nanoparticles in some ways to make them inactive. However, the cells may fail to do so, depending on the chemistry of the nanoparticle. For example, biodegradable polymer nanoparticles, will be destroyed by the cells, but nanoparticles of another material and shaped like asbestos fibres may damage the cells with the same mechanism that is thought to be the causation of asbestosis.

According to Krug, it is important to differentiate the nanoparticles in terms of chemical composition, because they give different reactions. Krug draws the analogy to chemistry and the toxicology of pesticides, where the molecular structure needs to be known when assessing the toxicity, as the molecular structure causes different effects. This is also true for nanoparticles where each type of nanoparticles' distinct form, size and chemical composition have to be looked at. All the interviewed experts stress that nanoparticles are such a diverse range of particles, which makes it impossible to say that one nanoparticle has the same hazard as another, as they cause different reactions. These reactions may even different between nanoparticles of the same material comparing the size of 10 nm with 50 nm.

The interviewed experts also point out that the knowledge database that suggests that the nanoparticles are hazardous is very small. Borm says: *“We are trying to find an explanation why very small amounts of particles, even small mass-wise, can have such tremendous effects. People are trying to find the magic bullet. Some say it is the metals in the particles, other says it is the agents and a huge group say it is the nanoparticle itself. The latter is an attractive theory, but it needs further investigation.”* The stand of evidence today, according to Curtis, is that we have no clear case of large scale damage done to humans by nanoparticles and we have some debatable cases on the effects on

⁵ Phagocytosis – The process by which foreign particles invading the body or minute food particles are engulfed and broken down by certain animal cells (known as phagocytes). (Oxford, 1999)

⁶ Reactive oxygen species are produced by activated phagocytes: macrophages and neutrophils. They are toxic for microorganisms but can also lead to tissue injury (Kimball, 2004a)

animals. Curtis says that we can only give answers that are partly right, but he is not sure how good they really are.

Donaldson states that the hazards of nanoparticles are likely to be different to people that already have diseases than to people that are healthy. Donaldson thinks the main pathophysiological response which induces all the adverse effects of nanoparticles is inflammation. People with respiratory diseases like asthma, bronchitis or COPD⁷ already have inflammation in the lungs. An extra bit of inflammation from particles will therefore make the diseases worse. It is more difficult to understand why cardiovascular⁸ effects occur as a result of exposure to particulate matter. There are currently two main theories, according to Donaldson, both based on inflammation: The first theory is that people who die from a cardiovascular disease, die with Acute Coronary Syndrom⁹ where the plaques in the vanes becomes unstable and ruptures. This means that there is a blockage of the blood supply to the heart, causing a heart attack, or to the brain, causing a stroke. If nanoparticles can get around in the body from the lungs and reach the plaques, they can destabilize the plaques. Air pollution studies have shown that 24 hours after an increase in the air pollution level, there are extra myocardial infarctions and deaths due to cardiovascular causes. According to Donaldson, there is therefore a link between the inflammation in the lung and the Acute Coronary Syndrom. The second theory is the following: The speed and rhythm of the heart is regulated by nerves. There are pathways from the lungs through this nerve-system so the rhythm of the heart can be changed by stimulating nerve-endings in the lung. Nanoparticles cause inflammation and irritations in the lungs that somehow stimulate this pathway and alter the rhythm of the heart, so that you die from dysrhythmia. These two theories do not have to be contradictory, as this sort of effects by inflammation on the plaques and of cloths forming in the heart, can change the rhythm of the heart.

However, most of the population is healthy. In occupation settings, Donaldson believes, there would be a high exposure in a relatively normal person that does not have plaques, asthma or COPD. Inflammation in the lung is then likely to lead to fibrosis and maybe emphysema¹⁰. Although nanoparticles like carbon black and titanium dioxide have been around in an occupational setting for a long time, there is no study looking at people that have been only exposed to this size of particles. However, in the laboratory experiments with rats you see inflammatory responses, lung fibrosis and cancer, but rats seem to be overly sensitive to particles. Donaldson says: *“With people involved in coal mining or quartz, you see inflammation and if people are exposed long enough you see cancer, so there is a possibility that nanoparticles can cause cancer too, but at least I would expect to see fibrosis.”*

According to Eva Oberdörster, we don't know what nanomaterials or even if nanomaterials are hazardous to the environment. The only data we have is one study, from one fish specie that was exposed for 48 hours to one concentration, of one type of nanomaterials.

7 COPD – Irritation of the lungs can lead to asthma, emphysema, and chronic bronchitis. And, in fact, many people develop two or three of these together. This constellation is known as Chronic Obstructive Pulmonary Disease (COPD) (Kimball, 2004b)

⁸ Cardiovascular disease - any of the diseases, whether congenital or acquired, of the heart and blood vessels (Encyclopædia Britannica, 2004)

⁹ Acute Coronary Syndrom - An umbrella term used to cover any group of clinical symptoms compatible with acute myocardial ischemia. Acute myocardial ischemia is chest pain due to insufficient blood supply to the heart muscle that results from coronary artery disease (also called coronary heart disease) (American Heart Association, 2004)

¹⁰ Emphysema - In this disorder, the delicate walls of the alveoli break down, reducing the gas exchange area of the lungs (Kimball, 2004b).

Oberdörster said she had recently repeated the study. In both studies she had done with nanotubes and fullerenes, the nanomaterials were taken up by the fish and were, with other words, bio-available. However, the fish was alive and looking good, but there was definitely some inflammation and some repair happening, which are normal processes that the body does when there is a foreign object present. However, this response can be either a good thing or a bad thing.

Another big question relates to the bio-persistence and whether the body can break down the nanomaterials. Oberdörster says that e.g. fullerenes are lipophilic compounds, so they will bio-accumulate just by nature, like PCB or DDT. She further says she saw in her study that the fullerenes activated an enzyme (P450) that is known to metabolize hydrocarbons. It is therefore possible that the fullerenes might be metabolized in the body and, by that, made less toxic. With other words, there might be a way for organisms to get rid of fullerenes through metabolizing them. However, as with a lot of crude oils, metabolism can also make the compound more toxic. An example is the PAHs where it is not the compound itself which is toxic, but it is the process of metabolizing that makes the PAHs toxic. Oberdörster says that up till now, we don't know whether fullerenes are toxic because they are being metabolized or they are less toxic because of metabolism.

Riediker sums up and states: *“For me there is increasing evidence that composition does matter and I see, due to the small size and the large surface, that you can get all kinds of effects, like surface catalytic effects or even different chemical behavior associated with the nanoparticles.”*

3.3.2 About the potential risks

The special risks about nanoparticles according to Henshaw is that they dissolve in the bloodstream, penetrate deeply in to the lung, can cross the placenta in pregnant women and reach the foetus and can cross the blood-brain barrier. There is a particular problem that nanoparticles are not confined only to the lungs, but can reach anywhere in the body.

Stone and Borm point out that are sub-groups of the population which have greater risk and that, in fact, will the majority of the population probably have low risks. The sub-groups with a higher risk can be people with for example a cardiovascular disease, diabetes or asthma. Kreyling emphasized that we need risk assessments not only for the healthy worker, but also for asthmatics and diseased, so it covers the general population, because applications of nanoparticles will be used by the general population.

Powell questions the level of risks of nanoparticles and asks the following: *“Even though smaller particles (i.e. nanoparticles) are extremely good at the induction of reactive oxygen species, and if you give enough you can overwhelm the cell with oxidative stress and the cell will die in an inflammatory fashion, the important question is whether this ever actually happens? My belief is that nanoparticles have a toxic level, and as such should be treated like any other group of toxins, but I have a big question about whether we normally ever get exposed to enough to overwhelm ourselves in a way that we see in these animal studies. I accept that rare, abnormal industrial exposure is a different situation.”*

Curtis emphasizes that everybody has been exposed to nanoparticles and he therefore believes that not all nanoparticles are harmful. There are probably some classes that are harmful, some that are slightly harmful and some that are not harmful at all. Nanoparticles will, in some cases, initiate inflammatory processes and Curtis says that we also know that some deliberate exposure to animals of nanoparticles has sometimes caused the death of these animals.

Nanoparticles, because of their very large reactive surface area, can bind to substances and transport the substances to areas in the body or environment where these substances cannot normally reach. This piggyback-effect is deliberately explored in drug-delivery where drugs are e.g. encapsulated into a nanoparticle, which is targeting a special organ in the body. However, Riediker is concerned and states that: *“The critical point of nanoparticles, because they are small, can move fast and easily through tissues is whether they can carry substances to targets like the cells, DNA or other. Nanoparticles are also studied for gene-therapy where genes are injected into the cells. If you can use nanoparticles for therapy, you can also think that other particles can do harm to the genes. Nanoparticles could carry transition metals, aldehydes, or other reactive substances that can generate e.g. reactive oxygen species and then cause oxidative damage to the genes”* Stone is worried about what happens if nanoparticles are mixed with for example a metal salt or there is a metal salt incorporated into the particle, which might exaggerate or synergistically enhance the activity of these particles and make them more toxic.

Kreyling points out that we need to consider the risks of the whole life-cycle of the nanoparticle. Nanoparticles can for example during the production be inhaled or the nanoparticles may be applied in a surface and later released to the surroundings in erosion like processes or other processes, where the nanoparticles might be inhaled or get in touch with skin. A risk estimation of each stage of the nanoparticles' life-cycle is therefore needed.

Oberdörster thinks it is even too early to begin asking the question about risks of nanomaterials to the environment, as we don't have enough data. According to her the risks of nanoparticles is going to be an exposure question.

3.3.3 Reducing the hazard of nanomaterials

There are research groups looking at how it is possible to reduce the potential of nanoparticles to cause harm. Currently one of the main focuses of researcher Vicki Stone is to identify what properties of particles that make them toxic and if they are contaminated with other substances like metal or organic substances, does this enhance their toxicity or change it in any way. The idea is that if you know that, a strategy can be put in place to reduce the toxicity. With occupational dust it might be possible to change the composition in any way, to reduce the risk of the exposed workers and with consumer products the composition can be changed, so the consumer is less affected. Curtis has shown in his research that there are ways of preparing nanoparticles so they are not phagocytosed by the cells or are interacting with the cell surface. He sees possibilities of powerful drug deliveries if you can prepare the nanoparticles in this way.

However, Oberdörster argues that coating or changing the outside chemistry so they are not longer toxic will not be possible in an environmental setting. She anticipates the problem will be UV light. If you put for example fullerenes under UV for as little as ten minutes, the coatings or the covalence surface modification get cleaved off by the UV-light, so what is left is the uncoated fullerenes. Coated fullerenes are not as toxic as uncoated fullerenes. In the body, Oberdörster says, we don't know if safety coatings will work, because we have enzymes that metabolize all sorts of organic coatings and covalence modifications, which could modify the safety coatings. It is not known how long the safety coatings can stay on, reducing the toxicity.

3.3.4 Is it possible to generalise about nanoparticles risks?

The view is strongly supported by the research community that it is not possible today to generalise or conclude about the risks of nanoparticles. This is not possible, because nanoparticles have such different characteristics and hence different reactivity and toxicity levels. Kreyling and Stone point out that we have to be very specific about which type of nanoparticle we are addressing when we are discussing nanoparticles and to not address nanoparticles in general. Powell states that “...*in one sense we shouldn't use the term nanoparticles, because it tends to lead us to believe that they share common physical, chemical and biological properties. They of course share one physical property (size), but their chemical and biological properties must differ widely within the group.*” Oberdorster describes the variety of nanomaterials: “*The quantum dots are going to be highly toxic, because they are made of metals. There is the group of fullerenes which are redox-active, designed to be catalysts so they are going to be toxic. The single walled nanotubes are either conductive or semi-conductive and we don't know what that will mean in terms of toxicity. So within the engineered nanoparticles there is so much different chemistry and sizes and in addition there is the group of non-engineered ultrafine particles. All what these particles have in common is the size distribution.* “

The smaller the particles get, the bigger the surface area gets and the more active the particles will be. Donaldson says that the surface area is very important, as even a nanoparticle that has nothing harmful on the surface, a low toxicity, low soluble particle, like titanium dioxide or carbon black, will still cause inflammation. If the surface area has some toxic on it, Donaldson says, the effect of a toxic surface will be multiplied with the effect from inflammation due to the large surface area.

Riediker points out that the particle size will only give a very basic common behaviour in terms of how nanoparticles move in air or in solutions. The interviewed experts say that we need to know more about the material composition and the surface to address nanoparticles as such. The material composition is important as different materials have different properties and, for example, different toxic effects. A larger surface area gives more possibility for interactions with the surroundings and hence increases the potential reactivity of the nanoparticle. However, Curtis says a generalization that can be made in addition to that the surface area and volume gives a more effective presentation to cells than larger compounds, is that nanoparticles also are more likely to be phagocytosed by the cells than larger compounds.

Riediker gives some examples why nanoparticles cannot be generalised on their characteristics: **Shape** - A question is how the shape of the nanoparticle influences the interaction with cell membrane receptors and whether the shape affects interactions between or with receptors, since such interferences could cause reactions inside the cell. Strange surface effects could also occur, as the surface tension is different and could possibly change the properties of the cell membranes. **Surface properties** – A large surface gives the possibility of having a large catalytic surface, if there are metals on the surface that can act like catalysts. Additionally, if you have soluble components on the surface of the particles, the components get dissolved very fast. This means you could get a toxic substance in a liquid that dissolves and peaks very fast. With a smaller surface area, the dissolution of those substances would give a more steady release of toxic substances, and there would be no dramatic peak. This could be quite important for the way organisms respond. **Chemical composition** – Ambient research shows that chemical composition plays a role in the toxicity, but how exactly, is an open question. The questions are which components and which combinations of components are important for the toxicity? For example, is it just the transition metals that are toxic or is it important that these metals are together with certain organic substances?

Stone sums up this topic saying that: *“There is no statement relating to the toxicology that would encompass everything. So I don’t think we can make a general statement yet, we don’t know enough.”*

3.3.5 The most potent risks from nanoparticles

The most potent risk for Donaldson and Riediker is the toxicity associated with the large surface area and that if there are some toxic properties like metals on that surface, the toxicity will be multiplied up. In the worst case, according to Curtis, there are nanoparticles consisting of materials that are toxic per se and cannot be destroyed by the cells.

All interviewed experts believe the most potent risk is lung diseases and cardiovascular diseases because the most potent exposure pathway to the body is the lungs. Krug and Riediker believe the skin does not take up nanoparticles so easily and that the gutter tract is associated with a low risk, because the environmental relevant nanoparticles are unlikely to be taken up in the epithelium in the gut. Krug says there might be a risk of accumulation in the liver. However, Kreyling finds the studies done on dermal exposure on for example on titanium dioxide in sunscreen to be of limited value, because it was only performed on healthy skin but not in wounds etc., and therefore is dermal exposure still a viable potent risk. Stone agrees and says that the dermal tests of nanoparticles are done on healthy skin. This is not adequate as you could have for example damaged skin as a result of a sunburn which means that the skin has a different susceptibility to exposure.

Stone also feels that situations where consumers can get exposed to a high level of a particular type of nanoparticles through consumer products are of great concern. She sees this is a very potent long-term risk as consumers are being exposed to many different products at the same time, accumulating a number of different nanoparticles over a single day. There are for example nanoparticles in food, suntan lotion, cosmetics, hair spray and in the environment and it is not uncommon for a single person to come in contact with all of those products during one day.

Borm also sees the nanoparticles used in medical applications as one of the most potent risks as these will be used in diseased people. Nanoparticles for drug-delivery must therefore be considered inert as a medical device and that they do not do any harm to the patient. This is especially important as we know that people that die from air pollution associated with ultra-fine particles are people with diseases. The tests of the medical devices should be well done and carried out not only on healthy human beings and animals, but also on diseased. Some interviewed experts on the other hand are confident that medical applications will be properly tested out.

Oberdörster thinks bio-accumulation will determine the level of environmental risks as, for example, fullerenes are lipophilic compounds and will bio-accumulate by nature. She also gives the example that engineered fullerenes are made to be redox active, to move electrons around, and when electrons are moved around, there is a chance of toxicity. With the combination of being lipophilic and redox-active there is a really good chance that the substance also is toxic, Oberdörster says.

3.3.6 Precautionary measures

Borm believes we should be very careful in situations where there might be exposure to nanoparticles and that we should make recommendations for good practise for companies handling engineered or synthetic particles. In Borm’s opinion, it is clear that nanoparticles

upon inhalation can cause strong effects, and that in itself is enough reason to move forward on testing of new nanoparticles. Companies should know how to use and produce them safely and know which nanoparticles are more hazardous and which are less hazardous.

Kreyling says we need individual measures to identify the risks and Powell also believes it is important not to extrapolate the findings of one nanoparticle to another nanoparticle, as each nanoparticle should have its own toxicity understood. We have to consider them like any other group of potential toxins, according to Powell, as we don't consider ethanol and methanol to have similar toxicities because they are both short chain alcohols. When tests are done with rat or cell models and specific nanoparticles, it is reasonable to use these findings to judge human exposure to those specific nanoparticles as with any toxin, but not use these findings to make absolute judgments about exposure to nanoparticles in general.

3.3.6.1 Precautionary measures in the handling and production of nanomaterials

In occupational settings the interviewed experts are clear that the awareness needs to be increased among producers and workers regarding the potential risks of nanoparticles to health. The interviewed experts have the opinion that most workers are not aware that nanomaterials can be toxic and are therefore not taking adequate precautionary measures such as using gloves and masks. Especially are the interviewed experts concerned about the people working in the laboratories with research and development of nanomaterials. In the production nanoparticles, workers are often protected against nanoparticle exposure as the productions require a clean environment and zero contamination of the products. Hence, the workers are protected due to the protection against contamination of the products. Curtis believes that preventing of nanoparticle release in high numbers when they are handled is needed and that the workers use high-grade protective equipment. A particular focus should be on avoiding inhalation of nanoparticles and workers should therefore be fed air from a novel source and not filtered local air, as most filters are not good enough. However, Borm states that: *"The best precautions start at the source with avoiding production or substitute nanoparticles to eliminate exposure."*

Henshaw says the producers need to be told very quickly that there might be a problem and that they should do something about the problem as it will be regulated in the future. Borm feels that it would be the role of professional organizations, research institutes or competence centres with a strong link to their member organizations to issue precautionary guidelines and to educate producers of precautionary measures.

Thomas from the ETC group wants agreed protocols on how you handle nanoparticles in a laboratory and says: *"You can produce nanoparticles in a lab as long as you have very strong protocols on how to handle them. Then we wouldn't want a moratorium."*¹¹

3.3.6.2 Precautionary role of producers

Kreyling and Curtis believe that producers should assure that the whole life-cycle of the products is taken into account when assessing the likelihood that nanoparticles in products are released into the local environment. The producers are, according to Curtis, legally

¹¹ The ETC group wants a moratorium on all synthetically generated particles used in the lab and new commercial products (ETC group, 2003b)

responsible for making products safe to use and should therefore identify the risks at a very early stage and be proactive. It would be a disaster to introduce harmful nanoproducts into the market. According to Kreyling, it is also important to check especially what the responses of the nanoparticles are on a cellular level. As it is today, it is not sufficient to follow the regulations. However, in occupational settings, producers are already often taking care of their workers, because the products need clean rooms and must be protected from contamination and thus, the workers are also protected against the products.

Powell argues that the ambient particle concentration should be kept below designated levels, gauged from normal toxicity testing, and that workers that could encounter high exposures and can be protected should be, such as with breathing equipment. As producers are working with potential toxins, they should treat the substance as a potential toxin with due care and attention and with due process. Although, we should be careful not to make nanoparticles into something special, super toxins.

Riediker says the producers' role is to protect their workers, measure the nanoparticles in the air and check the protective measures. He also sees that it is important to differentiate the type of application that the nanoparticles are used in. For example when nanoparticles exist in a solution as in paint, the producers should make an advisory. Even though the nanoparticles are made of a substance considered safe they should maintain the safety precautions such as masks and gloves.

Krug sees that producers should, under the precautionary principle, manage the nanoparticles as in a worst-case scenario. This means that producers should reduce the exposure of nanoparticles to the workers and limit the release into the environment, because we don't know whether nanoparticles bio-accumulate in the body or how they will impact the environment. This is totally agreed by Thomas from the ETC group who further states: *"The thing you don't do, is to release them [nanoparticles] into the market and into the environment. A good case is to recall the nanoparticle products that haven't been assessed. Dealing with the nanoparticles in the market is the first priority."*

3.3.6.3 Precautionary role of authorities

Riediker says that at the moment the authorities should keep an open eye, follow the research closely and also the occupational groups exposed to nanoparticles. All the interviewed experts point out that today, the regulations are in the range of mass/m³, but it needs to be discussed whether a more useful way would be to regulate in terms of surface area per m³ instead. However, as Riediker points out, there is sufficient evidence that fine and ultrafine particles in the air are associated with health problems in epidemiological settings. These particles should therefore be kept as low as possible and there are, for example, with combustion particles, enough reasons to regulate the combustion products.

Kreyling believes it is important that authorities work together with the producers and scientists, to find out what kind of precautionary measures should be taken, based on information from epidemiology and toxicity studies and the material scientists. The authorities have the role to implicate the new toxicology and screening tests, because if the authorities do not regulate, Kreyling says, the producers will not necessarily do them.

Donaldson says that authorities should initiate proper attempts to assess what the exposure is and do proper toxicology to get a feeling for what risks those different kinds of nanoparticles represent. This has not been done up till now.

Henshaw sees a problem that it takes too long before the scientists think there is a problem and until something happens from the authorities' side. Authorities should call for workshop meetings where regulators meet the scientists, bypassing the large number of scientific evidence that authorities sometimes ask for, and immediately start to think about what needs to be done. Riediker also points out, that authorities should at least start to discuss if new regulations are needed, although it may be too early to forbid substances. Henshaw sees a practical step from the authorities would be to employ professionals that read the literature, make an overview of which products involve nanoparticles and inform the producers about the results. It is not practical to expect that individual companies would think about health issues. Sauvain thinks that authorities could first inform and warn producers about the risks, and then give out precautionary guidelines.

