Health Council of the Netherlands

Working with nanoparticles: Exposure registry and health monitoring

Gezondheidsraad
Health Council of the Netherlands

To the Minister of Social Affairs and Employment

Subject : presentation of advisory report *Working with nanoparticles: Exposure registry and health monitoring*
Your reference : G&VW/GW/2009/18420
Our reference : I-254/JR/fs/818-J1
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Date : December 13, 2012

Dear Minister,

I hereby like to present the advisory report *Working with nanoparticles: Exposure registry and health monitoring*. In order to advise you, a committee of experts has examined the options for a registration and monitoring system, from a scientific perspective. I endorse the Committee's conclusions and recommendations.

Following the committee stage, the draft advisory report was checked by the Standing Committee on Health and the Environment. In addition, there were also two other deliberation sessions, which provided an opportunity for individuals to comment on the issues involved. The first was a working conference involving Dutch participants specially invited by the Committee. These included experts (and experts by virtue of experience) from industry, the research community and organisations operating in the area of occupational health. The second was a written public comment round for stakeholders both at home and abroad. The Committee has taken these comments into account in deciding on the definitive version of the advisory report.

The fields of nanoscience and nanotechnology are very dynamic, and much is still unknown. Accordingly, the same is true of our knowledge of the potential health risks associated with the use of engineered nanoparticles. The Committee therefore sees this advisory report as a snapshot. If developments proceed at their current pace, the Committee anticipates that, in a few years' time, it might have to make quite different recommendations in this regard.

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In the present report, the Committee presents outline details of an exposure registry and a passive medical surveillance system (health monitoring). This can be used to generate the data needed to determine whether there is an association between occupational exposure to engineered nanoparticles and certain diseases, or to disprove the existence of any such an association. These data are necessary to facilitate a more accurate assessment of the health risks involved. It is also needed to support decisions concerning the need to adapt such systems or to extend their operational lifetime. In addition, the Committee urges that more targeted research be carried out as soon as possible into the potential effects (both short-term and long-term) of occupational exposure to engineered nanoparticles.

If an exposure registry is to be established successfully, stakeholders must give due consideration to essential issues. Aside from commitment, this involves the traceability of engineered nanoparticles in nanomaterials, providing information about the properties of these particles, and raising awareness that materials which incorporate engineered nanoparticles are being used in the workplace. Moreover, employers and employees need well-considered and transparent communication about the uncertain risks of occupational exposure to these nanoparticles.

I have today sent copies of this advisory report to the Minister of Health, Welfare and Sport and the Minister of Infrastructure and the Environment.

Yours sincerely,
(signed)
Prof. W.A. van Gool
President

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Working with nanoparticles: Exposure registry and health monitoring

to:

the Minister of Social Affairs and Employment

No. 2012/31E, The Hague, December 13, 2012

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

The Health Council of the Netherlands is a member of the European Science Advisory Network for Health (EuSANH), a network of science advisory bodies in Europe.

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INAHTA

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Contents

Executive summary

Nanoparticles are particles with physical size limits of between 1 and 100 nanometres.* It has long been known that workers can be exposed to such miniscule particles. For example welding work, or the combustion of diesel fuel in engines can cause particles of this size to be unintentionally released into the air (nanoparticles generated by work processes). A new development is that humans have recently acquired the ability to assemble and produce very small pieces of material with well defined physical size limits. These engineered nanoparticles exhibit special physical and chemical properties, which offer the prospect of new or improved applications. The present report addresses these engineered nanoparticles (hereafter referred to as 'nanoparticles').

Their nano-specific properties give rise to the question of whether nanoparticles might be more harmful to human health and to the environment than larger fragments of the same substances. As regards the situation facing workers, the Minister for Social Affairs and Employment is concerned about this issue. This is because it may well mean that control measures normally used for these other substances are insufficient to protect workers' health. The Minister has asked the Health Council to examine the option of setting up an exposure registry. This would make it possible to link any health effects that occur (either immediately or at a later date) to occupational exposure to nanoparticles (or to rule out any such link). Secondly, he would like an assessment of the feasibility

* See the EU definitions of nanoparticles and nanomaterials in Section 2.1.

and usefulness of launching a health monitoring and/or early warning system. A Health Council Committee specially appointed for the purpose has examined these issues and has prepared this advisory report.

Increasing numbers of workers are handling products containing nanoparticles

More and more products on the market incorporate nanoparticles. These include textiles with antimicrobial action, self-cleaning windows, reinforced car tyres, paint products, and microelectronics. The nanoparticles that they contain consist of a variety of substances (carbon, metals, and metal oxides) and come in a variety of shapes (spheres, fibres).

The number of products that contain nanoparticles will probably increase over the next few years. This also means that increasing numbers of workers from various industrial sectors may come into contact with these nanoparticles at all stages of the supply chain, from research and development, manufacturing and production, to use, waste processing and recycling. Based on a small sample, it has been estimated that approximately three thousand people in the Netherlands are currently experiencing occupational exposure to nanoparticles. This is probably an underestimate, because by no means everyone is aware of the fact that they are working with nanomaterials. Moreover, even these random sampling studies were limited to certain parts of the supply chain.

While there are genuine concerns that exposure to nanoparticles can be harmful to human health, there is no direct evidence for this

There are genuine concerns that exposure (including occupational exposure) to nanoparticles can be more harmful to human health than exposure to larger fragments of the same substances. These concerns were prompted by animal experiments involving a just few types of nanoparticles, and by existing knowledge of particles and fibres (with physical sizes comparable to nanoparticles) created either naturally or, unintentionally, by human activities. Some investigators anticipate that respiratory and cardiovascular effects may occur. However, relatively little is known about this, and no systematic research has yet been carried out among those working with nanomaterials. It will probably be many more years before targeted epidemiological and toxicological research can establish (or rule out) any associations between adverse health effects and exposure to the many types of nanoparticles already in existence. Given the uncertainties involved, there is sufficient reason to be alert in the

workplace, and to take all due precautions when handling these particles and the materials into which they are incorporated.

An exposure registry is useful

Given the concerns and lack of knowledge involved, the Health Council considers it prudent to set up an exposure registry. Data from such a registry could be a valuable asset in the identification of health risks.

At what point should registration be considered?

Exposure registries of this kind should be set up for all insoluble nanoparticles (and for those that are poorly soluble in water) and for solid materials in which nanoparticles are incorporated. If the latter materials are in good condition, few nanoparticles will be released. However, wear and tear, and processing (e.g. drilling and sanding) may well cause such particles to be released.

The Committee intends to assign a lower priority to those nanoparticles that immediately disintegrate or dissolve on contact with water (or an aqueous environment), as they would not then meet the EU's definition of nanomaterials. It is assumed that these particles will dissolve in biological systems and that they will not behave any differently to regular substances (i.e. they will not exhibit any nanoparticle-specific toxicity). In the context of a risk analysis, they can be dealt with in the same way as other substances.

An initial understanding in the possible health effects of nanoparticles will most likely be obtained in occupational settings where frequent exposure takes place. Therefore, the exposure registry is intended for all companies and institutions in which it is clear that workers can be exposed to nanoparticles repeatedly and at fixed times. In the Committee's view, this does not include incidental use and accidents.

How should registration take place?

The purpose of the registry is to identify any relationships between exposure and health effects, or to rule them out. To this end, it must be determined whether and where exposure took place, and which nanoparticles were involved. The latter is important because it is nanoparticles' chemical and physical properties that determine their capacity to cause damage. In order to be able to establish whether exposure has actually taken place, data is needed to assess the risk of emission and exposure. In addition, it is the extent and duration of exposure determines

whether there is a risk of health impairment. Therefore data is also needed on exposure concentrations in the workplace. Regarding the latter, a number of questions concerning the capabilities and reliability of the measurement instruments still need to be resolved. For instance, what is the best exposure parameter for nanoparticles? In most workplaces, however, reasonable estimates of exposure levels can be made using currently available instruments.

These three types of data – chemical and physical properties, determinants of emission and exposure, and exposure concentrations – are the essence of a good exposure registry.

The Committee considers that, for effective registration, it is sufficient for data to be supplied at company level rather than at the level of individual workers. Furthermore, the registry should be updated whenever there is a change in the working situation. As soon as more knowledge becomes available on possible health damage, the company's personnel files can be used to find out who is (or has been) exposed and may, therefore, have run certain risks. In this connection, the Committee assumes that these personnel files contain detailed records of the positions that individual workers have held within the company.

With regard to those companies and institutions where nanomaterials are handled, as many as possible should take part. A systematic and uniform approach is vital if the registry is to be useful and effective. It is best if a registry of this kind is managed centrally, as this will facilitate the combination of data and checks for completeness.

The Minister enquired whether the exposure registry could be linked to existing registries, such as the Risk Inventory & Evaluation (RI&E) registry in the Netherlands, and the registry of the European REACH legislation. In both cases, data is included that the Committee considers to be necessary for the exposure registry, but the degree of data overlap is very limited. This is because RI&E and REACH were set up for different purposes. In brief, the Committee takes the view that there are limited options for linking to these systems. Nevertheless, part of their data can be used directly by the exposure registry.

Policy considerations affecting exposure registries

The Committee emphasises that a registry's chances of success could be adversely affected by issues outside the Health Council's remit. For instance, a number of measurement instruments are still in the test phase, and the physical and chemical properties of some nanoparticles are still unknown. Aside from this, there is also the question of whether the employers would be willing to contribute data. After all, property rights (including intellectual property rights)

are involved here. There is also the sheer size of the data set that has to be collected (in relation to production volumes and usage volumes). Furthermore, improved awareness on the part of the employers and workers is required, as by no means all labels indicate that products contain nanoparticles nor do they identify the nanoparticles in question. Efforts must also be made to achieve effective communication about the uncertain risks of working with nanoparticles. Stakeholders (policy makers, employers, workers) will have to discuss the matter and decide on the issues involved.

Medical surveillance could be used as a health-monitoring system

Health-monitoring systems can be used to detect changes in the health status of individuals or in the number of cases of disease in a population. A range of different methods are available. Like screening, health monitoring is used to detect previously-selected health effects. However, screening focuses on individuals, whereas health monitoring operates at population level. Medical surveillance, on the other hand, involves a continual focus on a wider range of as yet unknown health effects at population level. A system of health monitoring can be regarded as an early warning system, as it is capable of rapidly highlighting effects while they are still in the early stages.

The choice of system is dependent on the health effects that are expected to occur in response to nanoparticle exposure. If (as researchers suggest) these involve respiratory and cardiovascular effects, this raises the question of whether health monitoring should focus on these organ systems alone. This cannot be justified from the scientific point of view, given that much is still unknown and uncertain. By focusing on these two organ systems alone, less obvious effects (possibly of a severe nature) in other organs may be missed. Moreover, respiratory and cardiovascular diseases are common diseases in the general population, with a wide range of causes. Accordingly, this would make it very difficult to attribute, with sufficient certainly, any changes in the health status of an individual (and small changes in incidence or prevalence in the population) to nanoparticle exposure. For these reasons, the Committee does not advocate limiting a system of health monitoring to respiratory and cardiovascular effects. This means that it does not consider screening and health monitoring to be the best instruments for this purpose.