Thomas of the ETC group wants nanomaterials to be individually treated and would have preferred a moratorium until sufficient knowledge exists, but he says that at least a REACH approach should be introduced by the authorities. He further believes that we need an agreed protocol or model of how to do toxicology tests for nanoparticle producers. This should be agreed among scientists and done by independent assessment bodies. He further states "*If you don't have data, you don't get approval.*"

3.3.7 Nanoparticle applications

Oberdörster do not think that medical applications will be a risk, as they will have to go through very thorough testing. This opinion is not shared by Borm, which sees the greatest risks in drug-delivery, where nanoparticles are intentionally administered in the body at a high dose in the bloodstream or in the lung. He sees the risks especially high, because the people being treated already have an existing disease and we know that it is mainly people with disease who die due to inhalation of nanoparticles, not healthy people. It is therefore a must that producers of nanoparticles for technical or medical purposes, communicate with scientists that understand the material properties and scientists that understand the toxicology to develop safer particles.

Oberdörster is worried about the use of nanomaterials for environmental applications, such as for soil remediation without doing a thorough testing of potential impacts. Oberdörster gives the example from Pennsylvania, where lead and iron nanoparticles was injected into the groundwater to remediate trichloroethylene, but where no one looked into what those nanoparticles would do to the microbes and other organisms in the soil and the groundwater, whether it would disrupt the biological system. As these nanoparticles are catalytically active, they will be great for remediation, but also be catalyzing and could be toxic for the earth worms and all the flora and fauna of the soil. Oberdörster said in the interview: "*I worry about using nanotechnology for environmental applications without doing the homework, because it is already happening.*" She further believes that closely tracking of nanomaterials in applications is needed. She gives the example of a study that Mark Wiesner at Rice University recently did of tyres, showing that multi-walled nanotubes used for strengthening the tyres was being worn off and thrown out in the environment in numbers. The study showed a positive correlation between gas consumption per capita and the amount of multi-walled nanotubes in road runoff and effluent rains. This kind of tracking is very important to determine the exposure level to the environment from nanomaterials.

Krug divides the application of nanoparticles into two categories. The first category is where nanoparticles are used in a compact manner. In a compact manner, nanoparticles will have nearly no direct health risk to humans, but may have risks in the end-of-life stage, as the

application might decompose and release nanoparticles. The second category, involving the biggest risks, is where nanoparticles are used openly and as nanoparticles per se. An example of this category is the usage of nanoparticles in sunscreen, although there are no risks of inhalation, this may have other risks. This opinion is shared by Kreyling and Curtis that believe you should be most careful with particles that are floating and not tightly bound to a solid. The most potent applications would be nanoparticles in gas, liquid and air. Kreyling sees gases representing more problems than fluids of nanoparticles, as nanoparticles are individually acting with biological material. Borm says that 90% of all applications are probably completely safe. If nanoparticles are used somewhere they cannot be released into the biological system or where uptake is impossible, then the risks is probably negligible.

3.3.8 Further research

The interviewed experts are all saying that we need to test more types of nanomaterials and look at the whole range of nanoparticles that the nanotechnology industry is using. One example of the new nanomaterials is the nanotubes, because they might behave like fibres. According to Donaldson, these nanotubes may behave like asbestos because they are long and thin. The nanotubes are cleaned in acid which means that the lungs will not manage to dissolve the nanotubes. However, there are only two-three studies published on nanotubes and it is not certain that they will behave like asbestos.

Another concern is that the type of toxicity tests that are done, may not be adequate. Donaldson points out that a recent study showed that nanoparticles were able to move from the nose to the brain. The tests done up till today, has not looked in the brain after effects. There is apparently a need to change the testing protocols, as we need to think about new sites of toxicity for inhaled particles like in the liver, brain, spleen and other places where the nanoparticles are likely to go, if they get away from the lung and into the bloodstream. Donaldson further says that the fact that we think surface chemistry is important, is why the use of nanoparticles in medical applications are quite advanced. On the other hand, there is a risk that you might end up with nanoparticles in industrial purposes that show the same ability to interact on the surface with the biological system. Borm and Curtis therefore feel there is a need for a more basic understanding of the nanoparticles: How capable are nanoparticles of getting into the body? Where they go to within the body? According to Borm, this is especially important as nanoparticles are of the size of large proteins that can enter the mitochondrion and the nucleus, where they disturb cellular signalling functions. It is not yet known how this happens, so more fundamental and pragmatic testing is needed.

Henshaw and Curtis feel that we need more epidemiological studies on humans, where the effects of nanoparticles are separated out from the effects of other particles. Powell agrees and also believes that we have to look more at the mechanisms of cell activation and move away from only acute toxicity models, which have abnormally high levels of exposure that may not be relevant. By studying the mechanisms, we will know where in-vivo the likely target sites and susceptible sites of nanoparticles will be. Oberdörster argues that we need a more comprehensive toxicology of a number of wild-life species, so we need to test more types of species.

Krug sees that one of the most important questions to find out is the difference between ultrafine particles and engineered particles, as some studies show enrichment in the brain and a direct connection between the nose and the forebrain, but smokers have the particles distributed in the lung and not in the body and the brain. This peculiar finding makes it

important to find out whether there actually are a difference between ultrafine particles and engineered nanoparticles.

Riediker suggests that we could test nanoparticles that are inert, meaning they don't dissolve quickly, or have an inert surface, nanoparticles with a catalytic surface and nanoparticles with metallic or organic substance that can leach out from the particles. Then, compare the toxicity results also with the effects from larger particles or agglomerates of nanoparticles. Riediker feels that we can with these results answer many questions on how the different components play a role, and what the implications are of single nanoparticles versus agglomerates for the toxicity.

Powell and Sauvain believes we should follow people with high risk exposure and look at the long-term effects on their health, to see if they are more susceptible to certain diseases. Sauvain also believes it is important to find out what the best way to measure nanoparticles in the air is, whether it is the mass, surface area or number. Then this can be measured in an occupational setting and see if the results relate to health effects, like reduced lung capacity or changed blood properties.

There is a need to develop ways of screening the nanomaterials and then prioritize which nanomaterials that should be assessed first. This could, according to Curtis, be done through cell culture experiments where materials that are worrying for some reason are tested with inflammatory markers, which the cells would display. Then, refine the epidemiological study as to particularly look for inflammation. But the cell culture screenings would, according to Curtis, not give enough information on especially low risk substances. Kreyling also feels we need to be more effective and specific in our analytical devices and develop new methods to screen the new materials that come from the fast developing nanotechnology. Kreyling believes that nanotechnology provides the tools needed for these methods, for example genomic approaches in a high throughput system, which is able to screen very rapidly what gene is turned on, telling whether there is a reaction to the biological system. If this screening shows potential toxicity, more thorough testing should be conducted. The whole process would be faster and more specific, when you use test methods based on nanotechnology.

Krug suggests building up a database of the effects of nanoparticle, as is done in chemical toxicology. This database should contain information about what the nanoparticles are doing in the cell, on the surface of the cell and inside they cell after they have been taken up. Also covered, should be the potential transition from the lung through cell layers into organs and the blood and potential organs of accumulation.

3.4 Main findings

The knowledge base of the hazard of nanoparticles, the potential that these particles have to cause harm, is still very limited. What we know of the hazard potential is mainly based on knowledge from research done in the field of combustion particle research and coming from animal studies. The current knowledge base is especially limited regarding the long-term effects of nanoparticles to the environment or human health. We don't know how toxic the nanoparticles are or how high the exposure level is or will be. Without this it is impossible to do any sort of risk assessment of nanoparticles.

However, there is quite a lot of knowledge about the lungs reaction to small particles in general. One of the main explanatory theories why nanoparticles can exert such acute and chronic effects when they are inhaled is that there is a relation between the surface area of

particles administered into the lungs and the nanoparticles' ability to cause inflammation. This is a linear correlation for low toxicity, low soluble materials (titanium dioxide, carbon black or polystyrene B), but not for higher toxicity materials (silica, quartz or nickel). For such materials, the toxicity will be enhanced and they don't fit on the straight line as the reactivity is a function of both surface area and surface reactivity. If the level of inflammation is plotted against the particle mass ingested in the rat lung there will be no correlation. It is therefore generally believed that it is the increased surface area and/or in combination with the increasing number of particles that causes the inflammation. Nanoparticles are because of their size highly mobile and can translocate from the intake point to other parts of the organism and cause oxidative stress - producing oxygen radicals. The oxygen radicals are turning on a cascade of reactions in the biological system, which ends up in inflammatory processes and overreactions to various organs, not only the intake organ, but also secondary target organs like the brain, liver or the central nerve system. The inflammatory processes might be the beginning of an infection. In addition to the enhanced surface area are chemical composition, shape and surface properties factors that determine the hazard of the nanoparticle. The different characteristics will cause different effects and levels of interaction with the surroundings. As nanoparticles have such different characteristics and hence different reactivity and toxicity levels, it is not possible to generalise about nanoparticles. It is in fact, important to be very specific about which type of nanoparticles that are addressed.

The most potent exposure pathway to the body is the lungs, as nanoparticles behave more like a gas in the air. The skin is believed to have higher protection, but particles might cross the skin barrier. Intestinal intake could happen if nanoparticles travel in the soil and get into the groundwater and from there enter and bioaccumulate in the food chains, as some chemicals do.

The risks of nanoparticles are likely to be different to people that already have disease, than to people that are healthy. The majority of the population will probably have low risks, but the people with cardiovascular problems and people with COPD, bronchitis and asthma have a higher risk, when they are exposed to nanoparticles than healthy individuals. For healthy individuals, long term exposure is likely to lead to lung fibrosis and potentially emphysema or even lung cancer.

Today, there are no occupation health regulations in this area and it is therefore a need for precautionary measures. The precautionary measures should be individual measures and not based on extrapolated findings of one nanoparticle to another. Technical measures, like appropriate ventilation and engineering control, are recommended. Personal protective equipment in the handling and production of nanomaterials should be applied, such as gloves, masks and breathing equipment, however, only as a last option if the technical measures are not adequate. Until more is known should nanoparticles be managed as in a worst-case scenario. The exposure limit values should be assessed and it needs to be found out whether the particle surface area per m^3 should be the standard regulations instead of mass per m^3 as it is today.

The full life-cycle of the applications should be taken into account and the risks should be identified at a very early stage, as it would be a disaster to introduce harmful nanoparticles into the market. The applications of nanoparticles can be divided into two categories. The first category is nanoparticles used in a compact manner, fixed in a matrix, which will have nearly no direct health risks to humans or the environment, but may have a risk in the end-of-life stage as the applications might decompose and release nanoparticles into the surroundings. The second category are nanoparticles used in applications where they are not

fixed in a matrix, but used openly and as nanoparticles per se. This category involves the biggest risks when nanoparticles because it can follow a direct exposure to humans and the environment, for example through nanoparticles in cosmetics or food additives. It is therefore reasons to be most careful with particles that are free and not tightly bound to a solid.

There is a need for further research on more types of nanomaterials to get a basic understanding on how they interact with the biological system and where in the body they might go. It is also important to look at the test methods, as studies have shown that nanoparticles translocate within the organisms, so there could be new sites of toxicity like the liver, brain and the spleen. Additionally, it seems very important to find out whether there is a difference between ultrafine particles and engineered nanoparticles. As the variety of engineered nanoparticles increases every day and more of them find their way into commercialisation, screening methods determining whether the nanoparticles have properties that should be more thoroughly tested, is highly needed. It could then be possible to build up a toxicological database of the effects of nanoparticles that again can improve and speed up the screening and tests methods.

4 Perceptions and precautionary measures of producers of nanoparticles

Although nanoparticles are seen as new materials, they are only covered under the existing regulations as another type of the bulk material. It is therefore left to the producers themselves to take the actions they find necessary. This chapter investigates how producers of nanoparticles look upon the risks and what precautionary measures they take. The producers of nanoparticles can generally be divided into two main groups. The first group is the 'traditional' producers that have been producing substances in the nano-scale for decades or even centuries, like in polymer, carbon black and the chemical industry. The production processes has not changed fundamentally, but has been developed into more controlled processes, where the producers are fully aware of the characteristics of their substances. Although the size of the products has decreased, there has not been a fundamental process change, but the processes and products are now associated and labelled nano-products. The second group are the 'new' producers of nanoparticles with novel properties, like quantum dots and nanotubes. This second group of producers are often spin-off companies from universities and research centres and their production is more in the order range of kilos.

The companies were chosen based on literature review of nanoparticle products, from participation-lists in workshops and conferences and from suggestions by experts and other people working in the field of nanoparticle research and development. In total 13 companies were approached, whereas 6 chose to participate. The companies have different ways of responding to the questions as all the 'traditional' companies prefer to answer in written form, but the 'new' companies are more open to phone interviews. This gives different types of information, which need to be taken into account when assessing the information. However, the companies interviewed are believed to give a very good indication of the state-of-the-art, as they are some of the most prominent producers from both groups. The companies are shortly presented here:

Company A is one of the leading 'new' companies with a large staff of scientists working with the nanomaterials. They produce a range of metal nanopowder, as well as alloys. They also manufacture nano scale oxide particles with variable sizes and morphologies, in addition to a number of other types of particles. The size range of the nanoparticles produced is from 120 nm and below for the metals and 50-15 nm for the oxides. The particles are used in a wide range of applications as hard-cutting tools, pyrotechnics, explosives, medicals and textiles. Today, the production volume is in the range of 1-3 kg per hour.

Company B is a 'new' company, interesting as they are a specialized company involved in production with wet chemical solutions. The company is a 'spring-off' from university research. The nanoparticles are inorganic, mainly non-oxides, oxides and phosphates, and mainly smaller than 20 nm. They are used primarily as pigment for writing, printing, paints and coatings in addition to in-vitro diagnostics. The production volume is 10 kg per week for all types of particles.

Company C is a 'new' company involved in the production of carbon nanotubes. The nanotubes are used in a wide range of applications from advanced composites to fuel cells and are delivered in commercial quantities in the kg-range.

Company D is a big 'traditional' company that is involved in the field of chemical process engineering and is present in over 140 countries. They are specialized in one type of

nanoparticle which they offer in different forms. The nanoparticles improve the mechanical and optical properties in lacquer, coatings and polymers and in ceramic applications and have a narrow size distribution between 4-20 nm. These nanoparticles are produced for the industry in 'several tons'.

Company E is one of the biggest 'traditional' companies in Europe producing nanoparticles for decades. The company is a multinational corporation consistently aligned to high-yield specialty chemistry. Their product base ranges from carbon black to zinc oxide and has a production volume in the range of 'thousands of tons'.

Company F is also one of the biggest European based 'traditional' chemical companies and present in 170 countries. The company has been manufacturing products not previously associated with nanotechnology in the field of polymer and pigments used to colour coatings and plastics or to print papers. These fields have all involved nanoparticles for decades. The nanoparticles produced are metals, inorganic and organic compounds and polymers and the production volume is 'thousands of tons'.

4.1 Risks and hazards to health or environment from nanoparticles

Company A says it is a problem that nobody knows whether there are risks of nanomaterials, because the toxicological information is not there yet. With the particles that they are producing, the most likely risks are through ingestion or inhalation of nanoparticles, where inhalation is seen as the potent area as the nanoparticles can from the lung possibly enter the blood-stream. The skin is not seen as an area of biggest concern with their type of nanoparticles, unless the size of the nanoparticle is less than ten nanometers. The hazards of nanoparticles depend on the type of nanoparticles, as for example heavy metals are hazardous no matter the size of the particles. Company A, questions whether the size has an impact on the hazards. Does the size makes it easier for the particle to get around the body and interact with cells easier is one of the many variable in the toxicity question. People don't know the answer at the moment and even if the particles get into the cells, no one is sure whether it affects the cell or not. Company A don't believe these risks are very severe as there are already nanoparticles in the air and, according to experts they have talked to, the health risks of nanoparticles in the air are often not the particles themselves, but the chemicals bound to the particles which cause the problems. It could mean that particles they make could be in themselves safe, but if chemicals are attached to them they might cause problems. In any case the difference in production involving fumed gases and production of nanoparticles are not that big, so the difference of inhaling a fumed gas and inhaling nanoparticle, are not believed, according to the Company, to be so big.

Company B says the main risks to health of nanoparticles are from inhalation in whatever form they are produced, for example of particles in the atmosphere like soot from cars. There also nanoparticles used in cosmetics where it is not yet clear what the effects can be. The producers of the cosmetics say there is no risk, but the representative is not sure about this, because nanoparticles behave in a different way to other materials. The nanoparticles can get very reactive or have catalytic effects on the skin and for example a sun blocker containing nanoparticles has to be tested for photocatalytic activity on the skin. The knowledge base that currently exists is rather old and is contains information about asbestos, soot, wood and dust. Regarding nanoparticles, the representative thinks most of the studies are on the way and that we soon will get new data on these new materials. He has the impression that the old studies have not looked on the special nano-properties, with increased activity, catalytic effects and surface area, but rather focused on the pure size.

Company C says that at present, no risks to health or the environment have been established for carbon nanotubes (CNTs), other than the risk of physical overload of the respiratory system, associated with all fine particles. There seems to be ample evidence to suggest that ultrafine particles in general present a risk to the respiratory system, because of the relatively massive surface area presented to the natural defensive mechanisms of the respiratory system, which is designed to deal with particulate material. However, whereas clear biological toxic effects, largely independent of particle size, have been demonstrated with some materials e.g. vehicle exhaust particulates, quartz and some metal oxides, this is not demonstrated with carbon. So far, therefore, it seems that the only known risk is related to particle size. However, there is a certain lack of knowledge in this area and investigations into the health effects of nano materials, in general, are continuing. The company has no knowledge of any work done to assess the ecotoxicological or other environmental effects of ultrafine particles.

Company D says the toxicity of nanoparticles has not been completely evaluated. Certain nanoparticles may be toxic. The highest risk of chemical uptake, especially dusts, is through inhalation. Furthermore, because of the small size, nanoparticles might also trespass the natural skin barrier and with the blood stream reach organs where they are deposited.

Company E is aware that there are environmental epidemiological studies indicating that there might be a risk for systemic effects (cardiovascular diseases). There might also be other hazards from skin penetration, nanoparticles going into the brain (studied by G. Oberdörster et al.) and there could be hazards to fish (studied by E. Oberdörster). The knowledge base contains so far only environmental epidemiological data and data of materials consisting of aggregates and agglomerates greater than 100 nm.

Company F says they are well aware of new scientific studies on hazards of nanoparticles, as they are in close contact with scientists around the world and are also doing own studies. It is shown for example by G. Oberdorster, that nanoparticles can travel from the nose and enter the brain and that there are reactions in the alveoli by a factor 5 stronger than more coarse particles. On the other hand, some nanoparticles have similar toxicity as larger particles. It is also a question whether soluble particles have a different toxicity than insoluble. However, the toxic properties of the nanoparticles are still under investigation

All the 'new' companies (A, B, C) explicitly say they have not done any tests for assessing health and environmental hazards of their products. However, most of them will be involved in research projects in the future. Company A is also waiting to see what the REACH-regulations are going to prescribe as it could have a big impact on the tests being done.

4.2 Precautionary measures

Company A is operating from a precautionary principle, assessing the existing health and safety information about the materials. Then the Company is making a judgment whether they understand enough about the risks, in order to be confident about producing the nanomaterials so they do not to expose the staff to unnecessary risks. They are also involved in an EC research project and hope that the project will improve their knowledge and their preventative measures. The production takes place in sealed system for production reasons, as it is important to control the atmosphere, to get the right type of product. Also some metals require certain atmosphere conditions. The technicians are only in touch with the products when they, for example, are moving them from bigger containers into smaller containers. This takes place with special equipments where a constant stream of gas is

blowing the particles away from the technician. The technician is also wearing masks and hoods for protection. The nanoparticles agglomerate into clusters of a few micrometers, which makes them easier to handle. Company A believes a focus on precautionary measures when handling materials is, in any case, needed, because no matter what the material is, high enough exposure level will give problems.

Company B takes precautionary measures for the personal safety of their employees. In some steps of the production, the employees use gloves and masks for the dust to prevent inhalation of dust. Normally, the employees are working in fume cupboards where the air is sucked out. Most of the production stages are done in solutions, where there is no dust and when there is dust, for example when they isolate the products from the solution, the workers use masks to prevent inhalation. Masks and gloves are used just as a precaution, as in the isolation of the product, there could be dust exposure and then you avoid the risks that are possible. The gloves are used against spillage and dispersion of the solutions on the skin. The gloves are preventing dispersion of particles. They don't take precautions for environmental risks, because of the small production volume, and they believe that the nanoparticles are not released into the environment. As they have the particles in a matrix in nearly 99 % of the applications, they don't see the need for environmental precautionary measures.

Company C says that due to the lack of knowledge in this area, it is the policy of the company to minimise direct human contact with CNTs. During manufacture, CNTs are contained within the manufacturing equipment wherever possible. This is supplemented by the use of engineering controls during product isolation. The workplace atmosphere monitoring, has shown the environment to be free of fine/ultrafine particles. Respiratory protective equipment is also used by those involved in the manufacture, whenever there is the possibility of loss of containment. Similar advice is also given to their customers. They also take environmental protection measures, through that the exhaust points from the manufacturing plant are protected by fine mesh filters and giving customers advise on containment. The health, safety and environmental risks (if any) of CNTs have yet to be established. Until the risks are established, it is their policy to adopt a precautionary approach, consistent with the chemical industry's Responsible Care initiative.

Company D is in general taking the usual precaution measures of chemical environments. Next to their mills, there is a ventilation system installed with the purpose of exhausting dry particles or the vapour of the solvent. Furthermore are safety clothes used when working with nanoparticles, such as gloves, coat, mask, eye protection and safety shoes. The precautionary measures are there to prevent the direct contact with nanoparticles, as it would be done with any other chemical substance. Additionally, the products are not to be contaminated with other nanoparticles or contaminants, which is important for the quality of the product. However, the efficiency of the traditional protection systems in nanoparticle handling has not yet been completely evaluated. However, the respiratory protection like masks, are sufficient to block agglomerates but probably not isolated particles.

Company E says they take all measures they are required by law. However, these are measures and monitoring of the work environment related to the mass, which the company does not see as sufficient for nanoparticles. Therefore they are also conducting additional measurements, based on particle number and surface area. The company has, for example, measured the Carbon Black production plants for release of nanoparticles and found there was no additional release of ultrafine particles at the work places. The company is examining their own materials, doing toxicological screenings by in vitro methods that check the

reactivity of the materials. Additionally, is the company involved in research projects, which, for example, compare standard materials with the new materials developed and the effect of bigger aggregates versus smaller aggregates.