The Committee feels that medical surveillance is a viable option, as this is less dependent on prior details concerning the anticipated health effects. Effective medical surveillance requires that the following conditions are met. The data must be collected continuously and systematically, it must also be

complete and reliable. Furthermore, a high degree of participation is expected, and the surveillance must include as large a population as possible. Under these conditions, relatively small changes in health status can be detected.

Implementation through the exploitation of existing health registries: passive medical surveillance

The Netherlands has separate registries for the working population and the general population, both of which are continuously updated with health data. Accordingly, the Committee's initial approach was to determine whether these registries already contain sufficient information (passive surveillance). Despite the limitations of some of these systems, they do cover a great range of potential health effects. Collectively, therefore, they can provide valuable information in the short and long term. For this reason, the Committee takes the view that there is no point in setting up a separate medical surveillance system for nanoworkers (active surveillance). An extra argument is the high cost of setting up an entirely new system, given the current uncertainty about health risks.

The Committee emphasises the limitations of passive surveillance. It cannot provide quick answers about whether those who work with nanoparticles are exposed to any health risks nor, if this is indeed the case, can it rapidly identify the risks involved. However, the Committee believes that, when combined with targeted scientific research, passive medical surveillance systems of this kind could provide useful insights into the potential health risks associated with exposure to nanoparticles.

If such a surveillance system is to be of real practical use, it is essential that existing health data from the registries in question be linked to the new data in the exposure registry. Associations between exposure and health effects can be made using anonymised data, however these databases can only be linked by data that can be traced back to individuals. The Committee is fully aware that privacy legislation imposes restrictions on the provision of personal data. Informed consent must first be obtained. Other health monitoring systems are also bound by the same restriction.

Epidemiological research

This advisory report specifically addresses early warning systems for use in humans. The Committee also feels that epidemiological research has an important part to play. This type of research can provide valuable information, as passive medical surveillance may not be able to support reliable conclusions

about relationships between health effects and exposure. Indeed, epidemiological research is complementary to medical surveillance, and has the potential to enhance its focus. Accordingly, the Committee sees epidemiological research as an essential component of an early warning system.

Chapter 1

Introduction

1.1 Background

Nanoparticles are particles just a few millionths of millimetre in size. In recent years, with the emergence of nanoscience and nanotechnologies, the production of nanoparticles and nanomaterials has really taken off. This increase is reflected in the number of workers who are at risk of exposure to these materials. These engineered nanoparticles have special physical and chemical properties that differ from larger substances with the same composition.[1] Engineered nanoparticles, therefore, offer new or improved applications in areas such as cosmetics, electronics, medicines, clothing and building materials.

There is also the question of whether, as a result of their distinct properties, engineered nanoparticles might be more harmful to human health and to the environment than non-nano substances with the same chemical composition. The Minister for Social Affairs and Employment is concerned about the possible impact of this issue on workers, as the control measures normally used in connection with exposure to 'non-nano' chemicals may be insufficient to protect workers' health. In 2008, the Social Economic Council advised him (in line with the existing legislation) to get employers and workers to take all possible precautions to keep workplace exposure to engineered nanoparticles as low as possible.[2] The Social and Economic Council also reported that there is a need for an exposure registry, a health-monitoring system and/or an early warning system

in the area of health and safety at work. These two points prompted the Minister to approach the Health Council for advice.

1.2 Issues addressed

In September 2009, the Council received a letter in which the Minister requested its advice on an exposure registry and a system of health monitoring for occupational exposure to engineered nanoparticles. The full text of the request can be found in Annex A. In this request, the two main questions are phrased as follows:

1 What are the requirements for a registry of occupational exposure to nanoparticles that could be used to establish or rule out links to any subsequent health effects?
2 To what extent is it possible and useful when working with nanoparticles to set up a health monitoring system and/or early warning system? What conditions would such a system need to meet in order to work effectively?

The Minister has also asked the Council to examine specific sub-topics, such as the properties of the nanoparticles to be registered, high-risk groups among workers, anticipated health effects, options for linking up to existing registries, and international developments.

1.3 The Committee and its methodology

In December 2010, the President of the Health Council established the Committee on 'Handling nanoparticles in the workplace' (hereinafter referred to as 'the Committee') to prepare this advisory report. Details of the members of the Committee are given in Annex B to this advisory report.

The Health Council has previously issued advisory reports on related issues. In 2011, a horizon-scanning report was issued on the subject of the growing quantity of nanomaterials in waste, and the risks that this might pose to public health.[3] In a previous advisory report, the Council had addressed the significance of nanotechnologies to health.[1]

Outside the Health Council, in the area of safety and health, all kinds of activities are taking place in relation to the registration and control of occupational exposure to nanoparticles. In the Netherlands, an advisory report is being prepared by the National Institute for Public Health and the Environment (RIVM) on nanoreference values. In addition, a nano-specific module

'Stoffenmanager' has been developed by TNO, ArboUnie and BECO. Varies bodies are developing nano-specific control banding methods.* TNO is currently listing the applications concerned, as well as the relevant industries, and the number of workers who have been potentially exposed. Outside the Netherlands, too, there are a wide range of projects in progress. These include the European Union's Nanosafety Cluster projects, as well as projects by the British Health & Safety Executive's (HSE) Nanoparticle Occupational Safety and Health Consortium and the US National Institute for Occupational Safety and Health (NIOSH).

For the purposes of this advisory report, the Committee made use of publications by the above-mentioned institutions, as well as the medical and toxicological literature. It searched Medline and Toxline for terms such as risk assessment, nanoparticle*, toxicology, health surveillance, screening, industrial hygiene, occupational safety and the English names of nanomaterials. It also searched in publications which are not reported in these literature databases, via subject-specific internet forums and internet platforms.

In January 2012, the Health Council also held a working conference involving experts (and those who have become experts by virtue of experience) from Dutch industry, the world of research, and health and safety related organisations. Details of the participating individuals and organisations are given in Annex C. Furthermore in May 2012, the Council gave other experts (and those who have become experts by virtue of experience) from the Netherlands and elsewhere the opportunity to make written comments on the draft advisory report. Details of the individuals or organisations who responded to this are given in Annex D. The Committee made use of their comments and the information provided when drafting the final advisory report.

1.4 Demarcation

When describing nanoparticles or nanomaterials, the Committee has adopted the definitions used by the European Commission, with the restriction that this advisory report is limited to those engineered nanoparticles that are covered by these definitions. In the text, these particles are referred to as 'nanoparticles'. Natural nanoparticles and process-generated nanoparticles fall outside the scope of this advisory report. This document also relates to occupational exposure via inhalation in particular, as this is the most common exposure route in the

* See Subsection 2.6.2 for further details of control-banding techniques.

workplace. The advisory report does not address the guidelines derived from Dutch or European Working Conditions Policy, such as provisions concerning the preventive measures to be taken to prevent or minimise exposure, the Risk Inventory & Evaluation registry that companies are required to set up, and the REACH legislation. The associated guidelines have been drafted and reviewed both by government and industry.

1.5 Structure of this advisory report

In Chapter 2, the Committee defines the term ‘nanoparticles’, and describes their uses and potential adverse health effects. It also identifies those who can experience occupational exposure to these particles, and describes the steps taken by industry to determine and control the risk of exposure. Chapter 3 then goes into further detail about the exposure registry, while Chapter 4 addresses health monitoring. In the final chapter (5) the Committee answers the questions put by the Minister.

Chapter 2

Nanoparticles in the workplace

It has long been known that workers can be exposed to particles which are millionths of a millimetre in size. For example, during welding work and other forms of metal processing (e.g., cutting and surface treatment), mining activities or the combustion of diesel fuel in engines, particles falling within that size range are unintentionally released into the air (process-generated nanoparticles). Nanoparticles are also generated by normal physical and chemical processes, such as forest fires and volcanic eruptions (natural nanoparticles).[1,4-7] Recently, technologies to intentionally assemble and produce miniscule pieces of material with well-defined dimensions (engineered nanoparticles) have been developed. In so doing the material acquires different physical and chemical properties, which offer new applications for 'old' materials. This advisory report addresses the latter group of nanoparticles (engineered nanoparticles), referred to in short as nanoparticles.

Nanomaterials consist of nanoparticles, but what kind of particles are these? Are they really harmful? How many workers are likely to be exposed to these particles and materials, and what measures can be taken to ensure that workplaces are safe and pose no risks to health? These questions are answered in this chapter.

2.1 Nanoparticles and nanomaterials

When describing nanoparticles or nanomaterials, the Committee has adopted the definitions used by the European Commission*.

When describing nanoparticles, the European Commission in turn follows the recommendations of the International Organization for Standardization (ISO), which describes these particles as very small pieces of material with defined physical limits (ISO 146446:2007**).

The European Commission defines nanomaterials as natural, incidental, or manufactured materials containing particles (whether in an unbound state or as an aggregate or as an agglomerate), of which at least 50% of the particles in the quantified size distribution have one or more external dimensions in the 1 nm - 100 nm size range (see the Official Journal of the European Union L275, 20 October 2011). The European Commission also notes that:

- in specific cases and where warranted from the environmental, health, safety and competitiveness points of view, the threshold of 50% for the quantified size distribution may be replaced by a threshold of between 1% and 50%
- fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials
- an agglomerate is defined as a collection of weakly bound particles or aggregates, whose total external surface area is equal to the sum of the surface areas of the individual component
- an aggregate is defined as a particle consisting of strongly bound or fused particles
- materials can be described as nanomaterials if their specific surface area by volume exceeds 60 cm^2/cm^3. However, materials which qualify as nanomaterials on the basis of their quantified particle-size distribution should be recognised as complying with the definition of a nanomaterial, even if their specific surface area is less than 60 cm^2/cm^3.

The above definitions are based on a 2010 advisory report from the European Commission's European advisory body for new risks in science and technology (SCENIHR).[8] This body emphasises that, while a material's size can affect its physical and chemical properties, there is no scientific evidence to justify a lower and upper limit for all nanomaterials. However, it does indicate an upper limit for

* Source: http://ihcp.jrc.ec.europa.eu/, April 2012.
** Source: http://www.iso.org/, April 2012.

policy purposes (100 nm). As far as the lower limit of 1 nm is concerned, nanoparticles and clusters of nanoparticles of around 1 nm can scarcely be distinguished from molecules. In theory, with certain unnamed exceptions, molecules fall outside the definition of nanomaterials.

At the end of 2014, the question of whether these definitions need to be adjusted in line with new scientific and technological developments will be reviewed.

2.2 Diversity of nanoparticles

Developments in nanoscience and nanotechnology have resulted in nanoparticles of all shapes and compositions. These include nanotubes made of carbon and inorganic compounds, inorganic nanowires, organic nanofibres, biopolymers, nanoparticles of metals or metal oxides (nanosilver), carbon black (synthetic soot), and fullerenes (spherical molecules consisting of sixty carbon atoms). There are also films or plates that can be as little as a single atom thick, dendrimers (spherical, highly branched organic polymers), and quantum dots (nanocrystals of semi-conductor material). Most of these materials are made of carbon, titanium or silicon, but they also include metals (zinc, iron, cerium, zirconium, gold, silver, copper, lead, cadmium, germanium and selenium) and their oxides.[9]

Various bodies and researchers have attempted to impose a degree of order and harmonisation on the great diversity of nanoparticle types by creating systems of nomenclature, which are then used to classify nanoparticles into groups. In 2010, for example, ISO introduced the nanotree (ISO/TR 11360:2010*), a classification system that differentiates nanoparticles on the basis of structure, chemical composition and other characteristics:

- nanoparticles (all three external dimensions fall within the nano-range)
- nanofibres (two external dimensions fall within the nano-range), which can be divided into: nanowires (electrically conducting nanofibre); nanotubes (hollow nanofibre); nanorods (solid nanofibre)
- nanoplates (one external dimension falls within the nano-range).

For the purposes of toxicological research, Maynard and Aitken have suggested a classification that is partly based on physical and chemical properties, which are expected to determine toxicity:[10]

* Source: http://www.iso.org/, April 2012.

1 spherical and compact particles (homogeneous in composition)
2 high aspect nanoparticles (rods, fibres that are homogeneous in composition)
3 complex non-spherical particles (homogeneous in composition)
4 particles with a heterogeneous composition, where the surface has a different composition from the core, for example
5 particles with a heterogeneous composition, where one type of nanoparticle is incorporated into another (e.g. a spherical particle embedded in a non-spherical particle)
6 homogeneous agglomerates involving a single type of particle
7 heterogeneous aggregates involving several types of particles
8 active particles, in which the behaviour and properties of particles depend on external stimuli
9 multifunctional nanoparticles, in which the behaviour and properties of particles depend on functional responses and local environmental stimuli.

As yet, there is no standardised worldwide classification system for nanoparticles.

2.3 Applications

Nanoparticles display chemical, mechanical, optical, electrical and magnetic properties which can differ substantially from particles with larger dimensions, having the same chemical composition.[4,11,12] These differences are mainly due to the fact that nanoparticles have a much greater surface area per unit mass than substances in 'non-nanoform'.[4,11,12] This means that there are relatively more chemically reactive atoms on the surface, drastically increasing the particle's chemical reactivity. Furthermore, nanoparticles in the smaller nano-range behave in accordance with the laws of quantum mechanics rather than those of classical physics.[4,11,12] As a result, their optical, magnetic and electrical properties differ from those of substances outside the nano-range.

These 'new' properties have given rise to high hopes for new applications. Nanotechnology has already generated hundreds of consumer products which contain nanoparticles.[13] These mainly involve silver, titanium, cerium, silica and nanocarbon tubes. For instance, titanium dioxide and zinc oxide are used in sun creams. Normally these substances are white, but as engineered nanoparticles they are colourless, while retaining their ability to absorb and reflect ultraviolet light. Other examples include the use of carbon nanotubes as material strengtheners in car tyres and natural clay particles in car bumpers; nanocoatings used on spectacle lenses, scratch-resistant sensors and self-cleaning windows;

nanocrystals which make cutting and drilling tools extra hard and wear-resistant; nanomaterials which repel surface water and dirt; nanomaterials in the construction industry (paints, cement, glass); layers of nanoparticles used on foodstuffs and in textiles due to their antimicrobial effect; nanomaterials used to make clothing crease-resistant and dirt-repelling. Nanotechnology has also resulted in electronic devices that are becoming ever smaller, faster and more multi-functional. Nanomaterials have also found their way into medical applications, as in the development of new medicines, implantable materials and equipment, wound-care, and in diagnostic and analytical instruments.[13] In the food industry, nanomaterials are used throughout the entire chain (production, processing, packaging, preserving and supplements). They are also used in the energy and water technology sectors.[13]

The range of nanomaterials will expand further over the next few years, as many potential applications are still in the research and development phase.

2.4 Working population

Neither the Netherlands nor other countries have complete summaries of companies and institutions that are involved in the development or use of nanomaterials. Accordingly, it is difficult to estimate how many individuals might be exposed to nanoparticles in the course of their work. This is partly due to a lack of awareness in a number of sectors concerning the use of nanomaterials (particularly at the end of the chain of use). In addition, people are not yet familiar with certain applications, and nanomaterials are not clearly labelled nor are they mentioned in product descriptions.[14,15] This means that the published figures are probably an under-estimate. With this in mind, various studies carried out in the Netherlands and elsewhere give a rough impression of the number of workers who are potentially exposed to nanomaterials in given phases of the chain of use (based on small random samples). A brief summary is given below.

2.4.1 The Netherlands

Two studies have been published in the Netherlands. The first of these, by Borm et al. in 2008, deals with workers in the nanomaterial research, development and production sectors (first phases of the chain of use).[16] The researchers estimated that approximately four hundred employees in twenty-six companies and eleven research establishments regularly carried out activities involving nanomaterials. Approximately half of the cases involved the processing of carbon black, amorphous silica and metal oxides, in quantities amounting to several tonnes per

year. Other nanomaterials, such as carbon nanotubes, nanosilver and iron oxides were produced and used in much smaller quantities. The researchers also reported that 137 individuals in research establishments regularly worked on the development of new nanomaterials. In terms of quantity, the amounts of 'experimental' nanomaterials involved ranged from 1 gram to 100 grams per year.

In 2011, a joint TNO and RIVM report estimated that approximately three thousand workers could be exposed during the manufacture and use (including occupational use) of nano-end-products.[15] The conclusions in that report were based on different groups of workers than those used by Borm et al. (2008). The data in the TNO-RIVM report was obtained from 350 companies in various sectors. While they are mostly used in tyre production and concrete repair, nanomaterials are also used in the manufacture of paint and coatings, as well as in wet and prefab concrete. Nanomaterials are also regularly used by workers such as cleaners, motor mechanics, painters, coaters and textile cleaners.

2.4.2 *Europe and the United States*

A German institution, the BAuA* (working in cooperation with the chemical industry) submitted a questionnaire on the production and use of nanomaterials to 656 individual companies.[17] Of the 217 respondents, 45 companies indicated that they work with nanomaterials. Half of the latter group used no more than 100 kilograms of nanomaterials per year, while 11 percent processed more than 100 tonnes per year. In the majority (75%) of these companies, one to nine workers were handling nanomaterials. Only four companies had a workforce of more than 250 employees. Given the nature of this data, it is difficult to determine exactly how many workers were actually handling nanomaterials. Another study requested information from companies (87 of which were German and 48 Swiss) that were assumed to be working with nanomaterials.[18] Of the 40 companies that responded, 25 had fewer than 100 employees and six had a workforce of more than 1,000.

On the basis of questionnaires filled in by more than 900 Swiss companies, the Nano-inventory estimated that around 1,300 workers in the production sector were potentially exposed to nanoparticles.[19]

* The BAuA (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin) is a federal research institution in Germany which carries out specific research and advises on safe and healthy workplace issues.

In Britain, the HSE* estimated that, in 2004, approximately 2,000 nanoworkers were employed in British research facilities and in new companies that focused entirely on novel nanomaterials.[20] It also estimated that, in the same year, approximately 500 workers were involved in the production of carbon black on the nanoscale. Furthermore, it found that approximately 102,000 individuals (mainly in the pharmaceutical industry) might potentially be exposed to nanoparticles in the course of their work. Yet the HSE also stated that it is unclear how many of those in this group were actually being exposed to nanoparticles. The numbers involved were probably much lower, as some company employees (e.g. office workers) will not be exposed at all.

In 2007 the Nordic Council of Ministers, in which all Scandinavian countries are represented, published a report containing details of the uses of nanomaterials in these countries.[21] This showed that in Denmark, for example, around 50 companies from a range of sectors were using nanotechnology at that time. The corresponding figures for Finland and Sweden were 100+ and 85 respectively. No details were provided concerning the number of workers that might potentially be exposed.

In France, it has been estimated that, in 2007, between 2,000 and 4,000 workers were involved in the production of nanomaterials in various sectors of industry (excluding research laboratories).[22]

In the United States, 61 companies were found to be using carbon-based nanomaterials (such as carbon nanotubes, fullerenes, and graphene).[23] The study excluded those companies in which these activities were restricted to pure research and development, and which had no plans to scale up to commercial production within a period of five years. These companies had a total workforce of at least 620. It has also been estimated that the number of workers handling carbon-based nanomaterials increases annually by fifteen to seventeen percent.

2.5 Is working with nanoparticles harmful to health?

Various sources express uncertainty about the nature and magnitude of the health risks associated with exposure to nanoparticles. Yet, what is presently known about the risks involved? On the basis of scientific data, is there cause for concern? A short summary of the current situation is set out below.

* The HSE (Health and Safety Executive) is an independent advisory body whose task is to reduce work-related accidents and deaths in the workplace in the United Kingdom.

Table 1 Broad summary of toxicokinetics: mainly derived from animal research involving high dosages.

Route	Toxicokinetics
Inhalation	*Multi-walled CNT*: found in lymph nodes around the lungs and in the pulmonary pleura.[24,25] *Titanium dioxide*: found in the blood system.[26] *Silver particles*: found in various organs (lungs, liver, kidneys, spleen, and brain) in rats and mice. *Manganese and iron oxide nanoparticles*: found in brains of rats and mice.[27] Several studies indicate that nanoparticles (metals, carbon, quantum dots) could potentially be absorbed by the olfactory epithelium and then transported to the brain via the olfactory nerves.[28-31]
Skin	*Titanium dioxide*: capable of penetrating the skin, depending on the diluent and coating material involved.[25,32-36] *Silver particles in wound dressing*: present in the blood system of burns patients. *Gold particles*: smaller particles (12 nm in diameter) penetrate deeper into the skin than larger particles.[37] *Quantum dots*: depending on the composition of the coating, they were able to penetrate the skin and enter the bloodstream; they were subsequently detected in sites such as lymph nodes, liver and brain.[32,34,38-41]
Injection into the bloodstream	*Fullerenes*: found in various sites, including the liver, kidneys and spleen; capable of crossing the placenta.[25,42,43] *Titanium dioxide*: can cross the placenta; found in the foetal liver and brain.[43] *Nanoparticles of silver, copper and aluminium:* cross the blood-brain barrier.[44,45]

CNT, carbon nanotubes.

2.5.1 Toxicokinetics

The nature of a health risk mainly depends on whether exposure has actually taken place and, if so, on the level of exposure involved. However, the extent of the toxicity and the type of damage in question are also determined by the nanoparticle's potential toxicity, the area exposed, and the body's mechanisms for dealing with nanoparticles (toxicokinetics). The Committee briefly examines the issue of toxicokinetics below. In toxicokinetics, a distinction is drawn between absorption (absorption of a substance into the bloodstream via the airways, lungs, skin, and mouth), distribution (distribution of a substance through the body), metabolism (chemical conversion and breakdown of a substance into toxic or non-toxic breakdown products) and excretion (removal of the substance and its breakdown products from the body).

Table 1 summarises the findings for various types of nanoparticles. This data is mainly derived from animal experiments, as little human data is available. There is strong evidence to suggest that various types of nanoparticles are absorbed by the body (via inhalation and skin penetration), after which the blood system transports them to various organs. There are also indications that certain nanoparticles are capable of crossing the blood-brain barrier and the placenta, and that some can reach the brain via the olfactory epithelium and the olfactory

nerves. Remarkably, there is still very little data about the extent of their solubility in the body and about their excretion.