Company F supplies a diverse range of nanoparticles that are handled in different forms. Nanoparticles for cosmetic applications are handled in a matrix, nanoparticles for food are handled in liquids and there are also some applications where nanoparticles are handled in powder form. The company has closed systems during the processes, but the nanoparticles need to be handled manually during packaging and filling. The exposure is then limited through exhaust ventilation system and personal precautionary equipment is used. The level of personal precautionary equipment depends on the exposure potential of the process and the type of nanoparticles. The equipment used is, for example, filter masks, overalls, gloves and glasses. Company F is also doing risk assessments with an experienced team assessing the exposure situations and characterising the risk level, based on the process techniques used and the experience with similar processes. This is done without work place monitoring of the exposure levels. The company has an internal policy to minimize risks and thus, keep exposure of nanoparticles under certain limits.

4.3 Risk and occupational health

What can be done from a monitoring point of view is, according to Company A, limited, because the regulations are in the range of mg per m³ air for a substance. The company has measured the quantity of nanoparticles inside the factory and they are in the process of installing a continuous particle counting equipment. What they found was that the number of particle inside the facility, was considerably less than in a normal environment, because they have equipment continuously cleaning the atmosphere.

Company B says that particles in general are problematic and that there are studies showing that when you inhale the particles, size and geometry of the material gives more toxic effects than the chemical composition of the material as such. They say they know most of their products are safe as bulk material and are not classified as toxic material. These materials have been used for decades in industry in the form of larger grain size. There are no toxicological data showing that their products can cause health problems, but there are big uncertainties about the hazard of nanoparticles as such. The risks of their particles have to be looked at as the risks of particles as such and do not depend on their chemical composition. They try to make sure the nanoparticles are not set free to the atmosphere and are not inhaled or in contact with the skin. With their particles, they do not know of any catalytic activity, so they are just doing standard precautionary measures.

Company C says that nano (ultrafine) materials are respirable and therefore potentially (potentially is stressed by the company) harmful to humans. Some studies suggest that ultrafine particles can be transported from the lungs to other organs via the bloodstream. However, no adverse effects have yet been found, which cannot be attributed to the already known, specific toxic effects of particular ultrafine particles, due to their chemical activity. The company find it therefore paradoxically that the use of carbon nanotubes in sophisticated drug delivery systems is being investigated. As the known health risks are related to particle size and since such risks are easily controlled by containment and filtering devices, the occupational risks are not considered by the company as severe. The company says that the knowledge base is developing and growing, but that more work needs to be done. They are monitoring this knowledge base continually to ensure that they are up to date with all hazard information in this area

Company D believes that nanoparticles are not hazardous in general, but it depends on what kind of nanoparticles under consideration. Their nanoparticles are considered as non-toxic. The risk of nanoparticles will depend strongly on chemistry, size, and morphology. From the asbestos case, one might derive that fibres can be more dangerous than other morphologies. As in other chemical systems, the effect will be related to the dose. The potential risks of nanoparticles passing the skin barrier or being inhaled should be taken serious and therefore protection clothes have to be used. In general, the direct contact with nanoparticles should be reduced, just as it is recommended also with other chemicals.

Company E says it is not known for the workplace how severe the risks are. Epidemiological studies of carbon black workers showed there was no dose-response relationship. The most important question for risk assessment of manufactured materials is whether there exists a threshold limit value or not.

Company F says the toxic properties of nanoparticles are still under investigation, but the already known or possible toxic effects has to be taken into account, when implementing the safety measures. The health risks of nanoparticles are very different and can not be assessed very easily. Many different factors influence their toxic behaviour and the relationship between the factors are not sufficiently known. It seems that some nanoparticles are not more toxic than the usual alveolar dusts and some nanoparticles seem to be more toxic. Company F is very active in the science investigating the properties of nanoparticles. The company is in continuous contact with work partners through participation in industry, authority and research committees, in contact with the national health department and with international researchers. They are additionally doing continuous literature reviews and have own laboratories that are doing toxicology studies of inhalation and skin exposure. The results are confidential.

4.4 Occupational Health Regulation of nanoparticles

At the moment, Company A says, nanoparticles are currently covered under existing rules and regulations until there is strong evidence that nanoparticles is something different from the norm. Most occupation health regulations are looking at exposure levels and defining what those levels ought to be. There is an issue about how to measure the exposure level of nanoparticles. They think there are enough existing techniques to measure the exposure, so it is rather a matter of where those exposure levels need to be set and whether they need to be set differently for nanoparticles.

Company B believes there should be regulations specified on the individual material, because the reactivity of the material has to be taken into account and also whether the material produces dusts or agglomerates, which makes the handling easier. Also in which form the material is applied should be taken into account when regulating. Nanoparticles need special regulation as they are too diverse to only have one single regulation. The toxicology tests would be very expensive and nobody could afford to produce these data, so the representative does not have any good idea on how to do the regulations, but he is sure that there should be regulations. The regulations should be more in terms of guidelines than strict regulations, giving advice to the workers for handling the products, and study the production of dust and the reactivity of the particles when they come in contact with the skin. Mainly it should be information to the workers that are in contact with the material

Company C says they have a general legal duty to protect the health and safety of workers. It is on the basis of this duty and their commitment to Responsible Care¹² that they adopt the precautionary measures mentioned previously. However, they believe that it would be premature to introduce specific regulations relating to nanoparticles at this time. If and when the knowledge base matures sufficiently to demonstrate some significant level of risk, then specific occupational health regulations can sensibly be introduced. The company is working to firstly assess the risk and secondly to suggest appropriate control measures. Ultimately, the company believe it is for the elected representatives to determine the need for new policies in this area, while taking cognisance of the existing regulatory framework.

Company D says that the nanoparticles are chemical fine powders and therefore the respective regulations have to be observed. There are regulations applied for handling chemicals and powders today, but regulations specifically for nanoparticles could be useful, if specific knowledge on the toxicity of nanoparticles is gained. The existing regulations should be adjusted if this is considered necessary. This could be valuable for all companies. Such regulations would affect all areas as for example laboratory and personal equipment as well as social concerns such as work time and maximum work area concentrations.

Company E believes there should be established a health based occupational exposure limit, but the regulation of the workplace should not be by mass-concentration as they believe the particle number concentration and the surface area are more relevant for toxic effects.

Company F is continuously discussing with the authorities what the technical guidelines should be. The implemented occupational hygiene systems do not need new regulations today. Most of all, the no observed adverse effect level, the NOAEL, has to be investigated, and personal monitoring methods are needed to improve the workplaces. The existing safety measures for inhalable and alveolar dusts have to be adapted to possible additional hazardous properties of the nanoparticles.

4.5 Main findings

The companies are aware that there might be health and environmental effects of nanoparticles, but they point out that there are knowledge gaps on what these effects will be. However, inhalation is seen as the most potent point of entry where the nanoparticles could cause respiratory and cardiovascular diseases. The producers seem to be updated on the recent studies, but it also seem like the producers do not believe the nanoparticles they produce themselves are problematic.

The companies are using engineering control in production which protects the products from contamination as well as the workers from the products. When the workers are handling the nanoparticles they apply normal personal protective equipment, as is normal for a chemical environment, like masks and gloves. However, with masks and gloves there is always an issue whether they are of the right type for the job and whether they are correctly put on. There is also a specific concern with nanoparticles that, because of their size, they have the ability to penetrate most of the traditional personal protection equipment. Nanoparticles behave more like a gas in the air and should therefore not be treated as dust in terms of precautions. Therefore should nanoparticles be treated like in a worst-case scenario

¹² Responsible Care - A voluntary program to achieve improvements in environmental, health and safety performance beyond levels required by the government.

which means for example that air should be supplied to the workers not from a local, filtered source, but from a novel source. They also work in fume cupboards and have ventilation that reduces the concentration of nanoparticles in the work place. However, the nanoparticles are then release to the surroundings of the facility. This is also pointed out by Thomas from the ETC group that is sceptic of fume cupboards as a precautionary measure for the environment. He states: “*Fume cupboards don’t make sense, because then you are releasing the nanoparticles to the atmosphere*”. Furthermore the companies take the precautions, ‘required by law’, but the regulations at the moment does not cover nanoparticles. One company is assessing the existing health and environmental information when they decide about the production, but has themselves pointed out that this information is very limited and inadequate.

There seem to be a difference that the ‘traditional’ companies do some more toxicological tests of their nanoparticles than the ‘new’ companies. This is natural as the ‘traditional’ companies have knowledge and resources that the ‘new’ companies currently don’t have. But it seems like most producers will be involved in research of potential toxicological effects of their particles. It seems like no companies are doing studies on ecosystems interactions of their materials. However, these studies are not likely to be published, as the companies are afraid that competitors will use the studies as basis for their product developments and, hence, do not have to spend money for own studies.

The occupational regulations are not adequate at the moment for assessing nanoparticles, but the companies believe there should be regulations for nanoparticles. However, this is difficult because of the lacking knowledge on where to set the exposure limits, which need to be assessed for each type of nanoparticles depending on the size, chemistry and morphology.

5 Perceptions of regulatory bodies

The applications of nanoparticles show great benefits in many areas, but there are warnings from the insurance industry, research community and environmental pressure groups that some applications could also be of great concern to human health and the environment. In this chapter we will look at how regulatory bodies perceive the risks of nanoparticles. We will in particular investigate the perceptions of the occupational health authorities as it is in occupational settings it is first expected that the potential effects of nanoparticle exposure will arise. There are heavy investments in the research and development of nanotechnology on a European level and the perceptions of the EC is therefore of great interest.

5.1 European Commission

The European Union is heavily promoting and supporting the development of nanotechnology and new materials through the EU 6th Research Framework Programme (2002-2006) (FP6) with €1.3 billion to nanotechnology and new materials (NMP) (EC, 2002b). The applications of nanotechnology will need to comply with the European Community Treaty which has requirements regarding public health under Article 152: “a high level of human health protection shall be ensured in the definition and implementation of all Community policies and activities.”, requirements regarding consumer protection under Article 153: “in order to promote the interests of consumers and to ensure a high level of consumer protection, the Community shall contribute to protecting the health, safety and economic interests of consumers...” and “...shall be taken into account in defining and implementing other Community policies and activities.”, and requirement regarding the environment under Article 174 which has among others the following objectives: “preserving, protecting and improving the quality of the environment”, “prudent and rational utilisation of natural resources” and “promoting measures at international level to deal with regional or worldwide environmental problems” (EC, 2002a).

The following chapter is based on a phone Interview with EC Representative Dr Philippe Martin that took place July 22, 2004. Martin is the principal administrator for Risk Assessment in the Directorate-General for Health and Consumer Protection in the European Commission. He was also the convenor for a workshop organized in Brussels on 1-2 March 2004 which did a preliminary risk analysis on nanotechnologies (EC, 2004b). The full interview is displayed in Appendix V. The answers given are the opinions of Philippe Martin and do not necessarily represent the opinion of the EC.

5.1.1 How the EC works with the risk of nanoparticles

The Commission has taken a proactive stand by convening an expert group and producing a report to look at the hypothetical risks associated with nanotechnology, which is the beginning of the involvement from the Commission on the side of risks (EC, 2004b). However, the representative stresses that at the moment there are no risks as there is no exposure data. There are only identified hazards, either through lab experiments or theoretical considerations.

In the communication from the Commission ‘Towards a European strategy for nanotechnology’ (EC, 2004a), there are a number of actions, for example ‘identify and address safety concerns (real or perceived) at the earliest possible stage’ and ‘integration of assessment of risk... ..at all stages of the life-cycle of the technology’, that aim at promoting

a risk awareness and then safe development of nanotechnologies, including the production of nanoparticles. The document is essentially a policy declaration and it will be followed by an action plan that probably comes out in early 2005. This action plan is clearly for the development and promotion of nanotechnologies, but this development will be done, in as much as the EC can, in a safe and responsible manner. In the production of the communication document all Directorate Generals were consulted as the EC foresees benefits in these technologies, but want the benefits in a safe and responsible manner. The representative emphasizes that there probably will be problems, but that he thinks it is quite unique that risks are considered from the start when the EC is promoting a new technology.

At the moment, EC don't have any overview or statistics of the producers of nanoparticles, although they are aware that there are a number of nanobased products already on the market. But Martin thinks that the EC still is 'in pace with the game' as he points out that the nanotechnology revolution is still in the beginning phase and that the EC as an institution cannot move much faster than what they are.

5.1.2 Research on applications versus research on nano-toxicity

Some of the critique against the National Nanotechnology Initiative in the U.S. is that the environmental research of nanotechnology goes to promoting environmental applications and not for actually testing the whether the applications of the technology, in terms of e.g. toxicity testing (Service, 2004). Martin says this could also happen in Europe. However, the EC is trying to play their political role to make sure this is not the case, but there is always a possibility that a budget is set aside that does not go to funding research on nano-toxicity. But in that line of reasoning, through the declaration and the statements that the EC has made, Martin thinks that the EC supports the idea that a) it is very important to do nano-toxicology and nano-ecotoxicology research and b) that this research is at the same time fundamental and very applied with immediate repercussion for public policy and public health in particular. Because the properties exhibited by nanoparticles in particular are unique and different from the bulk substance, there is therefore a need to basically redo the toxicology that you have done for bulk substances.

5.1.3 Precautionary measures

At this stage the EC is being cautious. The EC is precautionous in the common language sense, but is not invoking the 'Communication from the Commission 2000:1 on the precautionary principle'. At this point the EC don't see the need to invoke the precautionary principle as defined by the communication from the Commission, because it is a legal formal definition of precaution which is linked to the idea that you will act in the case you have identified an issue, but don't have complete scientific information. Then there is a series of measures that can be used which range from asking for more research to requiring a moratorium. However, the EC see the need to be careful. In terms of legislation this is not the same thing.

The EC is trying, in terms of precautions, to make sure that Europe finances research and projects that includes elements of risk awareness and risk analysis, so at least on the European level there is coherence between policies. There will not be research policies financing dangerous research. The EC wants to make sure that research financed is not only safe, but that the scientists think about the long-term implications and include an assessment of the future or possible hypothetical risks. The EC communication on nanotechnology has a strong component on safety, which will be followed by an action plan involving both Community policy and the member states. The EC is also active in securing informal and,

hopefully in a longer term, formal agreements to ensure that we have a safe development of nanotechnology.

Health policy and health & safety policy are national competences, where the EC has to be careful not to trespass the limits of the EC competences and therefore has to leave it up to the national member states to handle those issues. However, the EC can make the member states aware of issues they should address. In the short-term it will be up to the member states to do something about these issues, but the job of the EC is to make sure they cannot say they didn't know. The same is the situation with industry. The EC feels that industry must know and also must be known as knowing that there are hypothetical risks. This awareness process will take place in an official way through the process of releasing communications, accompanied by awareness raising campaigns and contacts in conferences. However, Martin thinks it is fair to say that a number of companies are very well aware of these risks.

5.1.4 Regulations

When it comes to applications, Martin says that the EC is not ahead of the game. There is a pre-existing situation of market available products where indeed decisions have to be made on how to proceed. At the moment it is discussed if regulations have to be re-examined. Martin says that it is clearly fair to ask the question whether the legislation do apply in the same way if you have amounts of a different chemical substance when you look at the physics or the chemistry of nanoparticles compared to larger bulk substances. Then the question is: do we have the toxicological and ecotoxicological data that validates or invalidates the hypothesis that the two products are different? The EC does not have an official position on that yet, but it is a part of the job.

The different variety of nanomaterials is a very big challenge and the EC does not have a formal position on that yet. Martin says this is an important issue because you could have particles that are all in the nano-range, but still has different diameters and surface properties that are likely to be different. Martin believes it is too early to have a position on a possible REACH-approach also for nanomaterials, but he says that the EC is awake and the question has been raised informally.

5.2 Occupation Health Authorities in Switzerland, Germany and the UK

There are currently no occupational health regulations that address nanoparticles as such. In this chapter we will therefore look at the perceptions of occupational health authorities in three countries: Switzerland, the UK and Germany. The chapter is based on interviews with representatives from occupational health authorities. However, it is important to stress that the results provided here are given as the representatives personal views and are not necessarily the official standpoint of their organizations.

In Switzerland, the occupation health authority is represented by Dr Rueeger at the department of occupational medicine at SUVA¹³. The three main competences of SUVA are prevention, insurance and rehabilitation. SUVA is the Swiss equivalent to the federal institute of occupational health and is responsible for creating regulations, controlling workplaces and

¹³ SUVA – Schweizerische Unfallversicherungsanstalt [The Swiss Accident Insurance Institution].

stipulating threshold limit values. SUVA is also a public insurance company for workers in industries that are involved with heavy risks and are also involved with rehabilitation of workers that has been injured.

In Germany, the occupational health authority is represented by Dr Orthen and Dr Arndt at the Federal Institute for Occupational Safety and Health (BAuA). Dr Orthen works in Division 4 "Safety and Health regarding Chemical and Biological Agents", Unit 4.3 Toxicology of Hazardous substances and is responsible for the coordination of activities concerning dermal risks where nano-risks are one of the areas. Dr Arndt is the head of Division 4 "Safety and Health regarding Chemical and Biological Agents".

In the UK, the occupational health authority is represented by Dr Alexander Tsavalos who works in the Corporate Science and Knowledge Unit at the Health and Safety Executive (HSE). One of his responsibilities and areas of expertise is nanoparticles in occupation settings.

5.2.1 About the hazards and risks in occupation health

Switzerland: Health risks due to nanoparticles are still on a research level and not in everyday practice. Ruegger is quite well informed about the hypothetical risks the nanoparticles might cause. For example some experimental research has shown that nanoparticles are able to penetrate the superficial structures of the airways and of the airway epithelium. Nanoparticles can penetrate, enter into the cells and even pass through the cells to get in contact with the circulation system. This is a special concern for nanoparticles. Other experimental studies on rats has shown that exposure to nanoparticles also can have enhancing effects in terms of formation of blood cloths. Nanoparticles can probably stimulate coagulation. However, as there are gaps in the knowledge about which effects the nanoparticles have on humans, it is difficult to assess the risks. Normally the dose of the toxic substance is very relevant and the same must be true for nanoparticles too. Ruegger believes that if you get exposed to high enough concentrations of nanoparticles, it would be probable to expect quite harmful effect, which might be possible to compare with environmental pollution or gases.

Germany: BAuA is currently not informed about the whole variety of substances which are used in this new technology. What is known is that there is a problem with small particles, tubes and fibres, similar to the known problem of dust and fibres as asbestos. There is a concern and a need for further studies to know more in detail, in order to make a sound risk assessment. The representatives would focus the research on kinetics, inhalation, the dermal exposure routes, to be informed about the body-burden¹⁴ that could be reached through the exposure routes, and additionally to know what effects on organs that can be induced by these nanoparticles, tubes and fibres. The representatives know there will be an effect in the lung, but this needs to be elaborated in more detail, through studies of the mechanisms of toxicity. It is also possible that other organs can be reached and this needs to be found out. These studies are on their way, especially in the USA. Other studies should be made that summarizes primary the kinetics and dynamics of the nanoparticles and the existing tests should be elaborated. The present data gaps hinder a detailed and complete hazard and risk assessment. The representatives know that nano-sized fibres and dusts are produced and which are at present the most relevant risks. However, the representatives are not informed

¹⁴ Body burden - Refers to the total amount of toxic chemicals that are present in the human body at any given point in time (Body Burden, 2004).

about other substances of concern. The representatives say they have to wait until it is known which substances will be used in the nanotechnology and then assess whether these new substances represent additional risks.

UK: There are potential risks from inhalation and dermal exposure, as also would be considered with any new chemical. Tsavalos says he does not have a full understanding of the toxicology of these materials and would therefore look at what controls could be put in place. The problem is that it is not possible to determine what control is truly adequate until the whole toxicology is understood. The inhalation risks can range from the potential for pure transient irritancy to extreme risks related to long-term risks like lung cancer and death. With any new chemical coming to the market, it is not really known where the issues are until there are some data. It is suggested, based on a review of the literature, that there is an increase in toxicity when particles get under 300-100 nm, but it is not possible to say this is true for all materials and how much more toxic these materials become. Currently it would have to be a case by case examination. There is some knowledge about some materials on a nano-scale such as titanium dioxide and carbon black, but Tsavalos thinks it is unlikely that this knowledge can tell a lot about all the new nano-materials. What needs to be kept in mind is that pre-existing nanomaterials were kept in nano-scale for handling issues and some sort of enhanced power due to larger surface area. Some of these new nanomaterials have been made nano to exhibit a novel characteristic and it is the novel characteristics that make you think there might be an issue for toxicity. Tsavalos thinks, considering that nanoparticles have novel chemical characteristics, that nano-chemicals in terms of toxicity could be different than conventional chemicals in bulk form. It is not longer possible to say that this chemical formula has this toxicity. The nano-structure of the chemical could change the toxicity of the molecule in some fundamental way, due to greater surface activity on the particle and structural strain. It is also possible that the different toxicity is a response of a different dose kinetic, because you have smaller particles that dissolve a lot quicker or they deposit in lungs in a different way from the larger particle. The nano-chemical might have the same toxicity as the bulk chemical, but it is the way the nano-chemicals impact the body that has become different.

5.2.2 The severity of the risks in occupation health

Switzerland: The severity of the risks is difficult to estimate, because there are no epidemiological studies on humans done on this subject. It is difficult to find a group of exposed persons, who mainly are exposed to nanoparticles, because normally people would be exposed to a range of different particle sizes and it is difficult to sort out in an epidemiological study the effects caused only by nanoparticles, as there would always be biases and toxins from other subjects. Ruegger thinks these epidemiological studies are needed to find out and discuss if there are harmful effect on humans and how severe these effects can be. What is known today is mainly from experimental studies on animals, and it is difficult to evaluate the severity of risk for humans. Supposing there are risks, it is difficult to judge the risks' importance.

Germany: It is not easy to say how severe these risks are or can be, because there is no sound information about the magnitude of exposure as is necessary for a risk assessment. More information about the toxic properties of these nanoparticles is needed. BAuA has some overview of the companies producing nanoparticles, and because of technological opportunities, an increase of production in these companies is expected. BAuA is therefore trying to find out in a qualitative way which type of uses could lead to relevant exposure. Although the actual precise exposure situations is known, there is some experience which

activities would lead to relevant exposure. The next step BAuA is working on is how we can measure this exposure. Methods need to be developed and the toxicologists need to provide information whether the accurate measurement unit should be mass, surface area or volume and what influence aggregation of particles has. The question is what should be determined. Normally with dust you determine the mass which goes into the deeper lungs and the type and size of fibres and dust particles. If there are additional criterias, we need a harmonized way of doing tests which tells us what is effective; the mass, the volume or the surface. In Germany, there is also another organization active called Dechema¹⁵ that has requested experts in Germany to identify which tests are needed, also based on feedback from public agencies and the industry.