2.5.2 *Biological and toxicological effects*

Exposure to substances can cause biochemical, functional or anatomical changes in the body. These can consist of minor biological changes which occur rapidly but which then disappear again without causing damage or symptoms. Alternatively, there may be toxicological effects that damage organs and tissues to such an extent that they no longer function well, if at all. Sooner or later (if the body is unable to repair this damage), symptoms may appear.

Animal experiments

Data on the possible harmful effects on health are summarised in Table 2. Most of these studies addressed the short-term effects of exposure to carbon nanotubes, titanium dioxide and a number of other metal-containing nanoparticles, such as silver particles. Such research deals mainly with effects on the respiratory system and the cardiovascular system. This involves such conditions as rhinitis, inflammation in the respiratory tract and lungs, pulmonary fibrosis, and symptoms of thrombosis. There is also evidence that exposure to certain nanoparticles can lead to effects in the brain, skin conditions and pregnancy complications. One study found pulmonary tumours after an extended period (titanium dioxide), and, in a susceptible breed of mouse, mesotheliomas in the abdominal cavity (carbon nanotubes after intraperitoneal application).

As yet, it is by no means clear whether the effects found in animals can also occur at lower exposure levels in man. This is due to the high doses used in some animal experiments, and because the routes of exposure involved (injection into the bloodstream, insertion into the windpipe or abdominal cavity) are less applicable to human subjects. Furthermore a large part of this research was carried out just once, on one particular species of experimental animal, so it needs to be repeated by other researchers, preferably in other animal species. Also very little research has been carried out into the long-term effects of chronic exposure. On the other hand, the effects described are not species-specific and may well be relevant to humans.

Table 2 Broad summary of the reported effects in animal experiments.

Effects on:	
Respiratory system	Short-term effects. *Single and multi-walled CNT*: pneumonias, hyperplasia and pulmonary fibrosis.[24,25,30,46-54] Possible cause, overload.[55] *Fullerenes*: pneumonia, dependent on chemical composition.[25,38,56] *Carbon black*: rhinitis, pneumonia and pulmonary fibrosis.[57-59] *Titanium dioxide*: Pneumonia and pulmonary fibrosis; degree of effect dependent on particle size.[25,38,42,60,61] *Silver particles*: contradictory results as far as concerns pneumonia after inhalation.[25,37] Long-term effects. *Titanium dioxide*: one study found lung cancer in rats (but not in mice).[60]
Cardiovascular	Short-term effects. *Single-walled CNT*: accelerated formation of atherosclerotic damage in mice aortas.[62] *Single-walled* and *multi-walled CNT*, *carbon black*: evidence of vascular thrombosis (stronger reaction than *urban particulate matter*).[25,48,63] *Pure fullerenes*: no evidence of vascular thrombosis. *Quantum dots* (coated with carboxyl or amine): vascular thrombosis in the lungs (degree dependent on electrical charge of dots).[64] Long-term effects. No data.
Nervous system	Short-term effects. *Titanium dioxide*: damage to mice brains (particles introduced via the abdominal cavity).[27,29] *Nanoparticles of iron oxide or manganese oxide*: changes in brain activity.[29,65,66] *Nanoparticles of silver, copper or aluminium*: damage to nerve cells in brains (various exposure routes).[27,29,44,45] For aluminium, neurobehavioral changes have been described in mice (particles introduced into the nose).[67] *Silica nanoparticles*: evidence of damage in nerve cells in brain (particles introduced via the nasal cavity).[68] Long-term effects. No data.
Senses	Short-term effects. *Fullerenes*: negative for irritation and sensitisation to the eyes.[69] More research is needed for a definitive conclusion. Long-term effects. No data.
Skin	Short-term effects. *Single and multi-walled CNT*: skin disorders.[24] *Fullerenes*: negative for irritation and sensitisation.[69] More research is needed for a definitive conclusion. N.B., *silver particles in wound dressing*: discolouration of the skin and reduced liver function in patients with burns.[37,70] Long-term effects. No data.
Digestion and abdominal cavity	Short-term effects. No data. Long-term data. *Multi-walled CNT*: no tumours in rat abdomens after a single injection into the abdominal cavity (but these did occur in susceptible breeds of mice, and in rats, after the administration of asbestos fibres).[71,72]
Urogenitalia	Short and long-term effects. No data.
Locomotor system	Short and long-term effects. No data.
Reproduction and progeny	*Silicon dioxide and titanium dioxide*: pregnancy complications in mice, such as placental abnormalities (particles injected into the bloodstream).[43] *Titanium dioxide*: in mice, reduced sperm production in the progeny. *Fullerenes and silica particles* (> 300 nm): no pregnancy complications.[43]
Immune system	Short-term effects. *CNT*: exacerbation of allergic asthma. *Multi-walled CNT* may suppress the immune system.[30,58,73,74] Long-term effects. No data.
Hormone balance	Short and long-term effects. No data.

CNT, carbon nanotubes.

In vitro research

In vitro research (cell and tissue cultures) is used to determine whether nanoparticles have the ability to induce biological and toxicological reactions at the cellular level, and to identify the underlying mechanisms involved. It is used to explore issues such as inducing oxidative stress, cell death, DNA damage, pro-inflammatory reactions, changes in enzyme levels, and whether nanoparticles are able to penetrate cells and cell nuclei, binding to cell components to produce adverse effects. Similar effects have been described for carbon nanoparticles, fullerenes, carbon black, titanium dioxide, silver particles, cerium dioxide and quantum dots.[25,37,38,56,75-77]

Most in vitro research focuses on the oxidative stress caused by the formation of reactive radicals of oxygen and nitrogen.[4,78-85] Such radicals can damage proteins and genetic material.[86] The body has an efficient system for repairing such damage and for eliminating the radicals in question. However, that system can become overloaded by factors such as high exposure or reduced resistance (from various causes, such as illness or poor nutrition). Overloading results in oxidative stress. The damage to proteins and genetic material can then lead to cell death, tissue inflammation (which may be chronic in nature), and cancer.[86] Researchers assume that nanoparticles may induce greater oxidative stress than 'non-nano' forms of the same substances, due to their relatively high level of chemical reactivity at given mass concentrations. There is evidence that carbon nanotubes and engineered nanoparticles of titanium dioxide can cause oxidative damage.[48,49,54,87,88] In addition to oxidative stress, nanoparticles could mechanically interfere with components at cell level, ultimately leading to tissue damage and cancer.[78,79,89]

The Committee notes that in vitro research often involves exposure levels that are many times higher than might be expected in normal situations. There is also some doubt about whether current in vitro genotoxicity tests are a suitable way of determining whether fibrous particles have specific carcinogenic properties. This is because it is not known whether their structure would prevent them from reaching the cell nucleus, in which genetic material is stored. The results cannot simply be translated to humans on a one-to-one basis, as they do not take account of the organism as a whole. Nevertheless, in vitro research can support findings from animal studies and observational research. Alternatively, the findings from in vitro research may prompt such types of research, or they may identify a specific mechanism of action.

Observational research

There is still no epidemiological data concerning the possible short-term and long-term effects of engineered nanoparticles on health. Epidemiologists face a number of challenges, such as the enormous diversity of nanoparticles, the relatively short period for which nanoparticles are in production and use, problems in identifying the working population exposed, and a lack of clarity about the best health parameters to measure.[90-92,92] The most significant problem, however, is that observational studies require relevant exposure data. To date, little or no exposure data has been obtained for nanomaterials. The great heterogeneity of nanoparticles makes it difficult to find sufficient numbers of individuals who have been exposed to a given type of nanoparticle. Accordingly, it is difficult to establish an association between exposure and symptoms of disease. Until recently, exposure to nanomaterials was mainly limited to workers in scientific research establishments. In the coming years, however, such exposure will more often involve workers who produce and use nanoparticles or nanomaterials in various sectors of industry. This is a dynamic process, which makes it difficult to predict where occupational exposure will take place and who will be involved. There is also a lack of standardised exposure monitoring systems.

The first steps towards setting up epidemiological research among the working population have already been taken.[92] In Taiwan, a cross-sectional study has recently been carried out among 227 potentially exposed workers and 137 non-exposed workers. These individuals are employed by a number of companies that produce or handle nanomaterials with dimensions ranging from 20 nm to 100 nm. The aim of the study was to identify health effect markers for future research. The investigators found clearly reduced antioxidant enzyme activities among exposed workers, they also noted that the markers used to trace early cardiovascular defects (fibrinogen, intercellular adhesion molecules, and interleukin-6) showed elevated levels of activity. No abnormalities were found using markers for pulmonary inflammation, nor was there any difference in lung function between exposed and non-exposed groups.[93] In 2010, the Institut de Veille Sanitaire in France submitted a proposal to the French government for the establishment of an epidemiological surveillance system, consisting of a prospective cohort study and repeated cross-sectional studies.[94,95] The first phase involves the registration of workers who are likely to be exposed to nanomaterials, and the fleshing out of various emission and exposure scenarios. Health status will be assessed by passive health monitoring (consulting medical-administrative databases, accessing medical data from health services in the

workplace, and using questionnaires). In the United States, NIOSH is setting up an epidemiological study of individuals who are occupationally exposed to carbon nanotubes. Finally IARC is examining the feasibility of setting up an international epidemiological study into the health risks of nanoparticles.

2.5.3 *Knowledge acquired using particles (or nanoparticles) which arise naturally or unintentionally due to human activities*

The expectation that nanoparticles may be harmful to health partially stems from knowledge acquired with particles and fibres of comparable sizes that arise naturally or unintentionally (process generated) due to human activities. These include fine/ultrafine particles emitted during combustion, as well as occupational exposure to welding fumes and to asbestos and mineral fibres.[96,97]

Emission of fine or ultrafine particles during combustion

The fine or ultrafine particles released during the combustion of fossil fuels or domestic waste include soot particles, fly ash, and carbon black nanoparticles. Fine and ultra-fine particles (with diameters smaller than approx. 1,000 nanometres) from such sources can lodge in the deeper regions of the airways and the lungs for months and even years.[5] From here they can infiltrate into the lungs, enter the bloodstream and spread throughout the entire body.[42,98] Fine and ultrafine particles from combustion engines can cause tissue damage in the airways and lungs (inflammation, chronic obstructive lung diseases (COPD)), for example. They can also cause cardiovascular disorders, exacerbate allergic reactions (which can lead to asthma and COPD), and may also accelerate the decline of cognitive skills in the elderly.[5,42,51,63,96,98-105]

Some researchers feel that the results pertaining to fine and ultrafine particles in outdoor air are not necessarily valid for engineered nanoparticles.[106] They point to major differences between the outside environment and the workplace. In addition to fine and ultrafine particles, outdoor air often contains other substances that are known to cause health effects, such as sulphur dioxide, oxides of nitrogen, and ozone. It is unclear which components are specifically responsible for the reported health effects. Other factors, such as excessive traffic noise, can also have an impact on health. Studies into the effects of air pollution on the population also included high-risk groups, such as children, the elderly and the sick.[106]

Welding fume particles

Welding procedures can release inert welding fume particles into the air which, in terms of size, may fall within the nanoscale. These particles can then aggregate to form submicron particles, which just exceed the upper limit for nanomaterials of 100 nm.[107-111] Such particles consist mainly of iron and, occasionally, silicon. Articles in the literature describe various cases of welders who developed pneumoconiosis (welders'siderosis) or pulmonary emphysema during their working lives, resulting in reduced lung function.[112] There is some slight evidence from observational research to suggest that welding fumes may cause cancer (including lung cancer).[113] More recently researchers have found indications that welding fume particles may also increase the risk of ischemic heart diseases.[114,115]

Asbestos and synthetic mineral fibres

Some natural and synthetic fibres can lodge deep in the lungs after inhalation, of these asbestos fibres are regarded as the most harmful. In the long term, they can cause pulmonary fibrosis, lung cancer and mesothelioma.[51,116-118] In 2007, approximately four hundred people in the Netherlands died of mesothelioma, which – in almost every case – was attributable to asbestos exposure.[118] It has also been estimated that around nine hundred cases of lung cancer (12% of all cases of lung cancer) per year could have been prevented by avoiding occupational exposure to asbestos.[118] Of the synthetic mineral fibres, superfine glass fibres with a diameter of 100 to 3,000 nanometres come closest to nanofibres. Inhalation of these glass fibres can cause nasal inflammation and irritation.[119]

2.6 A safe and healthy workplace

A company's working conditions policy is aimed at creating and maintaining a safe and healthy workplace. Such policy is shaped by health and safety legislation and by Dutch and European policy on substances. This includes obligations regarding the listing and registration of any hazardous substances that might be present in the workplace, assessment of the exposure in question, and taking steps to prevent such exposure.