UK: The severity depends on how the materials are made and used. If they remain a small, high value niche product that has a contained use, the risks are likely to be quite low. The analogy of the microchip industry can be used as they are dealing with extremely toxic chemicals and very aggressive processes at certain stages, but the human risks are low. This is because they are worried that the people contaminate the products and therefore they already had very tight controls in place that also help protect the people. If we are talking about a nanopowder with bulk broadcast use and no containment, the risk could be much greater as the containment and controls are not in place. Another issue is whether the nanoparticles are in dry powder or in suspension, because particles in suspension are much easier to control.

Tsavalos says he has not seen anything to be a cause of great concern yet, but he also says he has seen very little. What is currently going on is mostly lab work and some small pilot operations. When a new technology and process are introduced, Tsavalos would like to know what the controls are, what the company has done to identify the hazards and make sure they are controlling the risks. If there was factory producing hundreds of tons of nanopowders, HSE would be very interested about what is going on at that site, but currently there are only small amounts of materials in the bottle of a test tube. Tsavalos thinks the risk today is quite low unless that chemical has a toxicity which is extremely high and containment is hard to achieve. This is something HSE are definitely keeping under review and are looking to see how the technology is developing in the UK.

5.2.3 The different types of nanoparticles and the concern

Switzerland: Whether there the different types of nanoparticles have different concerns cannot be answered today. However, it seems like geometry of the nanoparticles plays an important role, but so do also the chemistry and physical qualities. There is evidence from studies done by G Oberdorster that if you exposed rats to titanium dioxide with big particles of 1-3 μm , no harm was done, but when the rats were exposed to nanoparticles, the lungs altered and the rats got sick with a lot of pathological changes. If these nanoparticles do such harm to rats, it is plausible to admit that these effects can be for humans too. But Ruegger does not know any proven cases in humans where the lung disease was provoked by nanoparticles, although there are some diseases where you could assume that nanoparticles play a role, as in for example polymer fume fever or zinc oxide fever which are relatively short harmless diseases similar to having a flue. There are a lot of sources where

¹⁵ The Dechema is short for the Society for Chemical Engineering and Biotechnology and deals with technological advances in the areas of chemical apparatus, chemical technology, environmental protection, and biotechnology (Dechema, 2004).

nanoparticles are formed, but they aggregate so quickly that it can be hard to get somebody exposed to them.

Germany: It is difficult to perform a differentiation of the different types of nanoparticles. What is known in general is that the smaller the particles are, the greater is the hazards, but this has to be substantiated by further studies. The size is very important, but it is not very clear or elaborated whether the surface of the particle has an influence and what kind of influence that would be. The representatives know it is possible to create particles with a lipophilic surface and that these particles have a distinct profile, but says that today, it is not possible to perform a ranking which nanoparticles are of most concern.

UK: HSE would most like to see data on the new novel particles that people are generating in a dry powder form and also the new fibres. Tsavalos sees the insoluble particles more than the soluble as a potential problem and any particle designed to be active in some form. If nanoparticles are designed to have a novel catalytic function or a novel binding function then that would be an area likely to be of more concern. Tsavalos thinks that it is reasonable to be concerned with all nanoparticles that have a novel property.

5.2.4 Precautionary measures

Switzerland: Precautions are not taken at the moment, as Ruegger says SUVA is not aware of any place where nanoparticles are formed, but as soon as a source of exposure is known, measures of occupational hygiene can be taken. These are technical measures, organisational measures and personal measures. That means you change the material with a less harmful substance (technical measure), or build ventilation that suck the harmful away (organisational measure) and use for example masks (personal measure), although for the ultrafine particles it is hard to get masks that are capable of filtering out the nanoparticles. These are basic, standard measures of occupation health. However, other methods to measure the quantities of particles, the size and median size needs to be developed than what exists today, which only measures how much air particulate matter there exists in terms of mass. However this is difficult to measure as ultrafine particles have a tendency to aggregate together, which is not the result you are looking for. A system is needed that can count particles and characterize the particles in terms of size, shape and surface qualities, which probably are the main criterias that should be measured with nanoparticles and not the mass. Normally, in other fields, SUVA publishes booklets on how to deal with problems at the workplaces as for example working in warm ambient environment in the tunnel constructions or handling lead or gases and so on. This kind of precautionary guidelines could also be done with handling nanoparticles, but Ruegger does not see this coming within the next 24 months. Ruegger says they want to learn more about health effects, sources, characteristics and how they could protect people being diseased by nanoparticles. All these have not been clearly examined and without any knowledge you cannot take any good measures.

Germany: The representatives would recommend to have exposure as small as technical possible. This will be explored in an ongoing qualitative study looking at what relevant exposure would be. The representatives are no experts in the applied technology, but there might be a potential to keep the exposure on a low level, if a clean environment is needed and closed system technology is used. When it comes to more direct precautions, more is needed to be known about the real risks and what the problems are, such as what the role of aggregation of particles in the air and whether the aggregates get destroyed in the body when inhaled as larger particles. It is, according to the representatives, too early to discuss in which situations we should apply precautionary measures, because the first step is a qualitative study

that looks at where relevant exposure could be expected. This kind of qualitative study is done by a group of experts doing exposure measurements. This group is informed where the chemicals are produced and have the task to get an idea about what actually happens there, what the activities are that has exposure potential and to get some idea about the relevance of these exposures. This is now being done, but it has no deadline yet. The second step would be to work with those responsible to see what would be appropriate measures and then take measures from the range of measured used for dust, fibres and other chemicals.

UK: For the new novel nanoparticles, Tsavalos thinks that companies should be considering engineering controls, like containment, unless they have evidence that shows these particles are not a problem. As for all chemicals, personal protective equipment should only be relied on as a last resort. The HSE prefers engineering controls because these controls tend to be more reliable and reproducible in their effectiveness. With masks and gloves, there is always an issue whether they have been appropriately fitted and whether it is the right mask and glove for the job. However, there are situations where personal protective equipment needs to be relied on, either because it is difficult to put the engineering control in place, the engineering control has failed for some reason and needs to be repaired or cleanup operations after a spill must be conducted. In these situations people should contact the manufacturers, because many manufacturers have done some limited work to test their gloves and masks against ultrafine particles. The companies should contact the manufacturers as they would have done when they decide on any sort of protective system and ask if it is appropriate for their situation. In terms of filter masks, if there is a potential for a high concentration of particles, the companies should think about whether clean air from a safe source or a force respirator should be supplied, because that provides higher level of protection against any chemicals. When the companies do the risk assessment to decide which equipment is most suitable, it may be more appropriate to think of the nanomaterials more in terms of controlling a gas as opposed to a dust. Some of the particles are so small that they may act more as a gas in terms of how long they stay in suspension or how easily they can get through gaps and so on. This is also true in terms of engineering control where the companies should consider adopting a higher-level containment than they would for a classical dust.

In general, where there is doubt and scientific uncertainty you should ensure that your risk assessment adds more protection than you would if you fully understood the situation. Tsavalos would expect this in any situation where there is uncertainty. The philosophy of HSE has a risk based approach. The problem with the philosophy is where there are areas of scientific uncertainty as it becomes difficult, if not impossible, to do a sensible risk assessment. In those areas a more precautionary approach should be adopted with a higher level of control than if there was data that gave the answers. Tsavalos believes that more control should be put where there is doubt, but that it does not mean that the process should not be done.

5.2.5 Applications

Switzerland: Ruegger is not aware of any routine application of nanoparticles which is known to be particularly dangerous. Ruegger says he is not aware of any company which is applying nanoparticles, which might seem strange, but SUVA deals especially with professional disease and less with problems and general health risks at different work places as for instance an occupational physician who is in charge of a particular company will.

Germany: There are a lot of inorganic metal oxides produced on a nanoparticle level which are added to lacquer and colours, giving new properties e.g. a very robust surface. Additionally the representatives know about applications that protects from the sun. However, there are probably more applications which are not known to the representatives yet, as for example in the pharmaceutical field where it is discussed to apply those particles to transport drug. This is not a field of main interest for the occupational health risk assessment. BAuA looks at sources of relevant exposure, and would work on methods to measure exposure. Based on the experience with exposure reduction, the representatives would make proposals for standards on how to handle these chemicals. BAuA is not that far yet, as areas of concern and measurement methods are only qualitative looked at.

UK: Currently there are very few applications on the market in reality. Tsavalos says he knows of titanium dioxide on glass, but he does not see this as a great concern at the present as titanium dioxide is quite well understood by the toxicologists and the production process is quite well contained. What is mostly going on are in reality pre-existing chemical processes being re-batched as being nano. What normally would have been thought of as classic colloid chemistry is now being labelled nano and HSE inspect that as it does all other chemical manufacture. The fact that it has been renamed doesn't make any difference to the risk it had in the first place. Companies are doing now what they did before, but have come to the conclusion that it is nanotechnology and that it always was nanotechnology like in polymer design, colloid chemistry and some coating technologies. On these existing materials that we know about, although renamed, HSE and industry already have guidance and standards. HSE would take suitable action against those that are not controlling the risks appropriately.

5.2.6 Future regulations

Switzerland: Ruegger says SUVA does not know enough at the moment to regulate this effectively. SUVA needs to wait and see what is going on in this area, but if it is found necessary regulations would be set, but this is not planned at the moment. However, producers are responsible themselves for the products they produce and the potential health effects. For the moment, Ruegger does not know of any Swiss company that is producing nanoparticles, but there will probably be some. Afterwards if SUVA is aware that there is a problem, SUVA will look if it is necessary to take some measures in cooperation with producers.

Germany: At present there are no plans for regulations. The normal way is to look at the hazards, and at the same time develop measurement methods and limit values for nanoparticles in the air. If the normal technical measures don't work to reach those limits, then BAuA would plan for a special standard or technical rule that would prescribe very clearly how to work with nanoparticles of a certain type. The normal way would be through limit values that would guide industry and then secondly give a specific standard. However, this is not decided yet.

UK: The UK's regulatory system is risk based, meaning it is easy to accommodate new technologies, chemicals and processes, but data is needed to do a risk assessment. HSE always keep regulations under review and if new regulations seem to be required, HSE will move in that direction. HSE doesn't see nanotechnology as one subject, because it is in reality many different technologies, products and processes. Currently Tsavalos does not envisage that one set of regulations will be needed to cover nanotechnology, but rather sees that there may be a need for some of the existing regulations to be amended. For examples definitions of what a fibre is, do not currently cover nano-fibres although Tsavalos does not

know if they should, as he does not know what their characteristics are in terms of risks and hazards. There may be areas where certain regulations and guidance need to be amended to cover the nanotechnology. What Tsavalos thinks will happen when nanotechnologies become integrated in a wide variety of industries is that the sorts of guidance currently produced for industries or the industries themselves produce, will cover nanotech as they cover the risk from e.g. electric shock. This is because nano-processes will be just another part of what that industry has deal with on a day to day basis.

There is no plan for new regulations in the UK, but Tsavalos thinks there might be a need to amend existing regulations. These regulations are not worded so it takes into account particles of the nano size and there are additionally issues in terms of regulation based on particle weight per volume of air. There is some evidence that suggest that with nanoparticles it is the surface area rather than the total mass, therefore there may be a need to think of different sorts of control for nanoparticles, and different ways of measuring and counting how much workers are exposed to in the work place. This is not a fundamental change on how HSE regulate the risk to people's health. It will only be the way it is measured which is different, but the level of risk that someone can be exposed to, has not changed. Today, there is not enough data to amend regulations or draft new regulations. If there are processes which cause concern or unacceptable risk HSE have the power under the existing regulations to stop them now.

5.2.7 Awareness of other risks

Switzerland: The most important source of nanoparticles is diesel exhaust, but these aggregate very quickly, which means they don't belong any more to the nanoparticle size-range. This could be a category of particles which could be of special interest for the public and the environment, as it is a source which everyone is exposed to. These particles can give problems like reduction in lung function, respiratory infection, and eventually a certain increase in the risk for lung cancer. The particles can also form blood clots and impact cardio-diseases. These effects are not only due to the size, but also the chemistry of the particles. This could be quite important also for occupational health as these nanoparticles also exist there.

Germany: The representatives are not aware of any other risks, but are in contact with agencies from public health, environment and occupational health. The representatives have discussed more the general problem, whether there is a hazard at all and have not gone into details yet, as the representatives just started in this area earlier this year.

UK: It is the same problem in the environmental area where there is simply not enough information to do a sound risk assessment. One environmental issue is how these materials will be dealt with when they become waste, the problem of cradle to grave. For example carbon nanotubes can be disposed of by combustion, so it is probably not a problem as it is just carbon and it will burn. However, there are other issues with the nanotubes in terms of their solubility and the durability in the environment.

There is nothing so far that has been suggested for nanomaterials which is not an issue for chemicals in general. Nanoparticles might possibly cross the skin barrier that the larger particles cannot. There are, however, chemicals in existence that already cross the skin-barrier and HSE know about those and the ways of controlling those risks. This is also the same for the ability nanoparticles have to cause problem when they are inhaled, as there are chemicals that can do that as well at present. What is different is the issue of the size and structure

causing its characteristics as opposed to pure chemical formulation. That is the new aspect for nanotechnology and it is something that Tsavalos says he does not have a full understanding of and no one does. Tsavalos further says that he would like to push and encourage research to get those areas better understood. The risks are not fundamentally different from other risks HSE have dealt with before, but the way that these risks are generated is slightly different from what has been done before.

5.3 Main findings

The EC seems to be aware that there might be potential risks of nanotechnology. The EC have released a communication, which in reality is a policy declaration, that nanotechnology will be developed in a safe and responsible manner, where the potential impacts on human health and environment is taken into account. This means that research on the toxicology and ecotoxicology of nanoparticles will be funded. However, the EC is aware that there are a number of commercialised nano-based applications, where it needs to be decided whether these applications need to be regulated, but the EC does not have a position on this yet. Precautionary measures are at the moment left to the member states and it seems likely, as it is today, that this also will be left to the member states in the future.

In general, the occupational health authorities are aware and updated on the potential risk of nanoparticles and agree that it is not possible to do a risk assessment as further studies are needed on different types of nanomaterials. The nanoparticles need to be assessed on an individual basis. The authorities seem in general to give this area a low priority as they have not seen any scientific research that shows reasons for great concern. If the scientific research shows there are reasons for concern, the authorities would try to establish exposure limit values. However, the authorities sees this as a problem, as so far it is not known whether the exposure levels should be based on mass, volume, particle numbers or surface area. The authorities generally believe that there is no need for new regulations, but see it as more probable that the existing regulations are amended to also encompass nanoparticles.

The representative in Switzerland is not aware of any production of nanoparticles or companies applying nanoparticles in their production. Consequently, the issue of nanoparticles is currently not a concern for SUVA. However, in the NanoInvestorNews database there are 32 companies listed for Switzerland as nanotechnology companies (NanoInvestorNews, 2004a) and additionally is some of the Swiss chemical industry producing nanoparticles.

In Germany, BAuA, started this year to become interested in the issue of nanoparticles. They are aware of the potential risks and are in contact with producers of nanoparticles. One of their main focuses is assessing the potential exposure, but BAuA are not currently suggesting any precautions other than to limit the exposure.

In the UK, the HSE has taken a proactive role. They are updated on the potential risks, have good contact with producers of nanoparticles and have discussed the issue within the organisation and with external organisations. They are drawing a line between traditional manufacturers that have remanufactured their products down to the nanoscale, for handling issue and some enhanced power due to larger surface area, and the new companies developing novel nanomaterials. The representative believes that with the new type of nanomaterials, the novel characteristics will have different toxic effects on the body. The HSE have funded a report “Nanoparticles: An occupational hygiene review” (Aitken et al.,

2004) and have made a information note (HSE, 2004) suggesting precautionary guidelines for the production and handling of nanoparticles.

It is interesting to see the differences between the countries. The Swiss has a wait and see approach, where the representative does not believe that any precautionary guidelines will be given to the industry. The authority in the UK is taking a very different approach, actively going out with information about potential risks and is being proactive based on the precautionary approach, because of the high uncertainties. Germany has a stand somewhere between the UK and Switzerland and will probably move more towards a UK approach, becoming more actively involved as they get more knowledge in the topic. There are no plans for regulating nanoparticles in any country, but the UK has started discussing the issue and will probably take the lead if evidence suggests it is needed. The UK is the most active country at the moment in Europe.

6 Discussion

The term ‘nanoparticles’, encompasses particles made from very different substances and originating from different applications and sources. This chapter will discuss the implications of the knowledge level for human health and the environment, whether there is reason to be concerned about the hazards and risks of nanoparticles, in which situations these concerns are and possible ways of dealing with the risks and reducing the uncertainties.

6.1 Categories of nanoparticles

It is important that the hazards and risks of nanoparticles are not generalised, as nanoparticles as such only share the common characteristic of size. It is a great difference between nanoparticles generated from the frying pan, having one characteristic and a totally different exposure level, than engineered nanoparticles incorporated into a polymer where they cannot be released into the environment as single particles. Consequently is it very important that discussions address the same kind of nanoparticles. Thus, arguing that all nanoparticles are dangerous is a generalization that very carefully should be considered. On the other hand, claiming that because nanoparticles have always been around us, they can be considered a natural part of our environment and therefore are clearly not dangerous, is also a generalization that very carefully should be considered as there are large differences between the types of particles.

There are several attempts to categorise nanoparticles, which mainly have categorised the nanoparticles in terms of naturally occurring nanoparticles, by-products from man-made products or processes, and engineered nanoparticles¹⁶. However, there may be great differences between the different types of anthropogenic nanoparticles, compared to the natural occurring ones. As a way to structure and simplify the debate, a categorisation with a stronger focus on the different anthropogenic nanoparticles has been developed by the author and is suggested here. The categorization does not consider the different sizes, shapes, chemical compositions or furthermore not whether the nanoparticles exist in solutions or are airborne.

I. Ultrafine particles – e.g. combustion particles, food cooking.

Particles that are produced unintentionally as a by product in a process are called ultrafine particles. Ultrafine particles occur as e.g. components of urban environmental air pollution and can be found as both singlet and aggregated particles, typically originated from combustion processes or food cooking. They can also originate from anthropogenic sources like welding processes and from diesel engines. However, the ultrafine particles also include nanoparticles that have always been a part of our natural environment and are originating from e.g. volcanoes and forest fires.

II. Traditional Nano particles – e.g. titanium dioxide, carbon black, polystyrene B.

The traditional nanoparticles are produced in larger bulk quantities for already existing applications in the market and have generally a broader size and shape distribution. They may be formed from many materials including metals, oxides, ceramics, semi conductors and organic material and may be composites having, for example, a metal core with an oxide shell

¹⁶ Classifications are done for example by the National Nanotechnology Initiative in the U.S. (Teague, 2004) and CBEN, U.S (Ausman, 2004).

or alloys in which mixtures of metals are present. This category encompasses common engineered nanoparticles like carbon black, titanium dioxide and fumed silica and has generally been produced for decades, especially in the chemical industry and the polymer industry. Carbon black is for example produced in roughly 1.5 million tons every year (Holister et al., 2003). This category also includes powder processes like cement, paint, pigments, dyes and pharmaceutical products. They are engineered for utilizing the main properties related just to their physical size. A classic example is the application of titanium dioxide in sunscreen, which is applied because nanoparticles have due to their size, an increased transparency and surface area, protecting the skin better from UV-radiation and at the same do not form a white layer on the skin.

III. Novel nano particles – e.g. nanotubes, quantum dots

The novel nanoparticles are particles that are deliberately engineered to have properties only existing in the nano-range and with specific characteristics in terms of size and shape. Those properties and characteristics are utilized to fill a specific function. These types of nanoparticles are, as of today, typically produced in small quantities, typically in the kg range. However, the production is expected to increase very fast in the coming years. This category includes all new materials developed like nanotubes, fullerenes and quantum dots. The applications are however just recently commercialized, in the plan of being commercialized or are still on a research level. Because of the novel properties, it is likely that the novel nanoparticles can have a completely different toxicity than traditional nanoparticles.

6.2 Future exposure levels

The breakdown and categorisation of nanoparticles especially make sense if the production and hence the exposure to engineered nanoparticles is believed to be significant. One indication for an increased production of nanoparticles, is the steadily increasing number of patents that are filed and issued every year and the increasing amount of money invested by the venture capitalist companies (Paull, Wolfe, Hébert, & Sinkula, 2003). According to BASF Future Business, the market volume of nanoparticles of the total nanotechnology market in 2001 was 23%, but the market for nanoparticles is expected to almost double from 2000 to 2005 (BASF, 2002). In 2001 the novel nanoparticles only consisted of 4 % of the total nanoparticle market and it is the traditional nanoparticles that are expected to have the highest increase in production in the near future (BASF, 2002).

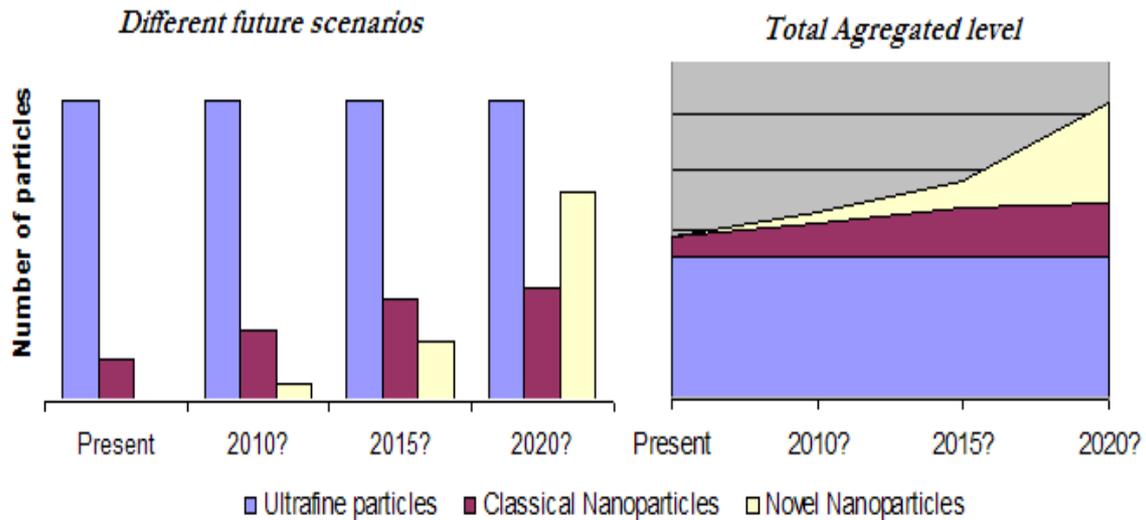


Figure 3: Number of nanoparticles present in our environment in the future

It is legitimate to ask whether the risk of engineered nanoparticles is really a concern for human health and the environment when you compare to the risks that ultrafine particles from combustion sources represent. Figure 3, illustrates that the different types of nanoparticles have different exposure levels and therefore represents different levels of potential risks. However, it is believed that in the next few years we will probably see a dramatic increase in the industrial generation and use of nanoparticles (VDI, 2004).