2.6.1 *Health and safety legislation and policy regarding substances*

The Working Conditions Act sets out the rights, obligations and rules for employers and employees regarding the improvement of working conditions.* In principle, employers are responsible for the safety and the health of their employees, with regard to all aspects of their work. To this end the employer implements a policy aimed at creating the best working conditions possible, in terms of state of the art science and occupational service provision. In terms of their behaviour in the workplace, workers are obliged to ensure their own health and safety as well as that of others involved, in accordance with the training and instructions provided by the employer.

European substances policy is also important, in terms of exposure to substances. Under Registration, Evaluation, Authorisation and Restriction of CHemical substances (REACH) legislation, all companies in a chemical substance supply chain (manufacturers, importers, users, customers) are held responsible for the safe use of such substances (production, import, trade, use), and for restricting risks to human health and/or to the environment.**

Given that there is currently no separate legislation for nanoparticles, our understanding of 'non-nano' substances is the guiding principle when implementing control measures. Some experts favour a special modification for REACH, to cover nanomaterials. Others take the view that, given their changed physical properties, it would be better for nanomaterials to be treated as entirely new substances, even though their chemical composition remains the same. These proposals are discouraged by the European Commission, on the basis that existing laws and legislation appear to be sufficient for the time being.[120,121]

The Social and Economic Council and the Minister of Social Affairs and Employment have also embraced the precautionary principle where occupational exposure to nanoparticles is concerned.[2,122,123] In cases of uncertainty, the goal is to be alert, careful, reasonable, and transparent. In an earlier advisory report, the Health Council stated that free, persistent nanoparticles lend themselves well to the application of the precautionary principle, given the great uncertainty about their behaviour, absorption and distribution in the body and their ability to cause and exacerbate disease symptoms.[124-126] Set against this great uncertainty, there is the fact of a plausible risk of health impairment, based on currently available

* More details about the regulations can be found on the Dutch government's website www.overheid.nl.

** For more details see http://stoffenbeleid.nl of the Dutch government.

data about fine and ultrafine particles and on current research into engineered nanoparticles. In the workplace, nanoparticles of any substance must be treated as hazardous substances.

2.6.2 *Inventory and registration*

Employers are under a statutory obligation to carry out a Risk Inventory and Evaluation (RI&E) procedure. Their compliance may be assessed by the Ministry of Social Affairs and Employment inspectorate.

Control banding is one of the methods that companies can use to produce an inventory of emission and exposure scenarios. This method is used to provide a qualitative opinion in situations where a quantitative opinion is not feasible, for example where there is a lack of information on toxicity, or where there are no appropriate standards (occupational exposure limit values). This is the current situation with regard to nanoparticles. Accordingly, new methods are constantly being developed specially for nanoparticles (examples: Cornelissen *et al*. (2010); Stoffenmanager Nano; CB Control Banding Nanotool; Control Banding by ANSES (France); Groso *et al*. (Switzerland); Brouwer 2012).[3,127-135] The essence of these methods is that a given nanoparticle is assigned a level of risk based on scores for a previously established series of factors (the severity of the risks and the probability of exposure). The levels of risk are then linked to specific control measures that have to be taken. For the moment, employers are not obliged to carry out control banding. They are free to use methods of their own, provided that these give good insight into the exposure and risks involved.

2.6.3 *Assessment of exposure*

In the event of exposure, the risks can often be assessed by checking the results of measurements in the workplace against occupational exposure limit values. A limit value is a substance-specific standard, a concentration in the air that is set by government or by industry. The value corresponds to the limit at which exposure becomes unacceptable. If measurements reveal a concentration in excess of the limit value, then mandatory control measures must be taken. An occupational exposure limit is based on scientific findings concerning the expected adverse health effects, and the relationship between the level of exposure and the occurrence of such effects.

The potential toxicity of many of the substances currently used in nanomaterials has been reliably determined for the regular (‘non-nano’) substances, and their limit values set.[136] Given the expectation that nanoparticles

are relatively more harmful than other forms of these substances, the limit values for inhalable and respirable dust (with low chemical toxicity) in Germany (DFG) and America (ACGIH) have been modified. In these countries, the relevant limit values no longer apply to nanoscale particles.[137-140]

Outside the Netherlands, separate occupational exposure limits have already been recommended for certain nanoparticles.[132] These are based on the results of a number of chronic (and sub-chronic) animal experiments. In America, for example, NIOSH* put forward a proposal for ultrafine titanium dioxide in 2005 and another, for carbon nanotubes, in 2011.[141,142] In addition, Bayer Material Science (a subsidiary of the German chemical company Bayer) has made a proposal for their Baytubes® (multiwall carbon nanotubes).[143]

Members of the international Organisation for Economic Co-operation and Development have also launched an initiative to generate the data needed to carry out a quantitative risk analysis on fourteen different engineered nanomaterials which are currently in commercially use (or will be shortly).[144,145]

A lack of information means that it is still not possible to set scientifically-founded limit values for on most nanoparticles. Accordingly, several countries have recently proposed various nanoreference values. These are temporary, pragmatic guidance values which are to be used until sufficient information becomes available. Nanoreference values are therefore not scientifically-derived standards, nor must they be used as such. Proposals for reference values have been made in Germany (IFA)**, the United Kingdom (BSI)*** and the Netherlands (RIVM).[146-148] Based on the IFA's proposals, RIVM has divided nanomaterials into four groups, and has indicated a nanoreference value for each group (see Table 3).

In 2012, the Social Economic Council examined RIVM's proposals, to determine whether they were feasible in practice.[149,150] Based on a pilot, it suggested some minor modifications to the system of categorising nanoparticles (see Table 4).

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* NIOSH (National Institute for Occupational Health and Safety) is a US federal agency that is responsible for carrying out research and making recommendations on the prevention of work-related disorders and accidents.

** The Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA) is a research institute which supports the German social accident insurance bodies and organisations in the area of scientific and technical problems relating to health and safety at work.

*** BSI is the equivalent of the English National Standards Body, a non-profit organisation, which, among other things, is involved in setting standards for chemical substances.

Table 3 Nano-reference values, as described in 2012 by RIVM.[148]

Description	Density	NRV	Nanomaterials
Carbon nanotubes for which asbestos-like effects cannot be ruled out.	-	0.01 fibres/cm^3	Carbon nanotubes for which asbestos-like effects cannot be ruled out.
Metals, metal oxides and other biopersistent granular nanomaterials with a diameter of between 1 to 100 nm.	> 6,000 kg/m^3	20,000 particles/cm^3	Gold, silver, iron, lead, titanium dioxide, cerium dioxide, zinc oxide, amorphous silica, aluminium trioxide, tin dioxide, cobalt oxide and nano clay.
Biopersistent granular nanomaterials with a diameter of between 1 to 100 nm.	< 6,000 kg/m^3	40,000 particles/cm^3	C_{60}, *carbon black*, titanium nitride, antimony oxide, polymers, polystyrene, dendrimers and carbon nanotubes.
Non-biopersistent nanomaterials with a diameter of between 1 to 100 nm.	-	Common occupational exposure limits	Examples: fats, hydrocarbons, siloxanes and ultrafine liquid particles.

NRV, Nano-reference value (8-hour time weighted average concentration).

Table 4 Nano reference values, as proposed in 2012 by the Social Economic Council.[149]

	Description	Density	NRV	Nanomaterials
1	Rigid biopersistent, nano-fibres for which asbestos-like effects cannot be ruled out.	-	0.01 fibres/cm^3	Carbon nanotubes or fibre-like metal oxides for which asbestos-like effects cannot be ruled out.
2	Biopersistent granular nano-materials with diameters ranging from 1 nm to 100 nm.	> 6,000 kg/m^3	20,000 particles/cm^3	Gold, silver, cerium dioxide, cobalt oxide, iron and iron oxides, lead, antimony dioxide, tin dioxide.
3	Biopersistent granular and fibre-like nanomaterials with diameters ranging from 1 nm to 100 nm.	< 6,000 kg/m^3	40,000 particles/cm^3	Aluminium trioxide, silicon dioxide, titanium dioxide, zinc oxide, nano clay, C_{60}, *carbon black*, dendrimers and polystyrene. Nanofibres for which asbestos-like effects have been specifically excluded.
4	Non-biopersistent nanomaterials with diameters ranging from 1 nm to 100 nm.	-	Common occupational exposure limits	Examples: fats, siloxanes and common salt.

NRV, Nano-reference value (8-hour time weighted average concentration).

2.6.4 *Control measures*

Employers are required to take certain control measures, based on their inventory and evaluation of exposure. To this end, they must adhere to the occupational hygiene strategy set out in the Working Conditions Act. Control measures can be introduced according to their priority. These can include source, organisational and technical measures, as well as personal measures. Prevention through design is a useful concept, with regard to sources of emission and exposure. This involves modifying nanomaterials and production processes at the design stage to keep toxicity and emissions as low as possible.

2.7 Evaluation and conclusion

Increasing use is being made of engineered nanoparticles in all sectors of industry. Accordingly, a growing number of workers are being exposed to these materials throughout the chain of use (development, production, use, recycling and waste). There is also the issue of the sheer diversity of nanoparticles involved, in terms of composition, shape and size.

2.7.1 *Are nanoparticles harmful to health?*

The initial toxicological studies (which mainly involved animal experiments) indicated that the inhalation of nanoparticles can be harmful to both the respiratory system and the cardiovascular system. There are also signs of effects on damaged skin, the central nervous system, and reproduction. Nanoparticles can enter the bloodstream more readily than larger particles. This gives them easy access to various organs and may also allow them to cross the blood-brain barrier and the placenta. Skin exposure can lead to skin inflammation, and damaged skin can give nanoparticles access to the bloodstream. A number of nanoparticles appear to have the potential to cause cancer in experimental animals, which the Committee sees as a cause for concern. This is all the more serious in view of what is already known about particles (and nanoparticles) and fibres that are created naturally or unintentionally by human activities (soot particles, fly gas and carbon black created by burning fuels, welding particles, asbestos and synthetic mineral fibres). Such agents have been shown to cause respiratory and cardiovascular diseases in humans.

This has to be set against the fact that the above-mentioned findings relate only to a very limited number nanoparticle types (carbon nanotubes, fullerenes,

titanium dioxide and silver nanoparticles). No toxicological research has yet been carried out on most other types of nanoparticles. Moreover, such research as has been carried out is limited to animal experiments and in vitro studies. These studies do not yet provide a comprehensive picture of the full range of possible adverse effects on health. For instance, very little research has targeted chronic exposure and long-term effects, such as cancer. The toxicological mechanisms that might account for this, such as oxidative stress and the resultant tissue damage, are indeed relevant to the human situation. However, it should be borne in mind that some animal experiments involved exposure routes (injection into the bloodstream or abdominal cavity, introduction into the trachea) and elevated dosage levels that would not normally be encountered by human subjects.

Ultimately, the risk involved derives both from exposure to nanoparticles and from their potential toxicity. As yet, there is no evidence to suggest that exposure to certain engineered nanoparticles might damage human health. However, the available data provides sufficient grounds for exercising caution when handling nanomaterials.

2.7.2 A healthy and safe workplace when working with nanoparticles

The Working Conditions Act dictates that employers must provide a safe and healthy workplace, and that workers must adhere to any measures taken in this regard. The same applies to nanoparticle exposure. Given the uncertainty surrounding the nature and magnitude of the health risks involved, every effort must be made to keep exposure as low as possible. Tools such as nano-specific control banding and nano reference values have been specially developed to effectively identify and evaluate the risks associated with handling nanoparticles.

Chapter 3

Exposure registry

An exposure registry is needed for companies and institutions where nanomaterials are handled in any way in the chain of use, which can potentially lead to exposure. In this chapter the Committee sets out guidelines concerning the type of information that would need to be collected by such registries. It also outlines the conditions that would have to be met if these registry systems are to succeed.

3.1 Why register cases of exposure?

The Minister primarily views a nanoparticle registry as a means of determining whether links between exposure and any detected health effects (occurring either immediately or at a later date) can be established or ruled out. In addition, registries are commonly used in situations involving known hazards and health risks, but they can also be used where such hazards are merely suspected. Registration systems are no substitute for scientific studies, but the data collected by this means (if applied in a systematic and well-considered way) can be a useful source of information for such research activities.[106,151,152] Nor, indeed, is registration the same thing as a notification system, as the latter involves a central authority and is generally subject to additional requirements. Nevertheless, these two systems can supplement and overlap each other.

In addition, exposure registries at individual level should make it possible to identify those who were exposed and to determine whether anyone is at greater

risk of health damage as a result. Within companies, exposure registries can be used to determine whether control measures are required and, if so, to identify the measures in question. They can also be used to determine whether current measures need to be tightened up. Finally, such registries can be a useful aid in risk communication and awareness-raising.[151,152]

3.2 Which cases should be registered?

A great deal of data on all types of nanoparticles or nanomaterials is needed to establish or rule out links between exposure and disease. Given the continuing lack of clarity concerning the potential toxicity of nanoparticles, the Committee is of the opinion that all nanoparticles which are either insoluble or poorly soluble in water must be registered, irrespective of their physical state or form. Accordingly, this also covers solid materials that incorporate nanoparticles and meet the European definition of a nanomaterial. If such materials are in good condition they will release few, if any, nanoparticles. However, they can be released as a result of normal wear and tear, as well as during handling (such as drilling and sanding). The Committee assigns a lower priority to nanoparticles which immediately disintegrate or dissolve on contact with water (or with an aqueous environment), such that they no longer satisfy the definition set by the European Union. It is assumed that such particles will dissolve in biological systems and will, therefore, behave no differently to 'non-nano' substances (i.e. they will exhibit no nanoparticle-specific toxicity). This does not, of course, mean that water-soluble nanoparticles do not cause adverse health effects.

An understanding of the potential health effects of nanoparticles will most likely be obtained in occupational settings where frequent exposure takes place. The exposure registry is therefore intended for all those companies and institutions where it is evident that workers may be exposed to nanomaterials repeatedly and at specified times. In the Committee's view, this does not include incidental use and accidents.

Given the current limited understanding of such matters, there are no scientific grounds for including or excluding specific groups of workers (or certain sectors of industry) that handle nanomaterials.

3.3 Examples of existing registries

3.3.1 Europe and the United States

A number of countries have launched projects to register occupational exposure to nanoparticles. In France alone (CEA) this results from a statutory obligation to register and to give notification of the occupational risks to individual workers that result from exposure to chemical substances. Various other initiatives are voluntary in nature, but differ in terms of their organisational form. For instance, Defra (a British government department) and the American Environmental Protection Agency have both developed registration programmes and are asking companies to supply certain data. All of these registries are centrally managed. There are also some in-house initiatives, such as the registration system developed for internal use by the AFRL/ASC in America.

Country, initiator	:	United Kingdom, Department of Environment, Food and Rural Affairs (Defra).
Name of programme	:	Voluntary Reporting Scheme (VRS), a two-year pilot study, launched in 2006.[153,154]
Aim	:	To gather more knowledge about the properties and characteristics of different nanomaterials to be able to better identify the potential dangers, exposure and risks, and be able to adopt more targeted control measures in the future.
Type of registry	:	Defra manages the data of all registered companies. Registration of companies and research institutions is on a voluntary basis.
What data is collected?	:	At company level: these include the identity of the nanomaterials in question, their chemical and physical characteristics, their use, production process, risk of exposure, data on the life cycle of the material, and toxicological data, if available (see Annex E).
Findings	:	Very few companies participated (just thirteen forms were filled in, eleven by companies, two by scientific institutes). According to Defra, the reasons for this include the large amount of detailed data requested (and the associated costs), concerns about property rights, and the fact that companies did not feel that the system was of any benefit to them. Both Defra and the British stakeholders involved are currently considering ways in which the VRS might be improved still further. The major issues under discussion include the question of whether all such matters might not be better regulated at European level, voluntary versus obligatory participation, and the employers' desire for a registration system which is limited to basic data.
Country, initiator	:	United States, Environmental Protection Agency (EPA)
Name of programme	:	Voluntary Nanoscale Materials Stewardship Program (NMSP), pilot programme in 2008.[155,156]
Aim	:	The collection of existing data, the generation of new data and the development of good practices.
Type of registry	:	Companies provide the data requested on a voluntary basis, the EPA then manages it centrally on their behalf.
What data is collected?	:	At company level: this includes general information about the company, information about identification, the chemical and physical characteristics of the nanomaterial in question, production and user information, information about exposure (qualitative and quantitative) and information about applied control measures (see Annex F).

Findings	:	By the end of 2008, 29 companies had supplied information which collectively involved 123 different nanomaterials. The EPA considers the NMSP to be successful, yet there are still some issues that need to be addressed. For example, participation is low compared to the total number of companies using nanoparticles, the data supplied does not always appear to be complete, and the EPA notes that a number of companies are unwilling to take part and to supply any information about their nanomaterials. The EPA is currently reviewing options on how to proceed, in order to obtain the information required.
Country, initiator	:	France, Commissariat à l'énergie atomique et aux énergies alternatives (CEA).
Name of form	:	Nanospecific individual exposure sheet.
Aim	:	The development of a registry for the routine collection of qualitative and quantitative data on the conditions and characteristics of exposure. The initiative was prompted by the introduction of mandatory notification.
Type of registry	:	CEA registers the exposure conditions for each worker.
Participation	:	Five to six hundred employees, mainly working in laboratories. Participation is obligatory in the context of French legislation on working conditions for those working with chemical substances.
What data is collected?	:	Use of nano-specific exposure forms developed in-house, which are based on a CEA general exposure form. Such forms must be filled in for each worker (see Annex G).
Findings	:	Not reported.
Country, initiator	:	United States, Air Force Research Laboratory (AFRL) and the Aeronautical Systems Center (ASC)
Name of form	:	Personal nanomaterial exposure record.[157]
Aim	:	The promotion of risk communication and management; according to the initiators, the data may in future also prove useful for epidemiological research.
Type of registry	:	Collection of data on individual employees of AFRL and ASC, who are mainly working in research laboratories.
What data is collected?	:	Each employee has a record. The records are digital (via WINGS™, Web-interface nanotechnology environmental safety and health guidance system) and can be filled in either by the workers themselves or by an occupational hygiene expert.
Findings	:	Not reported.

3.3.2 *The Netherlands*

There are already specific exposure registries for the workplace. For example, there is a national dose registration and information system (NDRIS) for occupational exposure to ionising radiation. This is managed on behalf of the Ministry of Social Affairs and Employment by the Nuclear Research and Consultancy Group. The registration of ionising radiation is a requirement of the Nuclear Energy Act, and notification is mandatory. It concerns individual dosage data that are retained for up to thirty years after the termination of the activity in question. The registry currently contains data on around one hundred thousand individuals. For the purposes of the registry it does not matter whether workers move to another company or institution. Any workers who go abroad (on a temporary basis) to work are given a radiation passport, in which exposure data

must be recorded. When the worker in question returns to the Netherlands, this data is entered into the NDRIS.

The Dutch Working Conditions Act also contains special provisions on the registration of carcinogenic, mutagenic, and reproductiontoxic substances. In essence, such data remains in the possession and management of the company or the institution at which the worker is employed. There is no central registry, nor is there is a system for updating a worker's exposure history when they take up a new post elsewhere. Supplementary provisions are included for asbestos, relating to the measuring methods and reference period used for the purposes of measurement. In addition, the sampling procedure used must be representative of the individual's exposure to asbestos dust. For each worker who is occupationally exposed to asbestos dust there must be an entry in the register giving details of the nature and duration of the work in question, as well as the level of exposure involved. The data must be anonymised for non-experts (employer, staff representatives).

In the Netherlands, there are no registries specifically for nanoparticles. However, companies are required to draw up an RI&E for all possible work-related health risks, which includes an inventory of the exposure conditions. Accordingly, this also applies to companies that produce or process nanoparticles.

3.4 What is the minimum data required to identify the health risks involved?

Any attempt to obtain a reliable picture of the nature and level of exposure, and of the associated risks, requires data on the physical and chemical properties of nanoparticles, on the determinants of emission and exposure, and on the level and duration of any exposures. These three types of data are closely interrelated. For example, it is the physical and chemical properties of a nanoparticle that determine its ability to inflict damage. If it is of only limited potency in this respect, then such damage will generally occur only in association with higher levels of exposure. Data on the determinants of emission and exposure are therefore necessary to obtain a picture of the emission and exposure scenarios, which in turn give an insight into the risk of exposure. If there is indeed a risk of exposure, then the level and duration of the exposure in question determines whether the individual concerned will ultimately suffer damage to their health. This is why the Committee feels that it is important for these three types of data to be collected in an exposure registry.