6.3 The uncertainties, hazards and risks of nanoparticles

In this world of uncertainties, the only thing I am certain of is that there are more uncertainties to come.

The degree of risk is determined by the probability of occurrence and the degree of danger. When the causal relation is established, it is possible to apply prevention and estimate financial risks which directly can be related to health problems or indirectly to public awareness or regulations. This is also the types of risks which is best managed by the insurance agents, since it fits the probabilistic approach. However, there are, at the moment, large uncertainties regarding the environmental and health impacts of nanoparticles, as we don't have information of the degree of danger, or the probability is known. This is a situation where it becomes very difficult to assess the risks in terms of quantitative methods and the outcome is hard to measure. This situation is characterized by a general state of suspicion where on the basis of early warnings (e.g. from the ETC group), indications and hypothesis on dangers that are not yet objectively established are gathered. In these cases, it is generally admitted that a precautionary approach should be taken. A precautionary approach would try to predict some of the risks so preventive actions can be taken. However, dealing with the uncertainties in the predictions is challenging as the uncertainties are on two levels (von Gleich, 2003):

- i. The as-yet-unknown – Knowledge that is basically attainable but not yet available, perhaps because certain tests have not been carried out or due to total unawareness of the potential problem or lack of resources

- ii. The unknowable – The ways in which unstable, complex and dynamic systems respond to intervention cannot be predicted. The “intensity” of the intervention in terms of quantity and quality can also play an important role.

As described in the previous chapter, there are different types of nanoparticles that share the same physical property of size, but have different characteristics and engineered purpose. The different types of nanoparticles have different impacts depending on whether we are discussing public health, occupation health or environment. There are also different levels of uncertainty regarding the impact the different types of nanoparticles can cause. This chapter tries to highlight some of the differences regarding risks and uncertainties depending on which category of nanoparticles that is addressed. However, some of the risks and uncertainties can be overlapping between the fields.

6.3.1 Public Health

Ultrafine particles are a concern for public health. Especially ultrafine particles originating from traffic, food cooking, and other combustion processes have a high impact on the public health. For example, the increasing level of traffic causes an increased level of ultrafine combustion particles in the urban environment which should be looked upon with increasing concern. The fact that these particles may cause diseases and increase mortality rate has a strong scientific support. There are sub-groups of the population with cardiovascular diseases or respiratory diseases that especially have a higher risk when the exposed concentration of ultrafine particles in the environment is high. Exposure to ultrafine particles can make the individual more susceptible to respiratory infections, if exposed to viruses or bacteria. Additionally, can exposure further decrease the respiratory function for those that already have the function damaged by conditions as bronchitis or asthma (Borm & Kreyling, 2004). For the general population the risks are less, but the long term risks are not clear.

Traditional nanoparticles are produced in large quantities and are delivered into the environment directly or through consumer products in several tons every year. The traditional nanoparticles do not have to be tested by the producers as they are currently treated under the regulations as only a different type of their bigger particle equivalents. However, the physical properties and characteristics are different. It is important to find out whether nanoparticles as such and even substances that are generally looked at as inert, are hazardous. Traditional nanoparticles should be assessed as we would assess a chemical being released in such quantities. This means tests of their environmental hazards and further health hazards. Although the uncertainty factor is still very high, there is reason to believe that these nanoparticles are not acute toxic considering that ultrafine carbon black can travel to the brain after inhalation (Walgate, 2004). However, titanium dioxide has shown to cause inflammation in the lung and it is therefore not unlikely that there could be other effects on the environment or humans. Traditional nanoparticles like titanium dioxide are increasingly being introduced in cosmetics. These nanoparticles are generally looked upon as inert material, and have therefore, as seen by many, not been adequately tested considering that it is not known whether nanoparticles can penetrate for example, damaged skin that is a result of sunburn. The hazard may be relatively small, but as long as it is unknown and the exposure level to the public of the traditional nanoparticles is high, the risks from these nanoparticles are still seen as medium. Additionally, another issue is whether nanoparticles bio-accumulate and adds to the total body burden, as during one day it is not unlikely that the public are exposed to nanoparticles from several different sources, for example in sunscreen and food additives. The production of these traditional nanoparticles is expected to increase in the near future as more applications areas are realized. The exposure level to humans from

a number of different products is therefore believed to increase in the future. Consequently are the risks estimated medium towards high in the future, as no regulations forces these groups of nanoparticles to be tested, hence reducing the uncertainty.

Novel Nanoparticles have new distinct characteristics, enabling new functions and applications. Exactly those new characteristics are of concern, as it is very likely that these characteristics also will cause different toxicological responses in the body. The responses are probably not unique to novel nanoparticles, but can be different than what is anticipated for a ‘normal’ particle in the same size range. Currently, there are not so many products out in the market containing the novel nanoparticles, but several products can be anticipated if we look at the increase of patents filed and issued every year. It is therefore very important to do a testing before they enter the market, as it would be more difficult and more expensive to withdraw or modify them, if they at a later stage should prove to be of great concern to the public health. There are currently only a handful studies done on novel nanoparticles. However, it has been known for decades that particles deposited in the alveolar region can lead to development of chronic lung diseases like asbestos (VDI, 2004) and the question whether nanotubes have the potential to act like an asbestos fibre in the lung has already been raised. The level of uncertainty is still so high that no conclusions can be made as nobody knows what the short-term or the long-term effects might be. Today, the exposure to the population of novel nanoparticles is very low and therefore is also the risk low. More and more novel nanoparticles are being produced as the application potentials are realized. This means that the exposure level will increase and as long as there is a high level of uncertainty of which effects these nanoparticles cause on human health, the predicted risk is high.

In Table 1, a categorization of risks and uncertainty of ultrafine particles is shown, summarizing the previous discussion. The level of uncertainty is classified as following: 1) Scientific evidence – the effects are known and the mechanisms behind are understood and scientifically fully verified. 2) Scientifically based concerns – the effects are known, but the mechanisms behind are not yet fully understood. Explanatory theories are established, but not yet scientifically fully verified. 3) Strong scientific suspicions – effects are seen in a number of studies, but the mechanisms behind are not known. Explanatory theories suggested. 4) Scientific suspicions – effects are seen in limited studies, but the mechanisms behind are not understood. Explanatory theories are formulated. 5) Weak scientific suspicions – effects are seen in some studies and/or thought to occur based on theoretical considerations. The mechanisms behind are not understood. Some explanatory theories are indicated. The risks are classified as low, medium or high. The same scale is also used for Table 2 and Table 3 in the following chapters.

Table 1: Risks and uncertainty in public health

Nanoparticles	Public Health		
	Level of Uncertainty	Risks	
		Present	Predicted/Future
Ultrafine Particles	Scientifically Based Concerns	High	High

Traditional Nanoparticles	Scientific Suspicions	Medium	Medium/High
Novel Nanoparticles	Weak Scientific Suspicions	Low	High

6.3.2 Occupational Health

The ultrafine particles have always been present in occupational settings, for example from welding processes. The creation of ultrafine particles is difficult to control and will also exist in the future. However, they are agglomerating fast and would normally take the size of some micrometers, but there are indications that the lung seems to recognize the ultrafine particles as individual particles being a part of a cluster and the surface area will therefore still be enhanced. Therefore, a worker should still be using extra precautionary measures when there are high exposure levels of ultrafine particles. In general should the level of ultrafine particles be as low as possible. There is scientific evidence that ultrafine particles are linked to cardiovascular and respiratory diseases, but the average worker will normally have no such diseases and will therefore have less health effects of ultrafine particles, although current occupational guidelines allow older workers and asthmatics to work in such environments. On the other hand, the total exposure during the day for a worker could be quite high as the worker is occupationally exposed and also exposed outside work from ultrafine particles. Therefore can the total aggregated amount of ultrafine particles give a pulmonary toxic response, as for example lung fibrosis in the lung run. In the UK, as many as 1 million workers are estimated being occupationally exposed to ultrafine particles (Aitken et al., 2004) and in addition comes the exposure from combustion sources. No data was available for Switzerland or Germany. The exposure level is not expected to go down, as there will always be industries with occupational dusty environment. The risk for the workers is therefore believed to be at the same level in the future.

Traditional nanoparticles has typically been produced in an industrial setting for decades and there are quite good routines in place for handling these materials. Most of the scientific studies of nanoparticles are done on carbon black and titanium dioxide. These substances are considered as low toxic low soluble particles, but they cause inflammatory responses in the lungs when they are inhaled (see chapter 3.4). Titanium dioxide has also been tested on skin which showed no effects of concern (Pflücker et al., 2001). But a number of experts are questioning the test methods, whether these tests are thorough enough and if they are relevant as they have only been tested on healthy skin. In an occupational setting, it is not unlikely that the workers have small cuts on the skin. As they are considered by the producers as inert materials and has the same type of material data sheets as the bigger material, adequate precautionary measures has maybe not been taken. On the other hand, as this is becoming more of a focus area of the occupational health authorities and more studies are being published, the awareness is raising and the right level of precautionary measures is believed to be introduced in the future. Additionally is the adequate level of control of these production processes manageable to achieve, through containment and so on. The number of workers exposed to this category in the UK is around 500 from existing ultrafine, manufacturing processes like carbon black and around 102 000 in fine powder processes, although it is difficult to estimate what proportions of the 102 000 are actually exposed to nanoparticles (Aitken et al., 2004). No data was available for Switzerland or Germany.

Novel nanoparticles require a controlled atmosphere during production to ensure the right quality of the product. The production therefore takes place in a way that protects the products against contamination, and hence, also protects the workers from exposure. The exposure to novel nanoparticles is greater in the handling and delivery of the products. Today, as the production is in such a small scale, the handling is done manually and therefore it is at this stage we find the greatest risks to workers. All producers are using personal protective equipment, but it is always a question if they are adequate for the substance apart from the fact that it is uncomfortable to use eight hours every day. From an occupational hygiene perspective, personal protective equipment is always the least desirable way to protect workers. An organisational change should first be considered where the processes and routines are looked at to see if it is possible to substitute the process or change the routines so exposure does not take place. If an organisational change is not enough, the technical solutions should be looked at and checked whether it is functioning as desired, for example exhaust and encapsulation. Nanoparticles act more like a gas in the air, so the most potent route of exposure is probably inhalation and therefore is an extra precautionary focus to minimize the risk of airborne exposure needed. Combined with the fact that almost nothing is known about the toxicity of these novel nanoparticles, precautionary measures used for toxic gas rather than dust should be introduced. Although producers are aware of some risks, the adequate precautionary measures are, in some companies, not introduced today and combined with the high level of uncertainty, the occupational health risks are seen as high. It is important for the authorities to keep a special focus on the occupation health, because if something goes wrong in the occupational health, it is most often also an indication of something more that is wrong in different settings. As more research will be done, the level of uncertainty will decrease. The results from the research will make it easier for the occupational health authorities to set the adequate precautionary measures in the future, as an occupational environment is relatively easy to control. The occupational health risk is therefore believed to be low in the future. However, there is always a risk that the regulations are not adequate or delayed because of for example intense lobbying from industry. Today, 2000 workers in the UK are estimated to get exposed to novel nanoparticles where most of the production takes place in universities, research centers and small nanoparticle manufacturing companies (Aitken et al., 2004). No data was available for Switzerland or Germany.

In Table 2, a classification of the risks and uncertainty in occupation health is suggested. As seen in the previous sections, some assumptions were made for the predicted/future scenario. The column 'No actions taken', estimates the risks if industries and/or regulators do not apply any precautionary measures.

Table 2: Risks and uncertainty in occupational health

Nanoparticles	Occupational Health			
	Level of Uncertainty	Risks		
		Present	Predicted/Future	No actions taken
Ultrafine Particles	Scientifically Based Concerns	Medium	Medium	Medium

Traditional Nanoparticles	Strong Scientific Suspicions	Medium	Low	High
Novel Nanoparticles	Weak Scientific Suspicions	High	Low	High

6.3.3 Environment

There is a relatively well established scientific knowledge base on how air pollution affects humans, but the research on the impacts of particulate air pollution on flora and fauna is very limited. This means that it is difficult to properly assess the impacts of ultrafine particles on the environment. There are recommendations given from authorities or the research community of the concentration of particles in urban air, but these are based on human health and not the impact on flora and fauna. The area of flora and fauna is not the focus for the research community or regulators at the moment. On the other hand, the anthropogenic ultrafine particles as such have been around us for centuries and have probably a very limited impact on the environment. What is new is the increasing amount of combustion generated ultrafine particles, where one possible risk occurs when these particles bind with pollutants and disperses the pollutants more effectively into the environment than previously. The role of particles in general are of vital importance in a number of natural processes like climate change, ozone hole and green house effect (PTL, 2004) but the uncertainty evolves around whether particles in the nano-range have different impact than bigger particles. However ultrafine particles as such can have more impact on the local ecosystems as they tend to form bigger particles quite fast and are deposited locally. Due to the high level of uncertainty and a high level of exposure, the risk is therefore seen as medium today and is not believed to change significantly in the future.

Traditional nanoparticles have been produced in numbers for decades and the likelihood that they are acute toxic is therefore fairly small. On the other hand, what we know about the environmental effects of the traditional nanoparticles comes from the limited knowledge from air pollution studies. It is not known how they behave in the environment and whether they accumulate. The risk is therefore estimated to be medium. Another potential type of long term risks due to the build-up of traditional nanoparticles in the ecosphere is the altering of the balance of eco-systems through mechanisms not yet known. This type of hypothetical risks could be for example in the cloud formation process because water vapour takes the easiest path in condensing to form clouds, making use of airborne aerosol particles (although soluble) in the size of 100 nm (Leck, Tjernström, Matrai, Swietlicki, & Bigg, 2004). As the production also of these particles is expected to increase and as long as the uncertainty is still very high, the predicted risks to the environment are increasing too.

Novel nanoparticles that have newly engineered properties not previously existing and known to the environment have many different layers of environmental risks incorporated. The risks are on two levels: 1) ecotoxicity and 2) ecosystem interference causing alterations of the established balance. There is a concern that the novel characteristics will react with surrounding organisms in a different, not yet known way than the 'normal' nanoparticles. On the level of ecotoxicity, there is the possibility that if the novel nanoparticles are bio-available, with other words, taken up in organisms, they can cause direct toxic effects on the target organ itself or might travel to different organs and cause damage there. Additionally are for example fullerenes lipophilic and will therefore bio-accumulate by nature. Depending on the level of bio-persistency the nanoparticles might enter the food chains with the following risks

to other species including humans. The bio-persistence depends on the chemical bindings and solvency of the novel nanoparticle and whether the organisms can find a way to metabolize or excrete the novel nanoparticles. This can also be a two-edged sword, as for example, some crude oils get more toxic after they are metabolized, because the chemical composition of the compound changes. The potential ecosystem interference can happen in different ways on a long-term timescale. There is a concern that because this category of nanoparticles is so reactive, the novel nanoparticles might bind with other substances and create a compound that is toxic. Another concern is if these nanoparticles bind to other toxic substances, create a colloid and due to the small size, can carry these toxic substances to areas in the environment they normally would not appear. Conversely, binding to for example nanotubes might neutralize pollutants, reducing the harm they cause (Kleiner & Hogan, 2003). The chemical reactivity of the novel nanoparticles could interfere with existing biological processes and alter, for example, the mechanisms around the pH-levels in the soil. On the extreme, the depth of interactions with ecosystems could alter mechanisms that we are not aware of today. A relevant analogy could be the history of the CFCs and the effects on the ozone layer. There are several phases in the life-cycle of an application containing novel nanoparticle, where an environmental exposure can take place, but as long as nobody knows whether there are mechanisms that can degrade these nanoparticles, there is a concern about a buildup of nano-waste in the ecosphere. The effects on the environment depend on the depth of interaction that the novel nanoparticles might have. However, the exposure level today is very limited and hence, is the risk today low. The potential level of exposure to these nanoparticles is very high, taken into account the many promising applications they are used, planned and researched to be used in. There is no doubt that the amount of novel nanoparticles that might end up in the environment can be considerable and combined with the high factor of uncertainty, the predicted risks are high.

Table 3: Risks and uncertainties in the environment

Nanoparticles	Environment		
	Level of Uncertainty	Risks	
		Present	Predicted/Future
Ultrafine Particles	Weak Scientific Suspicions	Medium	Medium
Traditional Nanoparticles	Weak Scientific Suspicions	Medium	High
Novel Nanoparticles	Weak Scientific Suspicions	Low	High

Another relevant question is whether the total aggregation of the three types of nanoparticles as already illustrated in Figure 3, can have combined effects on the environment. For example, this is also a concern in public health where there could be a potential overload level in the lungs causing toxic effects because the high amount of particles cannot be cleared out or handled adequately. There could also be similar concerns for environmental mechanisms.

Table 3 sums up the environmental risks and uncertainties and classifies them according to the discussion.

6.4 Producers

There are currently no regulations that address nanoparticles. It is therefore up to the producers themselves to be proactive. Nanoparticles might cause severe impacts on human health and the environment. There are therefore reasons to investigate whether a control of the nanoparticle production and application is needed and, if, what level of control should be set.

The industry has the duty to take care of their workers and it is their responsibility to take the precautionary measures needed to protect their workers. This seems to be agreed also in the nano industry. The major challenge is to find out what the right precautionary measures are. In some small companies, the experience with precautionary measures is limited, as well as the level of knowledge about potential toxicological impacts of their nanomaterials. It is therefore important that these companies can have a dialogue with the responsible authority which can give the latest update on the toxicology research, but also can help decide the right level of precautionary measures. In addition, most companies are or should be involved in research on health and safety and/or members of an organisation that deals with these issues.

An illustrative example of a successful control of technology in the last century was the regime established to regulate the use of recombinant DNA. Some research where feared to be able to create infectious forms of cancers and it was therefore established a moratorium

against this kind of research among the scientists in the field (Reynolds, 2002). In the context of nanoparticle production, a moratorium is not seen as an alternative, as nanoparticles are believed also to give benefits. A moratorium will slow down these benefits, as well as slow down research that can reduce the uncertainties of nanoparticles. The main point from the recombinant DNA example is that the self-regulatory policy coming from within the scientific community was very effective.

If precautionary measures are a strong focus within organizations the industry are members of, it could be possible through these channels, to build up a culture and a 'code of conduct' that takes the risks seriously and applies the necessary precautionary measures within the industry. Such an approach can have several benefits as given by Reynolds (2002). First, the co-members are more likely able to identify and respond to improper conduct by members that authorities are not likely to notice. Second, this approach is seen as morally binding and more likely to be carried out by the members even where there are no existing regulations. Third, it could spread also to organizations that these conducts are not originally applied to. A good example of this type of organisation could be the non-profit organisation Dechema in Germany, which has recently been involved in the EC project 'NanoSafe' that addresses the issues of health and safety (VDI, 2004).

However, as seen in the literature review and also confirmed during interviews, the companies are withholding studies of risks and hazards of nanoparticles that they have carried out. Although they are mainly doing it for reasons of competition, it reduces the public confidence and trust as the public may think the reason why the industry is withholding information, is because they have something to hide. This is seen as one of the possible downfalls of the biotechnology industry, where the industry itself only communicated after the public mistrust had been created and boosted by world headlines such as "GM pollen can kill butterflies" (See Chapter 6.7 for more discussions on public debate). Additionally, it makes the research go slower and increases the chances of 'double work', as the government might need to fund research that the industry might already have conducted.

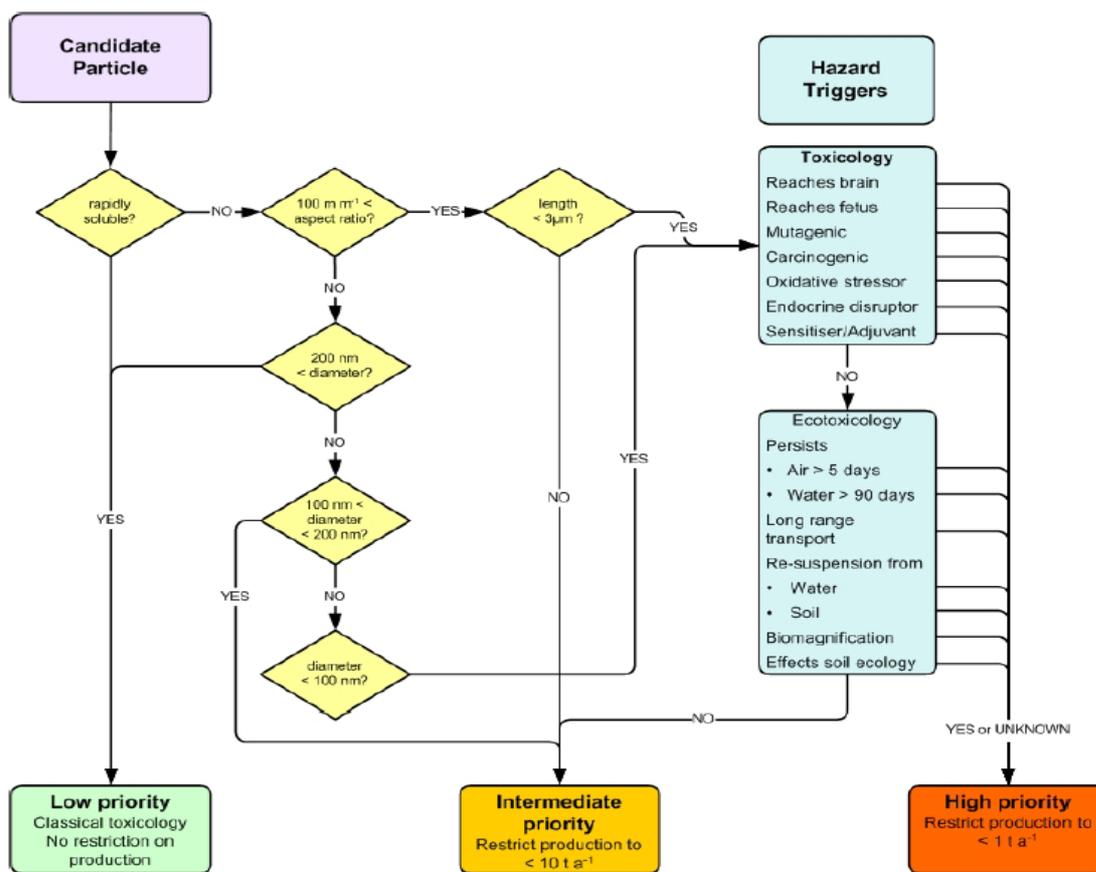
6.5 Authorities

As discussed in section 6.3, it is difficult to generalise about nanoparticles. In an occupational setting this causes problems for the regulators that are setting the exposure limit. They need to consider whether the nanoparticles are of 5 nm, 40 nm or 100 nm, have a coating or not, what kind of coating, the chemical composition of the particles and so on. This makes it very complicated to set a uniform standard for addressing nanoparticles in occupation health or assessing toxicity based on the bulk material, as the properties and the toxicity changes when you bring materials down to the nano-scale. It is vital for the occupational health of the workers to find a safe exposure level. However, producers, researchers and authorities are all aware of this, but it can take time to develop a good methodology. Meanwhile, there are thousand of people working with these materials in the industry and research. It is therefore fundamentally important as Hoet, Nemmar & Nemmerly brought up that "*Authorities and legislators support fundamental research to construct a scientifically valid low-cost fast-throughput test battery to screen nanomaterials for toxicity and biopersistence*" (Hoet, Nemmar, & Nemery, 2004). One possibility is therefore to take advantage of the potential of nanotechnology to develop these methods, as Kreyling pointed out in Chapter 3.2.8.

Regulators need a tool that makes them able to prioritise products into categories of urgency for attention. Although exposure assessments are missing and a full risk assessment is not

possible in most cases, it can be possible to do a ranking by using for example a hazard trigger algorithm as Howard and de Jung has developed, see Figure 4. The algorithm can help identify data gaps, guide the industry towards a more systematic testing and assist decision makers to prioritise. If it is applied as a preliminary hazard assessment by regulators, there will be several hazard trigger values that will be unknown. According to Howard and de Jong would a precautionary stance then be to assume any unknown value is equivalent to a positive hazard trip, leading to a high priority categorisation (EC, 2004b). Providing more information to fill in the gap can then lead to a lowering of the category.

To fill in the missing knowledge gaps the industry will no doubt have to play a role together with the funding agencies, as well as the regulators. The industry is involved in studies of their own, which the research community and the regulatory agencies today do not see. A regulation on a European level, where the industries are obliged to release the results of the studies after a specific time could contribute significantly to the international knowledge base. Another approach could be to introduce a European regulation similar to the REACH regulation, also for nanoparticles. If producers cannot show that their products are safe, the producers will not get approval for launching their products into the market. However, established standardized procedure for how the testing should be done is needed. It should also be found out, if it is possible to operate with classes of nanoparticles, in order to simplify the tests and not have to do new test of nanoparticles, if the producers change the physical characteristics of the nanoparticles just slightly. To find out where these classes start and end, as for example at what size the nanoparticles change behaviour in a way that they a new material data sheet, is some of the other issues regulators will have to decide in the coming future.



NOTE: At decision points, UNKNOWN values should be taken to equal YES.

Figure 4: Hazard trigger flow diagram¹⁷ (EC, 2004b)

However, adequate and rapid research on the hazards of nanoparticles is not sufficiently prioritised in the distribution of research funds. The National Nanotechnology Initiative (NNI), the governmental research program for nanotechnology in the USA, is using 11 % of the total budget of \$961 million on environmental studies (Service, 2004). However, there are critiques that the allocation of money goes primarily to research that uses nanotechnology to solve existing environmental problems, such as remediation of pollution sites, and not to assess whether this new technology can inflict new types of environmental damage or for screening the toxicity of the new materials. Eva Oberdörster points out that the grants for university based nanotoxicology studies, as illustrated in Figure 5, account for only \$5 million out of the current budget and says: “That’s on the silly side almost” (Service, 2004). A promotion of nanotechnology which allocates only a small budget part to safe development is possible also in Europe. There are 105 million Euros indicated for Co-ordinated Actions (CA), Specific Support Actions (SSA) and Specific Targeted Research Projects (STREP) in budget of the EU FP6, which has a total allocation of 1.3 billion Euros for nanotechnology. However, the topic ‘Impact on human health and environment’ is only one out of 18 topics. The FP6 NMP Infodesk answered the following, when asked how much is allocated for the area ‘Impact on human health and environment (FP6 NMP Infodesk, 2004): “FP6 NMP is run on the basis of competitive calls for proposals so the amount allocated to individual topics is not fixed. However, it is true to say that the amount of financing for SSAs and CAs is clearly substantially smaller

¹⁷ Aspect ratio: refers to the ratio of length to breadth of a particle. It is a way of classifying particles as fibrous.

than for Integrated Projects IPs and Networks of Excellence (NOEs) – running to maximum hundreds of thousands of Euros rather than up to tens of millions as in IPs and NOEs.” It seems like the EC is aware of the potential environmental and health implications of nanotechnology, but on the other hand, it is a difficult political game to make sure that the money will go where they are most needed.

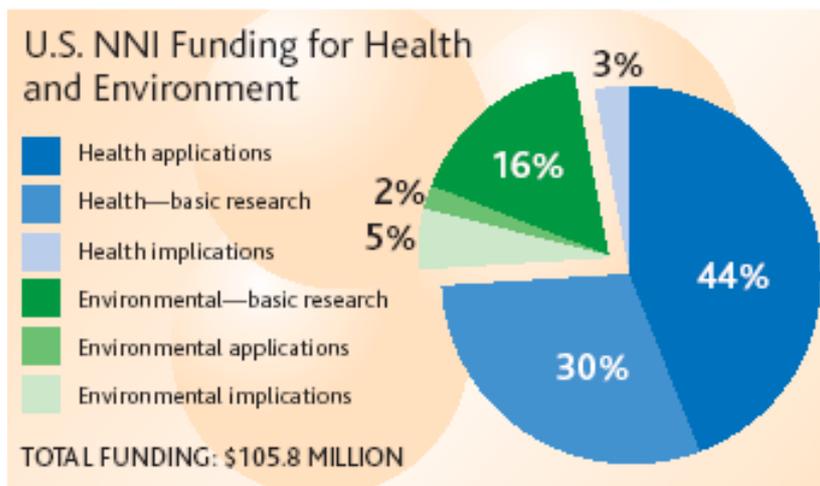


Figure 5: U.S. NNI Funding for Health and Environment (Service, 2004)

Although researchers, producers and authorities believe there should be exposure limits in workplaces, a legitimate question is whether this is the right approach. As there is such a wide variety of nanoparticles and the potential toxic effects are just as diverse, there could easily be an overregulation of the workplace with the result of lack of control due to lack of resources. For example the Occupational Safety and Health Administration in the U.S. has an extraordinary strict rule on workplace toxins, but has, according to Reynolds, failed to address all but a tiny minority of chemicals believed to be toxic (Reynolds, 2002). It is therefore important that authorities, industry and the scientific community get together and address the issue. However, the most effective form of regulation could in this case be self-regulation of the industry itself. It is the opinion of the occupational authorities that in this early stage of the development, it is the responsibility of the producers to take the necessary precautionary measures, but that authorities can help industry to implement the right level of precautions. The approach chosen by the HSE in the UK where they give out precautionary guidelines to the industry on how to handle nanoparticles, based on their experience with similar issues, seem to be a good way of helping the industry. A combination of pressure from authorities and self-regulation among industry can perhaps answer legitimate safety concerns. However, it is interesting to note that the countries examined have different approached towards the risks of nanoparticles. The very proactive approach of HSE in the UK and the public debate and involvement studies, initiated by the government and carried out by the Royal Society, is striking, compared to the low governmental profile on these issues in Germany and Switzerland. One possible explanation could be the experience the UK had with the BSE-scandal, where the lack of public openness and debate from the governmental institutions, is seen as one of the explanations why it got such devastating consequences.

6.6 Precautionary measures

It is generally accepted that if you have high uncertainties but also high potential risks, a precautionary approach should be chosen. Whether precautions should be taken or not, is not the issue, but it is what the adequate level of precautionary measures should be, that are highly debated. In this section, the different stakeholders' perceptions about the adequate level of precautionary measures will be discussed.

There are different opinions what that the right level of precautions is, also among the NGO groups. The ETC group believes that a moratorium should be posed on nanotechnology until more scientific evidence is established, proving that the technology and its applications are not only safe to the environment or human health, but also that the social implications are understood. However, Greenpeace do not want a moratorium of the technology, but wants a moratorium on environmental release of nanoparticles until nanoparticles are scientifically proven safe.

The producers in general seem to think that their own particles are not very dangerous, but producers often see nanoparticles from other producers as potentially dangerous. The levels of precautions the producer take differ, but are in general ranging from precautions taken for normal dusty environments, to precautions for chemicals. This means that nanoparticles are either looked upon as chemicals or as materials, with consequently different levels of precautions taken, as treating nanoparticles as chemicals requires a higher level of precautionary measures. However, no producers see that any environmental hazards could occur, because they believe their precautionary measures are adequate enough to protect the environment. In addition, as the producers in general don't see their own particles as dangerous, it is not believed that they will affect the environment in any adverse or different way, than any other 'normal' material or chemical do.

The regulators have just recently started to get interested in the issues around nanoparticles. It is clear that the occupation authorities in the different countries give the subject different priority. However, it is expected that the issues around nanoparticles gain increased priority as more knowledge is generated and more industries are applying nanoparticles in their production. In the UK, the occupational health authorities perceive nanoparticle as a potential toxic chemical in gaseous form, that should, in terms of precautionary measures, be handled thereafter. Germany and Switzerland has not worked so long with this issue and has not established any stand to how nanoparticles should be treated or what the right level of precautions should be.

The European Commission has different roles to play. On one hand is the EC heavily promoting the research and development of nanotechnology, as the EC sees it as a potential way of creating competitive advantage and thus revenues in the future. On the other hand has the EC also a legal obligation to protect their citizens. This is mirrored in the policy declaration of nanotechnology. The EC stresses that there are no scientific evidence today, that nanoparticles represent risks to human health or environment. It is, as of today, only identified hazards. This means that at the same time the EC is promoting nanotechnology, the EC is also supporting research on nano-toxicity. This duplex role becomes visible when it comes to precautionary measures where the EC claims to be cautious, but not precautionous. This means, not invoking the precautionary principle in the Communication from the Commission 2000:1, as the EC did with gene modified organisms (GMO). However, the EC did not promote and invest in the gene modification (GM) technology, in the same way as with nanotechnology. It is up to the individual member states and actors to apply the precautionary principle. It seems like the EC is not likely to take an active role in terms of

precautions, but will support a safe and responsible development of the technology through funding safe nano-research and at the same time research on nano-toxicity. The question whether the EC will succeed is still open. An interesting analogy is the mad cow disease (BSE) crisis in the UK, where the management of the crisis were handicapped by an institutional factor (Perret et al., 2004). The responsible department, the Ministry of Agriculture, Fisheries and Food (MAFF), was expected to promote the economical interests of farmers and the food industry whilst also protecting public health from food hazards (EEA, 2001). It failed to meet either.

The scientific research community believes that exposure in general should be minimized, until more is known about the potential risks of nanoparticles and that nanoparticles or the applications have not been thoroughly tested. More extensive research should therefore be done before nanoparticles are released into the market. In particular, there is a concern about the different effects that can arise during the whole life-cycle of the products, as the life-cycle has not been studied by the producers. However, the research community do not believe moratorium is the way to go, as they also see great potential in the technology, but some researchers believe that nanoparticles should be handled as in a worst-case scenario, because of the many uncertainties and potential high-level risks involved.

6.7 The public debate

The public debate illustrates the social concerns and opinions which will affect the both the political decisions allocating research funding, the regulatory structure and the consumer choices. This will all affect the industry. Although this study focuses on nanoparticles, it is also important to understand the wider context of the discussion, which means that a closer look at the debate of nanotechnology is needed. It is also interesting to look how the development of other technologies was affected by the public debate, to see whether it is reasonable to predict a similar development of the nanotechnology, as for example in the biotechnology debate.

6.7.1 The biotechnology debate

In 1995, the U.S. EPA approved marketing of the first genetically modified crop after doing a series of risk assessment studies (Schuler, 2003). In 1999, a study was published in *Nature* that suggested that a type of GM corn (Bt corn) might represent a risk to non-target organisms, as a laboratory experiment had shown that a butterfly larvae ate less, grew more slowly and higher mortality than larvae reared on leaves dusted with leaves without Bt-pollen (Losey, Rayor, & Carter, 1999). The next day, May 20 1999, in Europe there were sensational headlines at the BBC News: "GM pollen 'can kill butterflies'" (Kirby, 1999) and similar headlines appeared in the U.S. where the *New York Times* reported: "Altered Corn May Imperil Butterfly, Researchers Say" (Yoon, 1999). This caused an increased concern in the U.S. and intensified the fear in Europe. Among others did The Prince of Wales raise questions about GM in *The Daily Mail*, UK and wrote as a representative for the public opinion that: "*The public's reaction shows instinctive nervousness about tampering with nature when we don't know all the consequences.*" (*The Prince of Wales*, 1999). The EU later called for a moratorium on GM food in 2000. On the other side of the Atlantic the U.S. EPA announced in 2001 that "Bt corn has been evaluated thoroughly by EPA, and we are confident that it does not pose risks to human health or to the environment.", and approved the corn for continued usage (USEPA, 2001).

For the biotechnology industry this ‘war’ was and still is devastating for the public relations as the confidence in their products went down tremendously. It resulted for example in that the executive vice president of Monsanto, the world biggest producer of GM crops, announced in a press release on May the 10th 2004 that: "*As a result of our portfolio review and dialogue with wheat industry leaders, we recognize the business opportunities with Roundup Ready spring wheat are less attractive relative to Monsanto's other commercial priorities*" (Monsanto, 2004). The big biotech companies have been dropping out of several GM projects in Europe the last year due to lack of market opportunities.

There are also numerous NGO-organizations very actively campaigning against GM in this debate; traditional NGOs like Greenpeace and Friends of the Earth, but also several ad-hoc NGOs were formed like Corporate Watch and Genewatch. Greenpeace argues that GM-food is an inappropriate and unnecessary technology and additionally a manufactured risk, resulted from decisions and options based on commercial interest with no public involvement. This manufactured risk is unnecessary as other more low-tech solutions, like organic farming, provides ways with low or no risks involved.

6.7.2 The nanotechnology debate

In 1959, Richard Feynman gave at the annual meeting of the American Physical Society a speech called “There’s plenty of room at the bottom”, where he gave the visions of what we today call nanotechnology.

The debate around nanotechnology started in 1986 with a book called “Engines of creation”, where Eric Drexler, the founder of the Foresight institute, predicted that we would have small ‘nanorobots’ (size of cells) that could collect atoms and molecules, to convert them gradually into larger building blocks. In order to build on a scale useful for humans, these ‘nanorobots’ would need to reproduce themselves in massive numbers. Drexler further predicted if one of these auto-assemblers went crazy and reproduced beyond our control, the earth would be overwhelmed with gray-goo in just two days (Drexler, 1986). Later in 1992, Drexler in his new work, ‘Nanosystems’, did not even mention free-floating auto-assemblers. The term nanotechnology was originally posed by Drexler, for the field he recently renamed molecular nanotechnology after ‘everything’ was covered under the term nanotechnology.

In 2002 Michael Crichton published a book called ‘Prey’ and an abstract is presented here: *“In the Nevada desert, an experiment has gone horribly wrong. A cloud of nanoparticles -- micro-robots -- has escaped from the laboratory. This cloud is self-sustaining and self-reproducing. It is intelligent and learns from experience. For all practical purposes, it is alive. It has been programmed as a predator. It is evolving swiftly, becoming more deadly with each passing hour. Every attempt to destroy it has failed. And we are the prey.”* (Crichton, 2002).

‘Prey’ was apparently read by the ETC group, which in January 2003 gave out the report ‘The Big Down: From Genomes to Atoms’ where they describe some of the risks of nanotechnology. For example one risk they pose is: *“The self-replicating and assembly processes could go haywire until the world is annihilated by nanobots or their products.”* (ETC group, 2003a). The ETC group is known to be the most outgoing (and first) NGO that opposes nanotechnology and they call for a moratorium, until there are adequate tests done on the health, safety and environmental impacts (ETC group, 2003b).

In June 2003 the UK Government commissioned the Royal Society and the Royal Academy of Engineering to carry out an *independent study of likely developments and whether nanotechnology*

raises or is likely to raise new ethical, health and safety or social issues which are not covered by current regulation (The Royal Society & The Royal Academy of Engineering, 2004b). The Prince of Wales also asked the Royal Society to look into his concerns that “*swarms of rogue ‘nanomachines’ could one day reduce all in their path to ‘grey goo’*” (Highfield, 2003). A month later in July 2003, Greenpeace released their report “Future Technology, Today’s Choices” where they addressed the issue of ‘nanomachines’, but wrote that: “*The ‘runaway replicator’ concerns (also known as the ‘grey goo’ scenario) raised by Crichton’s novel are hideous, but the prospects of it remain way off.*” (Arnall, 2003). Greenpeace does not have a position against the nanotechnology as such but: “*We want to see a moratorium on the release of nanoparticles to the environment until evidence that it is safe (for the environment and human health) is clear. In the longer term nanotechnology could produce self-replicating ‘machines’ whose proliferation could be environmentally problematic.*” (Greenpeace, 2004).

The reinsurance company SwissRe released in May 2004, a report where they consider nanotechnology as completely new from an insurance point of view, because of the “*unforeseeable nature of the risks it entails and the recurrent and cumulative losses it could lead to, given the new properties – hence different behaviour – of nanotechnologically manufactured products?*” (Hett, 2004).

In an article in the newspaper Independent 11 July 2004, the Prince of Wales is rejecting self-replicating robots as science fiction. He is instead bringing up the concerns that the new properties of nanomaterials, can give risks that need to be addressed with proper attention (The Prince of Wales, 2004).

There has also started a debate around the potential that nanoparticles have to adversely affect environmental and biological system. In a meeting of the American Chemical Society in March 2004, Eva Oberdörster told that in her lab, she had shown that buckyballs (fullerenes) had caused damage to cell membranes in the brains of fish. This gave headlines in the Washington post; ‘Nanotechnology Linked to Organ Damage – Study’ and in the New Scientist; ‘Buckyballs cause brain damage in fish’ and the Boston Globe asked ‘Are tiny man-made particles a health threat?’ Headlines on different scientific findings of the hazards of nanomaterials were found across the world. In Europe, there has been headlines in the BBC like ‘Tiny Particles ‘threaten brain’’. After the release of a Royal Society and Royal Academy of Engineering report in July this year, Professor Ann Dowling of the report’s working group was interviewed live on the BBC News where she was calling for regulations of nanoparticles. The Science magazine asked already in 1998: ‘Nanotubes: The Next Asbestos?’ and this year in an article called ‘Nanotechnology Grows Up’, they addressed the risks of especially nanoparticles.

6.7.3 Learning from the biotechnology debate

Nanotechnology is an emerging technology, but the debate already sees clear divisions. On the one side, there is the group of ‘nano-no’ and on the other side, the group of ‘nano-go’. The ‘nano-no’ side is sceptic to the vested interests behind the science and is led by the ETC group demanding a moratorium, warning about a potential Pandora’s Box and followed up by The Prince of Wales, expressing his concerns about nanotechnology. On the other side, the ‘nano-go’, represented by the material researchers and the industry, reports on all the wonderful things that can be done with nanotechnology and the economic, social and environmental potentials following. This division has similarities to previous technology debates over nuclear power, GM crops or electromagnetic radiation. According to Willis and Wilsdon, is nanotechnology still at the research stage similar to that which was the stage of biotechnology in the late 1970s (Willis & Wilsdon, 2003).

It is striking how the popular press reports in a similar fashion, the findings that suggest hazards to some applications of the technologies in both nanotechnology and biotechnology. The press is associating risks concerning one type of application of the technology with the technology as such. One study that showed that the monarch butterfly could be damaged by GM-pollen, gave headlines associated with biotechnology in for example the Washington Post which had a headline: "Biotech vs. 'Bambi' of insects? Gene-Altered Corn May kill Monarch". A similar trend can also be seen in the nano debate. In the book 'Prey', Crichton writes that nanoparticles are a swarm of micro robots. Crichton is then mixing nanoparticles, typically represented by the material and chemical industry, with micro-robots which belongs to the field called molecular nanotechnology, operating in the bio-nano interface. Although they both belong under the term nanotechnology, they only share a common size.

Eva Oberdorster published the results of one study done she did that showed that fish exposed to fullerenes gave brain damage. However, this was, as pointed out by the researcher herself (Chapter 3.2.1), only one study, at one concentration, with one type of nanoparticles, done with one type of fish. The validity of this single study should therefore be carefully considered. This one study does not necessarily tell anything about the toxic potential of nanoparticles in general. However, this does not come through in the popular press as it generalised from fullerenes to nanotechnology, like the Washington Post did with the headline "Nanotechnology Linked to Organ Damage - Study". Although nanoparticles in general have a higher toxicity than bigger particles of the same compound, the toxicity varies between the types of nanoparticles. Nanotubes, as described as one type of nanoparticles, have been linked to Asbestos already in 1998 in the magazine Science (Service, 1998), because nanotubes has a fibre structure that is very similar to the one that the asbestos fibres have. However, nanoparticles of for example titanium dioxide, do not have the same structure and is unlikely to cause the same effects and therefore needs to be assessed differently. The basic line is that nanoparticles have applications that can be highly beneficial for the environment, like nanotubes in solar energy and hydrogen production or for the human health like hip replacements or drug deliveries. The risks need to be minimized to an acceptable level that is balanced against the benefits.