3.4.1 Data on chemical and physical properties

Nothing is known concerning the properties that determine the potential toxicity of nanoparticles, but this is likely to involve a range of properties of varying potencies.[10,26] Given that physical and chemical properties can vary from one type of nanoparticle to another, it is also likely that their potential toxicity will show similar variation. Researchers in this field have therefore proposed that toxicological evaluations should include descriptions of various physical and chemical properties.[10,158-164] Following these developments, the ISO has proposed a guideline for characterising engineered nanoparticles.[165] The eight properties set out in this guideline are:

- *Particle size and size distribution*. Due to their small size, nanoparticles can cross barriers in the body, allowing them to penetrate organs, cells, and cell components.[166] Another consideration is that, in practice, many nanomaterials contain nanoparticles of various sizes. For example, if different aerosols or suspensions of the same nanomaterial have a different particle size distribution, that can affect the degree of toxicity involved.
- *Tangling*. As they become further removed from the source of emission, nanoparticles which initially entered the air in free form generally form condensation nuclei, agglomerates or aggregates. The resultant particles can ultimately be larger than 100 nm.[26,167-169] Airborne nanoparticles can also bind to larger dust particles from other sources.[169] This means that, on inhalation, nanoparticles generally do not have the same shape and size as they did at the source of the emission. This also means that these agglomerates and aggregates may possess physico-chemical properties that differ from those of the 'free' nanoparticles, which in turn can affect their toxicity.
- *Particle shape*. Nanoparticles are engineered into all kinds of shapes, ranging from simple spherical particles to fibrous structures to complex non-spherical structures. Current knowledge about asbestos fibres and synthetic mineral fibres shows that biological systems have greater difficulty in removing fibrous structures than non-fibrous structures, such as spherical particles.
- *Surface area (and specific surface area) of particles*. The total surface area of nanoparticles is greater per unit mass than that of larger non-nano particles (see Table 5). A larger surface area also means that more chemically reactive compounds are in contact with the biological system in question. This means that, for a given unit of mass, nanoparticles have a higher level of toxicity than particles that fall outside the EU's definition of nanoparticles.[4,11,12]

- *Composition*. This involves information on aspects such as chemical composition, whether the nanomaterial in question has a crystalline structure, and whether contaminants are present.
- *Surface chemistry.* Some chemical compounds are more reactive than others. As a consequence, one compound may have a greater potential to induce damage than others. The compounds in question are located on the surface of nanoparticles.
- *Surface charge*. Various studies with cultured cells and bacteria have shown that strongly negative or positive charges (expressed as the zeta potential of particles in colloidal suspension) on the surface of nanoparticles can boost or reduce their uptake by cells relative to uncharged nanoparticles of the same type. This affects the level of toxicity involved. Tests have been carried out with a range of nanomaterials, including nanoparticles of cerium, silicon, gold and silver, as well as quantum dots.[64,170-176]
- *Solubility and dispergation.* Solubility is the extent to which nanoparticles dissolve in water and the rate at which they do so (either by binding to water molecules or by disassociating to form ions). Dispergation relates to colloids, emulsions and suspensions.

Other physical properties that, in the literature, have been associated with the potential toxicity of nanoparticles are polarity, density, and hardness, as well as their optical and magnetic properties.[10,158-164]

The Committee considers the eight properties listed above to be sufficiently relevant to merit their inclusion in an exposure registry.

Table 5 Diameter, number and surface area of particles in the same mass concentration of 10 µg/m^3.[4]

Number of particles per cm^3	Diameter (nm)	Surface area of particle (µm^2/cm^3)
153,000,000	5	12,000
2,400,000	20	3,016
1,200	250	240
0.15	5,000	12

µg/m^3, micrograms per cubic metre; µm^2/cm^3, square micrometres per cubic metre.

3.4.2 *Determinants of emission and exposure*

Two approaches can be used to analyse the determinants of emission and exposure.

One of these relates to process design.[177-179] Production processes are described in three dimensions. The first of these is the *production function*, which addresses the question 'what?' and the difference between the initial phase (before a process step is carried out) and the final phase. The second is the *production principle* which addresses the question 'how?', i.e. how the production function is carried out. The final dimension is the *type of implementation* which addresses the question 'with what?', and describes how production principles are actually implemented. A detailed explanation of these dimensions is given in Annex K. A number of examples taken from the scientific literature on design analyses for nanoparticles are given in Annex I.

Another approach involves a step-by-step analysis from the source of emissions to exposure in the worker's breathing zone (source-receptor approach), like the one recently developed for nanoparticles.[180,181]

The analysis of technical design and the source-receptor approach give comparable lists of determinants of emission and exposure, although they involve quite different approaches. They also complement on another very effectively, as a worker's risk of exposure depends on the strength of the emission source (or sources) and the level of transport between the source and the worker. The determinants of emission and exposure are, therefore, inextricably interlinked. The determinants listed point-by-point below trace the entire process, from emission to exposure in the breathing zone, in accordance with occupational hygiene strategy.

Emission determinants:

- starting materials (quantity, particulate nature of the product, whether or not they are incorporated in a matrix (e.g. particles in suspension))
- process implementation (mixing, separating, surface treatment)
- how the process is implemented (manually, mechanically or automatically; continuous versus batches)
- and the setting in which the process is carried out (open or closed systems).

Exposure determinants:

- shielding from the source (or sources) (e.g. separate work areas, local separation, and insulated cubicles)

- local control measures (e.g. ventilation and spraying of water during machining operations)
- data on general ventilation (mechanical and natural ventilation)
- surface contamination from contaminated work clothing, equipment, tables, or tools (can be reduced by measures such as good housekeeping and wet cleaning)
- the worker's position in relation to the emission source or sources (sources close to the worker have a greater effect on exposure in the worker's breathing zone than comparable sources at a distance)
- the work environment (inside versus outside; size of space).

The extent to which nanoparticles actually reach the worker's skin or breathing zone is determined by the use of personal protection equipment.

3.4.3 *Exposure measurements*

Exposure measurements can give a clear indication of whether or not an individual has been exposed, and if so, to what extent. In the workplace, the focus is on exposure through the air, as this is generally considered to be the main route of exposure. The Committee recognises that harmful effects on health can also follow exposure via the skin (by direct contact with suspensions or powders) or via the mouth (e.g. from food that has been contaminated by contact with unwashed hands, and by swallowing nanoparticles that have been captured by mucus in the respiratory system). However, the Committee has opted to disregard the latter routes and to devote the whole of this subsection to exposure via the air.

Exposure parameters

There is some question as to whether the usual measure of exposure for chemicals (mass concentration) is indeed the most suitable measure for nanoparticles. With regard to fibres, their specific dimensions in combination with the number of fibres involved has proved to be a good predictor for certain health effects.[182] Particle surface area could be another suitable measure. The greater a particle's surface area, the greater the likelihood of interaction and, therefore, of toxic effects.[183] Various experimental animal studies and laboratory studies (e.g. of titanium dioxide particles, carbon black particles, and amorphous silica particles) have shown that the use of particle surface area gives a better

relationship between exposure and response (as far as infections of pulmonary tissue and airway tissue are concerned) than mass concentration.[61,75,184]

In the literature on nanoparticles, exposure is reported using a range of different exposure measures. This makes it difficult to compare data. In an attempt to resolve this difficulty, various strategies have been devised to achieve standardisation and international coordination.[26,185] In America, for example, NIOSH has introduced the Nanoparticle Emission Assessment Technique.[186,187] This involves a determination of the mass concentration and number of particles in the air. Air samples are then filtered and any materials trapped on the filter are collected for further characterisation by electron microscopy. A comparable measuring strategy has been proposed by an international working group operating within the context of the European NANOSH project.[188,189] In Germany, various institutions have put forward a joint proposal for a tiered approach.[190] This involves a series of steps, with decisions at each stage about whether exposure measurements are needed and, if so, which measurements can be best carried out. Similar work is also being carried out in the Netherlands. The NanoNextNL* joint venture, for example, includes a project that is specifically aimed at characterising and measuring exposure to nanoparticles in the workplace. At the end of 2011, TNO hosted an international workshop aimed at harmonising the measurement strategies used in relation to nanoparticle exposure.

Measuring instruments

The most commonly cited instruments used to determine the above-mentioned measures of exposure are summarised in Annex J. This annex also contains details of some instruments that are used to characterise various particle characteristics, in particular particle size and size distribution.

However, these instruments need to be assessed to determine whether they are suitable for making routine measurements of exposure through the air in the workplace. Preference is given to instruments that are portable and easy to operate. These would permit personal exposure measurements to be made in the breathing zone, during working hours. Results can be read off straight away, and are specific to the type of nanoparticle that is being handled.[26] Ideally, such an instrument would simultaneously record all the measures of exposure.

* NanoNextNL is a joint venture between Dutch industry and knowledge institutes. For more information, see www.stw.nl.

None of the instruments referred to in the annex are ideal in this respect. For example, most of them are too heavy to be portable, which means that only fixed measurements can be made. Other instruments require specialist knowledge. Nearly all of these instruments are non-specific, i.e. they cannot distinguish between particles with different chemical compositions, nor between free particles and agglomerates or aggregates. It should also be noted that many instruments are designed to measure spherical particles, and their response to high-aspect-ratio nanomaterials is largely unknown. Furthermore, with current technology, the smaller the particle the lower the instrument's accuracy. Many instruments are unable to detect particles below the 10 nm to 20 nm size range.[168,182] Instruments that measure particle surface area are often based on the BET (Brunauer Emmett Teller) method.[191] The BET method calculates the total surface area (including internal surfaces), not just the active or outer surface area.[192] The BET area corresponds to the actual area, as it includes the areas of pores within particles. The BET can also be used to calculate the sum of the surface areas of every particle in an agglomerate. In such cases, however, data on particle surface area may not be entirely relevant, as aggregation and/or agglomeration affects the interaction with biological systems.[164] Although internal surface area generally correlates well with toxic effects, as yet there are no portable instruments that can be used routinely to measure the internal surface area of nanoparticles.[75,184,193,194]

On the other hand, there are a number of new instruments, either in development or in the test phase, that negate the objections mentioned above (the EU Nanodevice project; Cena et al.[195]; Asbach et al. 2012[196]). Examples of these instruments are given in Annex J, such as the NanoCheck and the NanoTracer. However, the NSAM, the Matter Diffusion Size Classifier or the Condensation Nucleus Counter (CNC/CPC) can also be used to obtain a fair estimate of exposure levels. A nanoparticle's shape can be determined by scanning or transmission electron microscopy. This involves collecting samples of particles in the workplace, and having them analysed in a specialist laboratory.

In addition to exposure instruments, there is also a need for certified reference materials to facilitate internal quality control of the analysis results. In this connection, the European Union's Joint Research Centre has recently developed twenty-five different nanomaterials that can serve as reference materials.*

* Source: http://ihcp.jrc.ec.europa.eu/our_activities/nanotechnology/european-repository-reference-nanomaterials.

This section has shown that currently available instruments are sufficiently accurate to provide reasonable estimates of exposure levels, although many issues still need to be resolved before ideal measurements can be achieved.

Examples of exposure measurements

Exposure to nanoparticles has been measured quantitatively in a number of workplace studies. In most cases, these were peak-related and task-related measurements, rather than eight-hour measurements.

Development and manufacturing. NIOSH carried out fixed exposure measurements in a research laboratory where carbon-nanofibre containing materials were produced.[197] When such material was undergoing wet grinding, elevated carbon levels of 1,094 µg/m^3 were detected in the air, yet the average levels in adjacent offices were no more than 17 µg/m^3. Processes such as weighing nanofibre powders and mixing them with solvents also resulted in elevated carbon levels in the air. Elevated levels were also found on work area surfaces and on benches near the grinding equipment. There were also indications that nanofibres had spread to the offices via the inside air and via the floor (on which particles had been deposited). Most of the airborne fibres and those on surfaces were present as agglomerates and not as free-fibre particles.