The developers in nanotechnology look to the biotechnology debate with fear, because they see how the withdrawal of the billion dollar company Monsanto in GM wheat production, could be a fate that also could strike them. A tremendous amount of money has been, is and is planned to be, invested in this field and if the public opinion is afraid of the products, there will be no market for the products. Many of the developers would therefore be wise to listen to the public and learn how a proactive public involvement can be used to reduce the risks of history repeating itself. In Europe, the Bt corn controversy was framed by the mass-media by headlines like "Bt corn = monarch killer", which insidiously stressed the negative consequences of Bt corn. This ultimately pushed the burden of proof over to the Bt corn producers and the scientific community, where they have to thoroughly prove that their products are harmless to get access to the European market. This is what pressure groups like the ETC group, also want to achieve with nanoparticles, as they are calling for a moratorium, until we have enough data to prove the products safe. In an interview Thomas from the ETC group said¹⁸: *"At the very, very least you treat nanoparticles and nanomaterials as new materials. This means you treat them at the very least as in the REACH-regulation. If you don't have data, you don't get any approval. At the moment, that would mean that nanoparticles are not allowed to be commercially used, as there is no data on them."* However, this depends on whether adequate

¹⁸ Phone interviewed 14. July 2004

toxicological and ecotoxicological tests can be developed fast and cost efficient enough, in order to deal with the steady increase of new types of nanoparticles.

Reactions to risks very rarely take a rational path and aggregation of evidence which is the scientific tradition of doing a risk assessment, is not necessarily the same way that the public does their risk assessment. The individual response to risk is rooted in human values, common sense, intuition, imagination, memory and past experience (Schuler, 2003). In the biotechnology debate, some of the scientists and authorities believed that the open debate over technology would take irrational paths and result in bad social judgements. Therefore was no public debate encouraged, especially in the U.S., and the industry did not engage in the public debate until the monarch butterfly article was published and stirred the public opinion. However, it seems like the UK has looked to the biotechnology debate, as they initiated the Royal Society to look at the risks of nanotechnology. In Europe, there has not been any attempt in any other countries to involve the public in the development debate of nanotechnology.

In general, factors that affects the risk estimation of nanotechnology is according to Schuler: the lack of familiarity with nanotechnology among the public, the uncertainty over equitable distribution of knowledge and of risks/benefits, the difficulty in predicting the potential hazards, and the association of nanotech to the public backlash of genetic modified foods in addition to beliefs, conviction, morality – what is wrong, what is right – and ethics – what is good, what is bad (Schuler, 2003). So far this has not been addressed by the industry, material scientists or the governmental funding agents, but has been left to toxicologists and environmental pressure groups like the ETC group.

The traditional risk assessment and management is by many seen as inadequate, as it ran as follows: defining the potential risk; using scientific analysis, define the scope of that risk, using assessment technologies, decide how to proceed, using cost-benefit analysis and finally, defend the decision to the public (Willis & Wilsdon, 2003). This approach is not working with modern complex risks, or with complex modern societies. New approaches are needed and the previous simple stages of identification, assessment, management and communication needs to be adjusted, so it is seen as a subjective, open to debate and interpretation way of dealing with risks, which needs to be communicated in every step with the public stakeholders. There is a fear among the scientists that people do not know enough, so they cannot deal with the risks, and will make rash decisions. The public need to be presented hard facts and absolute certainties rather than uncertainties. According to Willis and Wilsdon, research shows that the public understand scientific uncertainty and are prepared to deal with it. When the people are aware of the risks, they will make their own calculations on whether benefits outweigh the risks. It is when the people are denied the risk information and discovers attempts to cover up risk or uncertainty, that the people are alarmed. It is the denial of uncertainty that corrodes the trust. The reinsurance industry sees that risks associated with nanotechnology, as well as risk communication efforts, should concern all involved stakeholders: industry, scientists, regulators, consumer organisations and the insurance industry (EC, 2004b). The reinsurance industry sees this as the only way to prevent a polarized debate about nanotechnology, which may slow down future research and economic growth, in order to find a common approach to reduce the uncertainty and to provide some answers for pressing questions concerning potential nanotoxicity and pollution issues.

Greater public involvement can help government to make better decisions in which direction the research and development should go, because the decisions are made on a broader basis.

The governments can draw from the opinions of the people, thus better understand the issue and will be better capable to make informed decisions. Research and precautionary measures can be focused into areas where the public sees the risks as acceptable and the benefits attractive. Better regulations that has seriously considered the concerns of the public, and hence, increases the trust to the governments, can also be made.

However, a study done in the UK, showed that only 29% of the public claim they have heard of nanotechnology, while only 19% are able to give some definition of it, whether accurate or not (BMRB Social Research, 2004). To talk about a public debate is therefore too early, as people do not in general know what nanotechnology is. This debate is therefore still in the realms of the scientists with some special media channels monitoring and reporting the debate from time to time. It is noticeable that the industry involved with nanotechnology has not so far been involved in the debate. The debate has been formed in the media by the opinions of NGOs with the ETC group at the head, researchers in nanomaterials and toxicologists. This has similarities with the biotechnology debate, where the biotechnology industry only communicated with the public and sponsored studies after the release of the monarch butterfly article in 1999.

7 Conclusions

This chapter presents the main conclusions drawn from the study of the hazards and risks of nanoparticles to human health and the environment, perceptions, and precautionary measures taken by regulatory bodies and producers. The conclusions are structured in summary answers to the research questions. Additionally, suggestions for recommendations on precautionary measures, further research and focal points are discussed.

7.1 Knowledge base, perceptions and precautionary measures

In this section are the research questions revisited, and an attempt to answer them is given.

Research Question 1: What is the current knowledge base of the risks of nanoparticles to human health and the environment?

Nanoparticles cause more inflammation in the lung than larger particles of the same material, which is believed to be caused by the increased surface area that follows a decrease in particle size. This theory is well established. Inhaled nanoparticles are able to translocate from the point of intake to secondary organs in the body. The effects nanoparticles cause in the secondary organs is not known. However, nanoparticles cause different levels of interaction with the biological system and has different mobility based on the size, shape and chemical composition. Therefore, it is not possible to address the hazards and risks of nanoparticles in a general way, as each nanoparticle need to have its own toxicity understood. There are some studies that have shown that nanoparticles have caused deaths of rodents and caused brain damage in fish. However, studies conducted on environmental impacts are very few and it is not able to give any answer what the effects on the environment will be.

There are different types of nanoparticles that share the same physical property of size, but have different characteristics and engineered purpose. A categorisation was therefore developed and suggested, separating nanoparticles into the following three categories: ultrafine particles, traditional nanoparticles and novel nanoparticles. The ultrafine particles are produced unintentionally as a by product in a process and are typically originated from combustion processes or food cooking. The ultrafine particles are both naturally occurring and man-made. The traditional nanoparticles are produced in larger bulk quantities for already existing applications in the market. This category encompasses common engineered nanoparticles like carbon black, titanium dioxide and fumed silica and has generally been produced for decades, especially in the chemical and polymer industry. The novel nanoparticles are deliberately engineered to have properties and characteristics only existing in the nano-range in terms of size, shape and chemical composition, which are utilized to fill a specific function. These types of nanoparticles are, as of today, typically produced in small quantities, typically in the kg range. The uncertainties and risks are on different levels, according to which category of nanoparticles is addressed as the different categories have different impacts on public health, occupation health or environment.

Air pollution studies shows that an increase in particle concentration in the air is directly correlated with an increase in morbidity and deaths. Nanoparticles can destabilize the plaques in atherosclerosis, which in turn can lead to clogged blood vessels with heart attacks or strokes following. Whether there exists a threshold level of what humans can take of nanoparticle exposure is an important question to find out. People are through combustion processes exposed to small particles (diesel soot) in a much larger extent than before and an

increase of the exposure through engineered nanoparticles on top of it can tip the total level of particle exposure above a potential threshold limit. Nothing will happen if the exposure is below the critical threshold level, but this level can vary among people and therefore is, for example, people with cardiovascular or respiratory diseases, children or elderly people of particular concern as they might have a lower threshold level than the average, healthy people.

At present the occupational health risks due to inhalation of novel nanoparticles in the production phase seem to be the most potent risk. This is where the exposure first happens and where the possible signals of hazards first will arise. However, an occupational setting is relatively easy controlled and there is reason to believe that it will be controlled within the next five years, both from the producers' side, but also from the authorities' side. As long as we don't know what the hazards are of nanoparticle exposure, it is advisable to use precautionary measures that minimize the exposure to workers and the environment as far as possible. The occupational risks are potent, but can be considered as still small, as workers are or should be aware that there is a risk involved in the production of these materials. The workers have then the possibility to do an informed choice. Furthermore, it is the group of people with cardiovascular diseases that has the highest risks, but these people do not work in a dusty environment. The workers are therefore likely to be healthy and the acute toxicity of nanoparticles is not believed to affect healthy people as much as diseased people. The risks of nanoparticles to the workers are therefore long-term risks due to chronic exposure of a special kind of nanoparticles. In the long run, this chronic exposure could lead to diseases like lung fibrosis.

Even though nanoparticles in occupational settings seem like the most potent risk at present, it is reasonable that in the future, the most potent risks will be due to exposure from applications of nanoparticles, as occupational settings are easier controlled. Release from applications of nanoparticles in the usage phase directly, as ingredients in spray cans, or indirectly, being worn off from consumer products like tires, and the release in the end-of-life when the applications are degraded, are phases where nanoparticles may be released into the ecosystem in numbers. A release of large quantities of nanomaterials with novel properties not previously known to nature is certain to cause some kind of environmental impact. The main question is whether engineered nanoparticles will have a different behaviour than, for example, the ultrafine particles we find in air pollution originated from traffic. Will novel nanoparticles bio-accumulate and can they be broken down in the organisms, are questions that still need to be answered. If novel nanoparticles are bio-persistent and additionally toxic, we might have a new type of hazardous waste.

Research Question 2: How are the hazard and risk of nanoparticles perceived among authorities and producers in occupational settings?

The producers seem to be updated on the recent studies, but it also seem like the producers do not believe the nanoparticles they produce themselves are problematic. The occupational regulations are not adequate at the moment for assessing nanoparticles, but the companies believe there should be regulations for nanoparticles. There seem to be a difference that the 'traditional' companies, that normally are bigger and have more resources, do some more toxicological tests of their nanoparticles than the 'new' companies that is producing nanoparticles with novel properties in small volumes. The producers further believe that the nanoparticles do not represent a risk to the environment, because of the measures they are taking, although nanoparticles are released into the environment during manufacture and through applications.

The occupational health authorities are aware and updated on the potential risks of nanoparticles and see the need to assess nanoparticles on an individual basis. They are prepared to amend the existing regulations, but are also aware of the problem, that it is not known, whether the exposure levels should be set based on mass, particle numbers or surface area. However, the authorities seem in general to give this area a low priority, as they have not seen any scientific research that shows reasons for great concern. The authorities in the different countries have different levels of involvement; the Swiss are awaiting the situation, the Germans are recently becoming more involved in the scientific debate, while in the UK, the occupational health authority is active in the debates and workshops and has already financed an overview report on nanoparticles in occupational settings.

The European Commission believes that the benefits of nanotechnology will outweigh the potential risks, but stresses that today, there are no identified risks of nanoparticles, only identified hazards. These hazards need to be further investigated and understood before taking any actions, but the EC are aware that there could be potential risks and tries to support research that will direct the development of nanotechnology in a safe and responsible manner.

Research Question 3: What precautionary measures are taken to prevent harm?

The companies are using engineering control in production, which protects the products from contamination, as well as, the workers from the products. When the workers are handling the nanoparticles, they apply the personal protective equipment normal for a chemical or dusty environment like masks and gloves. However, nanoparticles show signs of hazards, behave more like a gas in the air and have unknown penetration potential. Nanoparticles should therefore not be treated as simply dust in terms of precautions, which means that the precautionary measures applied by the producers, need to take the uncertainties into account and address nanoparticles as in a worst case-scenario.

There are limited precautionary measures taken to protect public health and the environment from exposure to nanoparticles. Precautionary measures for these purposes seem today to have a very low priority.

The European Commission has a duplex role as they are both promoting nanotechnology, but at the same time has a legal obligation to protect the citizens and the environment. The EC is therefore not taking any precautions of today, and it is likely that questions of precautionary measures will be left fully to the individual member states. However, there are as of today, no precautionary measures initiated by the occupational health authorities in Germany and Switzerland, but the occupational health authority in the UK has published an information note on the health and safety of some aspects of nanotechnology and seems to give the risk and safety of nanoparticles higher priority than the other countries.

7.2 Recommendations, further research and focal points

This chapter suggests a number of areas for further study, as well as actions that could be taken, in order to reduce the uncertainties and be able to conduct a proper risk assessment.

Authorities

The authorities on both the EC level and the national level need to coordinate their activities and responsibilities in this field, as the development of nanotechnology will be on the table of many different departments ranging from environment and public health, to research and labour. A clear structure among the different departments is needed to deal with the complex issue of nanoparticles. The authorities have just recently started to be interested in the issues of nanoparticles, but there are already applications launched in the market, that has not been tested for toxicity or ecotoxicity. The applications have further not been investigated for different issues in the end-of-life, such as the need of a different waste treatment or the potential for build-up of new types of pollution, nano-pollution. Furthermore, there are no standards that monitor the exposure levels of nanoparticles today. The normal monitoring is today done on mass, although the surface area is probably a more adequate unit of measurement. The authorities could therefore be more proactive, raise the awareness among the industry and give the industry incentives to do proper tests and take proper precautions. An approach similar to the REACH approach should also for nanoparticles be discussed where producers have a legal duty to show that their products are safe. It should be in the interest of both regulators and industry to establish safety limit values and take precautions, as well as a prerequisite for the insurance industry, as they see that nanoparticles can easily be a liability issue.

Producers

Producers need to get involved in the public debate and create more openness around their own studies, so that the research community can take part in their knowledge. The producers should also treat nanoparticles as a potential toxin in gas form and take adequate precautionary measures thereafter. The producers should assess the effects of the whole life-cycle of their products and assess the exposure of nanoparticles to the environment that could take place during the life-cycle.

Environmental Release

Environmental release of nanoparticles should be minimized. Nobody knows what kind of impact nanoparticles has on the environment and according to the precautionary principle, such release should therefore be restricted, until adequate research has been conducted. A moratorium on environmental release is called for by NGOs like Greenpeace and ETC group, but also the Royal Society in the UK recommends that it should be prohibited until significant data shows it is safe (The Royal Society & The Royal Academy of Engineering, 2004a). However, there are also other reasons in addition to the environmental concern why industry involved in nanotechnology should be interested in avoiding nanoparticle exposure to the environment. As seen in the biotechnology debate, biotechnology got a bad publicity after the butterfly article which damaged the public confidence in the actors involved in the field. This could easily happen with nanotechnology too. An environmental release to nanoparticles that can be traced to fish deaths or ecosystem disruption, could give negative publicity in the media and damage the reputation and trust in the nanotechnology as such, but also the actors involved in the technology. The way the media works, it would not be

unlikely that a test of one type of nanoparticles for environmental remediation that was not properly conducted and caused damage to the local ecosystem, would in the media be linked to nanoparticles in general, and moreover nanotechnology, causing public concerns about other nano-application fields. As nanotechnology and nanoparticles also incorporates very promising applications in for example solar energy utilization, applications involved in areas with very high uncertainty and risks, should therefore be carefully considered by the involved parties, in order not to damage the general trust in the nano-industries as such.

Assessing exposure levels

Whether nanoparticles truly will represent a risk to human health and environment will depend on the level of exposure. The exposure could happen in all the stages in the life-cycle, as illustrated in Figure 6, for example as a result of wear in the consumption phase. As nobody knows what the impacts of the exposure are, a life-cycle screening should take place before any application is launched in the market. Such a screening could find out in what stage exposure is likely to happen and then the risks could be better estimated. There are probably greater impacts on public health, due to direct exposure in the usage phase, as for example free usage of nanoparticles in an application, than with nanoparticles that are fixed in a material, that probably only will be released into the environment in the end-of-life stage. An impact study on applications with high direct exposure potential would therefore be more urgent, than applications where nanoparticles are gradually released in numbers.

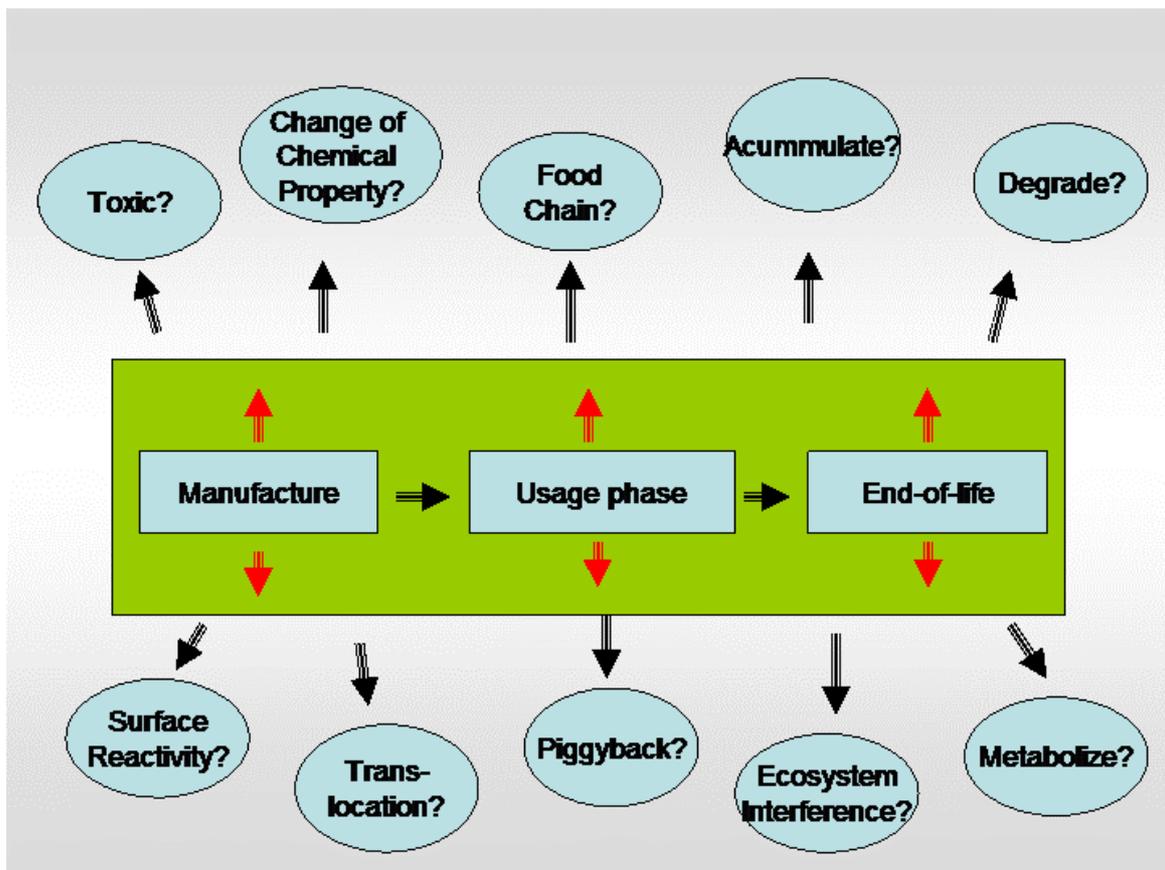


Figure 6: Some possible fates of nanoparticles released into the ecosystem

Applications

A precautionary approach is needed, as no one currently knows the application range of nanoparticles, what kind of exposure we will have, where in the life-cycle the exposure will take place or the effects the nanoparticles have on human health or environment. It is necessary to know how much nanoparticles and nanomaterials will be present in our society, to determine what the exposure level to humans will be and how much nanomaterials the environment has to deal with in the future. It can be of vital importance to develop methods to deal with the stream of nano-based product waste, as they can potentially give a high risk to the environment, if they prove to be of harmful nature. This can for example be done through a predictive substance flow analysis, tracking the life-cycles of the applications. Especially as nanoparticles will be applied in such different fields of applications, it could be important to have an overview over which applications contains nanoparticles. A register of nanoparticle products where producers are obliged to register their products should be discussed. In the register, it should be possible to find out the short-term applications and long-term applications, because they represent different time-lines. This could be important, if it turns out that special waste treatment processes should be in place for nanoparticle applications. There should furthermore be a labelling of products containing nanoparticles, especially of products where direct exposure to consumer could happen, such as in cosmetics, food additives or aerosol products. The labelling could be one of the functions that such a register served. Such a labelling could also prove necessary for the insurance business, in order to differentiate and insure certain exposures, originating from different products or applications (EC, 2004b). The register could be important, if the ongoing testing show potential hazards to types of applications or types of nanoparticles in applications, by enabling a rapid tracking of the exposure so the necessary measures can be taken. Combined with a life-cycle screening, this could serve as a fundament for a database like in the chemical sector, where possible risks can be estimated by comparing the risks of similar applications or similar types of chemicals.

Traditional nanoparticles have been a part of the chemical, polymer and carbon black industry for decades and have traditionally been regarded as classical chemistry. Nanoparticles are in many ways to be regarded as chemicals incorporated into consumer products. It is therefore likely that schemes and regulations that aim to protect human health and environment similar to the ones addressing chemicals can also be applied for nanoparticles. Schemes that addresses consumer products as such, like take back schemes, does not seem as applicable for nanoparticles.

Risk Assessments

In order to do a proper risk assessment, several parameters need to be known. A typical risk assessment is built up like in Figure 7. However, when it comes to especially traditional and novel nanoparticles, only the particle characteristics are known. With ultrafine particles there has been more research and there is some more knowledge. As illustrated in Figure 7, we are not able to make a proper risk assessment on the traditional or novel nanoparticles, as there are too many uncertainties and knowledge gaps.

1 Hazard Identification	2 Dose Response Assessment	4 Risk characterization
Particle characteristics: <ul style="list-style-type: none"> • Aspect ratio • Diameter (particle/aggregate) • Surface area/properties • Water solubility • Chemical composition <p style="color: red; text-align: center;">Known</p> Emission <ul style="list-style-type: none"> • Production volume • Material flows • Potential particle release (production, use, disposal) Health Effects <ul style="list-style-type: none"> • Humans • Experimental animals Environmental effects <ul style="list-style-type: none"> • Persistence • Biomagnification • Long range transport 	Epidemiological studies <ul style="list-style-type: none"> • Workers • Consumers • Exposed population In vivo studies <ul style="list-style-type: none"> • Acute/chronic • Different species In vitro studies <ul style="list-style-type: none"> • Human/animal different cell types • Models (lung, skin, systemic effects) 	Susceptible extrapolation models <ul style="list-style-type: none"> • High dose → low dose • Animal → human Threshold value calculation <ul style="list-style-type: none"> • Intake, immission concentration, maximum workplace concentration
	3 Exposure Assessment	5 Risk Management
	Exposure routes <ul style="list-style-type: none"> • Inhalation, dermal, ingestion Environmental monitoring <ul style="list-style-type: none"> • Biological uptake Occupation Monitoring <ul style="list-style-type: none"> • Personal Exposure 	Preventive Measures <ul style="list-style-type: none"> • Personal protection equipment • Modification of processes Standardization <ul style="list-style-type: none"> • Measurement techniques • Toxicological assessment Regulation <ul style="list-style-type: none"> • Exposure/immission standards • Production standards/restrictions

Figure 7: Risk Assessment of Nanoparticles (modified form (VDI, 2004))

For nanoparticles released into the market in bigger amounts, as in bulk applications, a proper risk assessment should be done. It is the responsibilities of the producers to prove their products safe before market release, rather than authorities should prove that the products are hazardous, after the product is established on the market. It will be more difficult and devastating for the industry to redraw products from the market, than to do proper testing before releasing them.

The product should not only be assessed in terms of toxicity or ecotoxicity, but should also be assessed in the end-of-life phase, where questions of degradability and waste handling should be addresses. An approach, similar to the REACH approach for chemicals planned for the EU, should also be appropriate for nanoparticles and should urgently be discussed. However, the authorities are already behind when it comes to some applications that already are established in the market, for example nanoparticles in cosmetics. These kinds of nanoparticles are defined as a sub-class of the parent material on the material data sheet. This is not adequate as these nanoparticles have different properties, in fact that is why they are nano-sized, and are likely to have different potential hazards too. These applications should be immediately assessed and the necessary data be comprehended. Basic screening models based on the particle characteristics could be developed and applied, to get an idea whether a particle might prove to be hazardous or not. These kinds of screening models could be very effective for regulators, in order to find out how much data is needed to assess the risk. The models should be further developed so regulators and producers can have a good idea whether there could be health or environmental hazards related to the substance before commercialisation. There are high expectations on the return on money for the investors and it is therefore essential that rapid test methods are developed, so the time from research to the market is reasonable for the investors.

The Public

The perceived risks of the experts in the field, industry or authorities are not necessarily the risks that concern the public. The public will be the applicator and the consumer of the products of nanoparticles and will therefore have big impact, not only on the choice of products, but also on the decisions made from the regulators, as regulators are chosen by the people to represent their opinions. It is therefore important when assessing risks to look at the public opinion, to see whether there are social risks or other types of risks that also should be addressed. Additionally, the public can be used as a way of broadening the knowledge base on which decisions are made on.

Human impacts

There are several factors that are currently not known about the impacts nanoparticles have on the human body. It is not known whether the particles accumulate in the body, how toxic they are, where they travel or if the body can secrete or metabolize the particles. That there will be some long term effects to human health and environment is very likely. However, these long-term effects are also likely to be different depending on which type of nanoparticles addressed. It could also be relevant to consider in which form the nanoparticles exists in: Are they mainly single particles, or do they agglomerate, and if latter, under which conditions do they agglomerate and is this agglomeration stabile? These factors may impact the potential hazard of the nanoparticle. In the best case, novel nanoparticles would be biodegradable, agglomerate rapidly, forming bigger particles with no penetration potential of tissue, and which are additionally easily cleared out of the lungs. In the worst case, we have a high level of exposure of novel nanoparticles consisting of a material that is toxic per se, can travel to the lungs and inflict damage there, enter the bloodstream and go to organs like the brain with unknown results.

The test methods are a further discussion point, as it is unclear whether it is possible to use the dose-effect toxicological tests, because it is unknown whether the response is linear scaled or whether it exists a threshold value. It is also difficult to estimate what dosages in a laboratory setting that are relevant in the real world. There is also a question whether today's test methods can identify potential long-term effects. Whether toxicological tests on animals are representative for humans, is also unclear. For example is the rat model questioned, because the respiratory tract of a rat is only a few centimeters, whereas the respiratory tract of humans is in the range of tens of centimeters, which apparently will result in differences in the deposition pattern of inhaled nanoparticles.

7.3 Concluding remarks

The bottom line is not whether nanoparticles are hazardous or represent risks to human health or environment. The bottom line is whether the applications of nanoparticles can substitute applications that are more hazardous and represent a larger risk to human health or environment. If the benefits prove to be as true as the most enthusiastic supporters of nanotechnology believe, the risks may prove to be acceptable. Until that day comes, reducing the uncertainties and the risks should be the main focus. That would, according to the precautionary principle, mean to handle nanoparticles as in a worst-case scenario and take adequate precautionary measures to cope with the worst-case, because it is better to be safe than sorry for all parties involved.

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Abbreviations

BSE	Bovine Spongiform Encephalopathy
CA	Co-ordinated Actions
CFC	Chlorofluorocarbons
CNT	Carbon Nanotubes
DDT	Dichlorodiphenyltrichloroethane
EC	European Commission
EPA	Environmental Protection Agency
FP6	6 th Research Framework Programme
GM	Genetically Modified
GMOs	Genetically Modified Organisms
HSE	Health and Safety Executive
IP	Integrated Projects
NGO	Non Governmental Organizations
NMP	Nanotechnology and nanosciences, knowledge-based multifunctional materials and new production processes and devices
NNI	National Nanotechnology Initiative
NOE	Networks of Excellence
PAH	Polycyclic Aromatic Hydrocarbons
PCB	Polychlorinated Biphenyls
REACH	Registration, Evaluation and Authorisation of Chemicals
SSA	Specific Support Actions
STREP	Specific Targeted Research Projects
SWCNT	Single Walled Carbon Nanotubes
UK	United Kingdom
U.S.	United States

Appendix I: List of Interviewees

Nanoparticle experts:

Prof. Paul J. A. Borm

Toxicological aspects of nanoparticles

Phone interview: 12.07.2004

Center of Expertise in Life Sciences

Heerleen, The Netherlands

Prof. Adam Curtis

Cellular and biological aspects of nanoparticles

Phone interview: 27.07.2004

Centre for Cell Engineering

University of Glasgow

Glasgow, UK

Prof. Ken Donaldson

Lung toxicity of nanoparticles

Phone interview: 23.07.2004

Centre for Inflammation Research

The Medical School

University of Edinburgh

Edinburgh, UK

Prof Dennis Henshaw

Nanoparticles and health effects

Phone interview: 12.07.2004

Physics Department

University of Bristol

Bristol, UK

Dr Wolfgang Kreyling

Toxicological aspects of ultrafine aerosols

Phone interview: 08.07.2004

GSF Research Center for

Environment and Health

Neuherberg, Germany

Dr Harald Krug

Toxicological aspects of nanoparticles

Phone interview: 06.07.2004

Forschungszentrum Karlsruhe,

Department of Molecular and

Environmental Toxicology

Institute of Toxicology and Genetics

Karlsruhe, Germany

Dr Eva Oberdörster

Ecotoxicological aspects of nanoparticles

Phone interview: 23.07.2004

Department of Biological Sciences

Southern Methodist University

Dallas, Texas, USA

Dr Jonathan Powel

Cellular response mechanisms of ultrafine particles

Phone interview: 13.07.2004

MRC Human Nutrition Research

Elsie Widdowson Laboratory

Cambridge, UK

Dr Martin Riediker

Lung toxicity of nanoparticles

Phone interview: 19.07.2004

Institute of Occupational Health Sciences

Lausanne, Switzerland

Dr Jean-Jacques Sauvain

Lung toxicity of nanoparticles

Phone interview: 12.07.2004

Institute of Occupational Health Sciences

Lausanne, Switzerland

Dr Vicky Stone

Molecular and lung toxicity of ultrafine particles

Phone interview: 21.07.2004

Biomedicine Research Group

School of Life Sciences

Napier University

Edinburgh, UK

Jim Thomas

Environmental impacts of nanotechnology

Phone interview: 14.07.2004

ETC group (Formerly RAFI)

Oxford, UK

Appendix II: Questions to Nanoparticle Experts

(Date, Name, Position, Institution)

What have you studied in detail more recently? What did you find out from the studies?

Risks of nanoparticles

How would you describe the hazard and the risk related to nanoparticles? In relation to other hazardous substances/risks?

What do we know about the risks involved with nanoparticles today?

Is it possible to generalise or conclude anything on hazards and risks of nanoparticles?

What do you think about the hazards and risks? Which are the most potent risks as you see it? Why?

Hazards and risks of applications of nanoparticles

What kind of applications containing nanoparticles involves the greatest risks to your opinion? Why? What needs to be done?

Further research

What kind of research must be done? For instance: studies on hazards and risks, development of test methods, distribution of nanoparticles from products, risk analyses?

Precautions and risks

What kind of precautionary measures do you think should be taken to manage the risks? By the authorities in terms of regulations? By producers?

Final question

Do you know anybody else I should interview regarding the knowledge and perceptions of the hazards and risks of nanoparticles?

Appendix III: Questions to Producers

Status of precautionary measures survey

This questionnaire has been designed as a part of Master Thesis (Diplomarbeit) studies, where one theme is potential precautionary measures in occupational health and safety in nanoparticle industry.

As your company is handling nanoparticles, I would like to ask you some questions about the status in your company regarding the potential occupational health & safety precautionary measures.

Kind Requests:

- Answering the questions will not take more than 25 minutes of your precious time.
- If there is not enough space, please use the backside or an extra sheet.
- Please return it in any case even if you have only answered a few questions, by **FAX POST or E-mail by 30th of July 2004 at the latest.**
- All information will be confidential and will only be used in anonymous form
- Any questions or comments on the form, please contact me.

Your Details

Name:

Title/Position

Company:

Address:

Tel. No:

Email:

Return to

Asgeir Helland

Fax no.: +41-(0)71-274 78 62

Technology and Society Lab,
Research Unit Innovation and Technology Analysis,
Swiss Federal Laboratories for Materials Testing and
Research (EMPA), Lerchenfeldstrasse 5,
CH - 9014 St. Gallen, Switzerland
Tel. No + 41 (0)71-274 78 48
E-mail: Asgeir.Helland@empa.ch

Part A: In general about nanoparticles at your company

1. What kind of nanoparticles is the Company producing? Which size and for what use?

2. In what form (pure particles, bound to a matrix/coating/other) and size are they handled and delivered?

3. What is the production volume?

Part B: Risk and precaution

4. Are there any risks to health or the environment from nanoparticles as you are aware of? What kind of risks?

5. Does the company take any occupational health and safety precautionary measures when producing and handling the nanoparticles? (Use X mark)

	Yes
	No

6. Does the company take any precautions for reducing any potential environmental risk? (Use X mark)

	Yes
	No

7. What kind of precautionary measures does your company take (please be detailed)?

--

7.1 Why do you (not) take any precautionary measures?

--

Part C: Risk and occupational health

8. Are the nanoparticles hazardous to health or environment? (please elaborate)

--

8.1 How severe are these risks to your knowledge?

--

9. In general, what knowledge base is there regarding the hazards and risks of nanoparticles?

--

Part D: Test methods and regulations in occupational health

10. Which tests for assessing the health and environmental hazard has your company done?

--

11. Do you believe the existing test methods are good enough for assessing nanomaterials? Why/Why not?

--

12. Do you believe there should be occupation health regulations for the workers handling the nanoparticles? If any, what kind of?

--

I allow further contacts for clarification (Use X mark)

	Yes
	No

Thank you very much!

Technology and Society Lab,
Research Unit Innovation and Technology Analysis,
Swiss Federal Laboratories for Materials Testing and Research (EMPA),
Dr. Hans G. Kastenholz
E-mail : Hans.Kastenholz@empa.ch

Subject: Survey of the status of precautionary measures in occupation health.

To Whom It May Concern:

EMPA, a Swiss federal research institute belonging to the ETH domain, is heavily involved in researching nanotechnology and has several national and international projects going on. A part of this research is conducted in our group of Technology and Society Lab, where we are looking at the impacts of technological developments on society and environment.

EMPA confirms that Asgeir Helland is writing a Master Thesis (Diplomarbeit) for us, where a part of his work is to give an overview of the status of precautionary measures in occupational health and safety in industries involved in nanoparticle production. Asgeir Helland is a master student from the International Institute for Industrial Environmental Economics at Lund University, Sweden.

We would kindly request You to assist Asgeir Helland in his studies, as Your input would be very valuable for him and for us, giving a just overview of the status of precautionary measures. If You have any questions or comments, don't hesitate to take contact.

Sincerely,

Dr. Hans G. Kastenholz
Head of Innovation and Technology Analysis (ITA)

Appendix IV: Questions to Occupational Health Authorities

Questionnaire to Occupational Health Authorities

(Name, Position, Authority, Date)

Risks of nanoparticles in occupation health

What kind of hazards and risks are you aware of concerning nanoparticles in occupational health?

How severe are these risks to your knowledge? What other risks could they be compared to?

What kind of nanoparticles are known or thought to be of most concern? How do you know? Why is it a concern? (specify what is known and what is thought)

On which information sources is this based on? Scientific studies or is there someone who knows about this?

Nanoparticles and precautions

Would you suggest any precautionary measures for producers of nanoparticles? Why/why not?

And if any, what kind and in which situations would you suggest precautionary measures? Why? How would you follow up on them?

Future regulation of nanoparticles

Is there any plan to further regulate the occupational health conditions for workers in the field of nanoparticle production? In your country? EU? Elsewhere? Why/why not?

Nanoparticle risks in general

Are there any hazards or risks to the environment from nanoparticles as you are aware of?

Final Question(s)

Is there anybody else in your organization I should talk to?

Is there anybody else among the authorities I should talk to?

Appendix V: Interview with EC Representative

Phone Interview with EC Representative Dr Philippe Martin, 22.07-04.

Subject: EC-Representative Dr Philippe Martin, Directorate General for Health and Consumer Protection, Unit C7: Risk Assessment.

Does EC at the moment have any statistics or information over who the most important producers of nanoparticles would be?

I don't have information about who the most important producers of nanoparticles would be, but I am expecting to know this soon. The EC does not have any statistics on volume. This is not easy information to get, but it would appear that the greatest producers of nanoparticles would be in Germany and some activity in UK and France.

How is the EC working with the risk of nanoparticles?

The Commission has taken a proactive stand by convening an expert group and producing a report to look at the hypothetical risks associated with nanotechnology, which is the beginning of the involvement from the Commission on the side of risks.

What I would really like to stress is, as the experts pointed out, we cannot really yet talk about risks. We can talk about identified hazards, either through lab experiments or theoretical considerations. But as we don't have sufficient data on the exposure of populations, although you can infer that workers in factories producing nanoparticles would be the first one to be concerned, we don't really have data on exposure. We don't have enough data on dose-response either. Formally speaking we cannot say that we have produced a risk assessment, because you have to go from identified hazard to the exposure, to the dose-response and to a full characterization of the risks in the populations. However, this does not block the fact that we are moving. The other aspect is that we do know that a number of nanobased products are already on the market. I think it is generally agreed that we are still at the beginning of this nanotechnology revolution, therefore I think we are still in pace with the game in some ways. In the 'towards a European strategy' document, there are a number of actions that aim at promoting a risk awareness and then safe development of nanotechnologies, including the production of nanoparticles. This document is essentially a policy declaration and relatively non-binding for any of the parties mentioned in the text. In terms of following up this document, it will probably come out in early 2005 an action plan on nanotechnologies. Clearly this action plan is for the development and promotion of nanotechnologies, but this development will be done, in as much as we can, in a safe and responsible manner. All the actions that are boxed/mentioned in the Communication, they will be developed and in particular those that concern safety, responsibilities will be identified whether those are Community responsibility, responsibilities for other international bodies or national responsibilities.

How is the coordination between promotion of nanotechnology on one hand and 'going slower' with risk assessment on the other hand?

You will always have a chief-in-field Directorate General, but the Communication-document is a product of the whole Commission. In the production of this document, all the Directorate Generals were consulted and in particular we had very detailed and in-depth

discussions between the Directorate General of Research that launched the process, Directorate General of Employment that looks at the health and safety of workers, the Directorate General of Environment, Directorate General of Information Society and ourselves the Directorate General of Health & Consumer Protection. The original attempt is that we foresee benefits in these technologies, but we want the benefits in a safe and responsible manner. This was the approach chosen and found satisfactory to all the parties involved. I am not saying we will avoid all problems, but I think it is quite unique to have a new technology promoted in the way that from the start stresses the need to consider risks. It is early in the game, but being the institution that we are, we cannot move much faster. In parallel, the Health and Consumer Protection Directorate General has the responsibility of managing scientific committees composed of external experts who deliver opinions on questions that come either from within the Commission, mainly from the Enterprise Directorate General or the Environment Directorate General, as well as from outside the Commission, the European Parliament. Those committees will not remain idle, between now and 2005. Because we see this as an important issue, I can already indicate that the likelihood that those issues will be addressed is very high. Questions on nanotechnology will be asked to the committees.

Would it be a likely approach also in Europe, which is some of the critique against the National Nanotechnology Initiative in the U.S., that the environmental research of nanotechnology goes to applications and not for actually testing the technology in terms of e.g. toxicity testing?

Yes, it could go this way. But we are trying to play our political role to make sure that this is not the case. There is this possibility that you set aside a budget and it does not go to funding research that would help you on nano-toxicity. But in that line of reasoning, through our declaration and the statements that we have made, I think we support the idea that a) it is very important to do nano-toxicology and nano-ecotoxicology research and b) that this research is at the same time fundamental and very applied with immediate repercussion for public policy and public health in particular. Because the properties exhibited by nanoparticles in particular are unique and different from the bulk substance and therefore you basically have to redo the toxicology that you have done for bulk substances. I was very satisfied to know that a new journal was created which is the Journal of Nanotoxicology. We (EC) may have strengthened the position of the scientists that were developing this idea by expressing our position which is that this is a clear need, (nanotoxicology) and it has to be researched by European and national research budgets. Internally we make sure that money goes to that, and externally we make it known to national bodies of the EC and international bodies that this is a priority. There is series of things that can concern formal agreements, international agreements, new regulations or things that is written up, and then there is another effort which is getting messages through and encouraging the scientists who we believe are doing interesting works and give them references when they need them to promote their good work. Those are the two main approaches.

What is the role of the EC in terms of precautionary measures?

At this stage we are being cautious. We are being precautionary in the common language sense, but not invoking the Communication from the Commission 2000:1 on the precautionary principle. At this point we don't see the need to apply the precautionary principle, but we do see the need to be careful. In terms of legislation this is not the same thing.

We have to be precautionary, but we don't see right now, today, the need to invoke the precautionary principle as defined by the communication from the commission, because that is a legal formal definition of precaution which is linked to the idea that you will act in the case you have identified an issue, but don't have complete scientific information. Then there is a series of measures that can be used which range from asking for more research to requiring a moratorium. We are not placing ourselves in this legal framework.

We are now trying, in terms of precautions, to make sure that Europe finances research and projects that includes elements of risk awareness and risk analysis, so at least on the European level there is coherence between policies. You will not have the research policies financing dangerous research, so we want to make sure that research financed is not only safe, but that the scientists think about the long-term implications and include an assessment of the future or possible hypothetical risks.

We have also this communication on nanotechnology, which has a strong component on safety, and will be followed by an action plan involving both Community policy and the member states.

At the third level, the EC is active in securing informal and hopefully in a longer term formal agreements to ensure that we have a safe development of nanotechnology.

What about EC and precautionary guidelines, e.g. in occupational health?

Health policy and health & safety policy are national competences. There are other competences where the EC can be much more present, but here we have to be careful not to trespass the limits of our competences and therefore we have to leave it up to the national member states to handle those issues. However, we can make them aware of issues that we think they should address. In the short-term it will be up to the member states to do something about the issues, but our job is to make sure they cannot say they didn't know. And the same is the situation with industry, because we feel that industry must know and also must be known as knowing that there are hypothetical risks. I think it is fair to say that a number of companies are very well aware of these risks.

How would this awareness process happen?

It will take place in an official way, either through the process of releasing communications, accompanied by awareness raising campaigns and contacts in conferences. Communications are always accompanied by numerous contacts with public and private bodies. It is difficult to anticipate when this will happen for various reasons, but the action plan will probably be released in early 2005. The action plan will reinforce the issued raised in the communication, but we cannot say that we have identified any risk, only hazards.

What about Applications of Nanoparticles?

In this area we are not ahead of the game. We are facing a pre-existing situation and indeed decisions have to be made how to proceed. If it is perceived that the matter has to be re-examined, it will be, but this is something that is discussed at the moment. Clearly, if you look at the physics or the chemistry, it is fair to ask the question whether the legislation do apply in the same way if you have amounts of a different chemical substance. And then the question is: do we have the toxicological and ecotoxicological data that validates or

invalidates the hypothesis that the two products are different. We don't have an official position on that yet, but it is a part of our job.

How does the EC address the different variety of nanomaterials?

This is a very big challenge and we don't have a formal position on that yet. This is an important issue because you could have particles that are all in the nano-range, but still has different diameters and having different diameters, they will have different surfaces and hence surface properties likely, in particular reactivity properties that are different. This question is being studied also in U.S. at the moment, as it is no easy way out of this question at this point.

How would you see an REACH-approach as a possible approach for assessing nanoparticles?

It is too early to comment. It is also a question of policy/legislation formulations, which is not a part of the risk-assessment mandate I have. However, I do interact with colleges that do this. Anyway, I think it is too early to have a position on that, but clearly the EC is awake and the question has been raised informally.

What is going on concerning environmental risks of nanoparticles in Europe?

This has not been looked at a lot, even in the U.S. But people at the highest levels in Europe are interested in having research projects that look specifically at that. This is research that will advance science and be useful for public health and environmental health.