More recently, NIOSH also carried out exposure measurements at six companies where carbon nanotubes/carbon nanofibres were handled. The samples (both individual-based and task-based) were analysed by measuring the inhalable and respirable mass concentrations of elemental carbon. In addition, the structure of the carbon nanotubes in question was analysed by transmission electron microscopy. At two companies, concentrations in excess of 7 µg/m^3 were found. These levels were measured during powder handling processes, such as mixing and weighing. The levels measured in the other manufacturers' workplaces were below this level.[198]

End-users. Arbouw* recently published the results of a small-scale exposure study of construction industry workers.[199] These subjects were exposed to nanomaterials such as titanium dioxide, silicon dioxide and zinc oxide (in cement and concrete, paints and lacquers, and glass), as well as to nanoclay (in paints and lacquers). The greatest risk of exposure was during cutting, blasting, drilling and machining, or when inhaling the aerosols released during paint spraying (using wall paint or other paints). All of these cases involved brief, high peak

* Arbouw is a foundation established by Dutch employers' and employees' organisations to improve working conditions in the construction industry.

exposures. When converted into eight-hour values, the concentrations in question were 258 particles/cm^3 (spraying of a self-cleaning coating) and 1,014 particles/cm^3 (mixing NanoCrete mortar). Both cases involved personal measurements. At another site, where workers were drilling into hardened concrete, measurements were carried out in fixed positions. These values varied from 46 to 132 particles/cm^3 (Nanocrete concrete) and from 35 to 64 particles/cm^3 (normal concrete). In this connection, it is worth noting that the nano reference value advised by SER is 20,000 particles/cm^3. It is not clear to what extent this study is representative of the construction sector as a whole.

A TNO report gives details of indicative exposure measurements at six different companies.[15] The number of particles entering the air was mainly influenced by the application technique being used and by the conditions (ventilation, outdoor air). Spraying and squirting for example produced the highest particle concentrations (8,000 – 39,000 particles/cm^3), indeed these even exceeded the background concentration. Activities involving rolling, brushing or pouring did not result in any noticeable increase in the number of particles in the air relative to background values.

The literature contains a wealth of such measurements, many of which involve studies performed outside the Netherlands.[25,186,187,200-204]

3.4.4 *Registry form*

In Annex K, the Committee outlines the type of data that it considers to be important, in terms of deriving a good picture of the nature and level of exposure. It also gives details of the data needed to establish (or rule out) a link to any subsequent health effects. In addition to the three types of data described in Subsections 3.4.1 to 3.4.3, this also involves general information on the company or institute in question, details of the identity of the relevant nanomaterials (if applicable) and nanoparticles, and workers' job-related tasks. The registry distinguishes between situations in which nanoparticles are incorporated into products, and those involving the production or use of discrete nanoparticles. Ultimately, the Committee’s main focus is on the nanoparticles themselves, and details of their physical and chemical properties have been requested.

The Committee sees Annex K as a starting point for a dataset that is as complete as possible. The data contained in this annex show a degree of overlap with data requested for various registry projects outside the Netherlands (see Annexes E to G), and with a registration form designed in the context of the European Union's NANEX-WP2 programme (Annex H).

3.5 Preconditions for implementation

To be successful, a registry must have the right structure and it must be properly implemented. To this end, a number of preconditions have to be met.

- *Registration at company level.* The Committee is currently of the opinion that it is acceptable for data to be supplied at company level, provided that this is sufficiently detailed. For example, in the light of new knowledge, it may become necessary to trace individual workers who are likely to have been exposed, as matter of urgency. Such individuals can then be easily traced from the data contained in personnel files. The Committee is assuming here that the personnel files in question will also contain details of each worker's tasks or job description.
- *Updating*. The registry is not intended to store one-off data records. Emission and exposure scenarios can change over time, so it is important to register these changes.
- *Non-voluntary registration.* Examples of practice outside the Netherlands show that voluntary schemes have relatively low participation levels, and this is a matter of concern for the Committee (see Subsection 3.3.1). The low level of participation is due to problems with property rights (product information) and intellectual property rights. In addition, employers are reluctant to provide what they see as excessive amounts of data. They indicated that the time taken to collect this data was out of all proportion to the production and usage volumes involved. The Committee believes that everything should be done to achieve a high level of participation. Given the present shortage of data, each individual contribution is immensely important.
- *Central management.* For a registry to be truly effective, it must be based on a systematic, structured and uniform system. This will ensure that any data collected can be combined into a single, uniform dataset that will make it possible to identify any links between exposure and adverse health effects. According to the Committee, central management (by a government body or an independent organisation) would be the best option. Also, experience has shown that the lack of a central management system tends to undermine the effectiveness of registries.
- *Who has access to the registry?* This is a difficult question for the Committee to answer as it involves many issues that fall outside the Health Council's remit, such as privacy legislation and property rights. However, it is important that anonymised data be made available for research purposes.

- *Raising awareness*. Under current regulations, manufacturers and importers are not required to indicate that their products contain nanoparticles, nor are they required to identify the nanoparticles in question. As a result, some people may be unaware that the company handles nanomaterials. This can be an obstacle to an effective exposure registry. Accordingly, it is essential for companies to be properly informed.

3.6 Linking up with existing registry systems (or co-implementation with such systems)

The Committee looked into the question of whether it might be possible either to link an exposure registry for nanoparticles to existing exposure inventory systems, or to implement the registry within these systems. The Netherlands, for example, has RI&E and REACH registration systems. Some of the information that has to be collected for these systems is also required by the exposure registry, and could be used directly. However, the degree of data overlap in question is rather limited. RI&E and the registry for REACH were created with different objectives in mind. Furthermore, their structure and operation differs from that required by the exposure registry envisaged by the Committee. RI&E, for example, is intended to provide an assessment of the anticipated occupational risks within a given company. Its design varies from one company to another, or from one industrial sector to another, which makes it impossible to combine data. With regard to the REACH registry, producers and importers are required to supply details of the substances they produce. Producers are not currently required to indicate whether their products contain nanoparticles. Moreover, they are only required to register if production (or import) levels exceed one tonne per year. Finally, this only applies to producers, which only account for a portion of the chain of use. Although a small proportion of the data collected in RI&E and REACH might also be usable for the exposure registry, the Committee does not believe that it is feasible to link this registry to these systems (or to implement it within them).

Foreign registry projects (see Subsection 3.3.1) also have a degree of overlap with the data that the Committee would like to collect. However, they are less compatible in terms both of their design and the amount of data that they require. In addition, many of these are trial projects, so it is not clear whether they have a long-term future. For this reason, the Committee is hesitant about participating in these projects. Nevertheless, the results obtained in these projects could prove very useful to a future exposure registry.

3.7 Does the registry require a distinction to be drawn between different categories of nanoparticles?

The SER has proposed classifying nanoparticles into four categories, each with its own mandatory control measures:[2]

a fibrous, insoluble nanoparticles (length > 15 µm)
b nanoparticles which in their molecular or 'larger particle form' are known to be carcinogenic, mutagenic, reprotoxic and/or sensitising
c insoluble or poorly soluble nanoparticles (which are not included in one of the above categories)
d soluble nanoparticles (which are not included in one of the above categories).

The classification is based on the physical properties of nanoparticles, their anticipated health effects, and their toxicological mechanisms of action. With regard to the nano reference values, the SER follows the classification proposed by RIVM (see Subsection 2.6.3). These categories are based on biopersistence, particle size, and whether the nanoparticles can be expected to produce asbestos-like adverse health effects. The categorisation differs from the above classification, moreover, it is not comparable.

The primary aim of an exposure registry is to be able to establish or rule out links to any adverse health effects. Since so little is known about nano-specific toxicity, there are no scientific grounds for excluding certain nanoparticles from the registry. An exception to this are nanoparticles that immediately disintegrate or dissolve on contact with water or an aqueous environment, at which point they no longer satisfy the EU definition of nanomaterials (as stated at the beginning of this chapter).

Thus, there is a great need for information on all types of nanoparticles. In addition, the data required for the registry is universally applicable, as the same types of data are required to obtain a reliable picture of the nature and level of exposure, regardless of whether the particles in question are spherical in shape or biopersistent nanofibres. In short, the Committee rejects the use of a nanoparticle classification system for the purposes of an exposure registry.

3.8 High-risk groups

Those who regularly work with nanoparticles and who are at risk of exposure can be regarded as a high-risk group. This is the group of workers who are the first to come into contact with nanomaterials. In addition, they probably encounter

higher and longer-lasting exposures than members of the working population who do not work with nanomaterials, and the general population.

In the workplace too, environmental factors associated with the work (degree, duration and pattern of exposure, and exposure to mixtures) can mean that one nano worker is at greater risk than another. The exposure registry will identify the circumstances in which this is the case.

3.9 Evaluation and conclusion

Given that exposure to nanoparticles is expected to involve health risks, the Committee believes the establishment of an exposure registry to be a useful precautionary measure. A registry of exposure should be kept in companies of all sizes where workers are potentially exposed to nanoparticles repeatedly and at fixed times. This applies to all nanoparticles, regardless of their physical form or composition, except for those that disintegrate or dissolve immediately on contact with water or with an aqueous environment.

Three types of data are required to obtain a picture of the nature and level of exposure, to make it possible to establish or rule out any links between exposure and health effects. These are: a) data on the chemical and physical properties of nanoparticles that enable their toxic properties to be identified; b) data on the determinants of emission and exposure, to understand the circumstances of exposure; and c) data on the exposure concentrations involved. The measurement of exposure concentrations involves a number of questions relating to the potential and reliability of the instruments use to measure nanoparticles. In most situations, however, reasonable estimates of exposure levels can be made using currently available instruments.

The data required should be provided at company level, and the registry should be updated if there is any change in the situation. Furthermore, as many companies or institutes as possible should take part. It is also important that a systematic and uniform approach is used, and that the registry is managed centrally. The advantages of a central registry are that the data can be combined and checked for completeness more easily. It is also important to raise companies'awareness concerning the handling of nanomaterials.

The Committee has assessed the options for linking the registry with RI&E and the REACH registry (or for using them in its implementation). In both cases, some of the data collected is identical to that required by the exposure registry, but the degree of overlap involved is very limited. This is because RI&E and the REACH registry were set up to meet different objectives. Accordingly, the Committee feels that there are limited options in terms of linking and

implementation, nevertheless some of these systems' data could readily be used by the exposure registry.

While the potential lifetime of this registry cannot yet be determined with any certainty, this will mainly depend on any future scientific insights that may be obtained.

Chapter 4

Health monitoring and early warning systems

On the basis of the limited scientific knowledge on nanoparticles (whether engineered or produced unintentionally), there are well-founded reasons for vigilance when working with these materials. Health monitoring and early warning systems can be a useful way of maintaining such vigilance.

A health monitoring system offers a means of detecting any ongoing changes in the health status of individuals or in the number of cases of disease in a given population. If this system enables early effects to be detected rapidly and systemically, it can be regarded as an early warning system. Current health tracking systems include screening, health monitoring, and medical surveillance. Which of these systems is selected depends on the extent of available knowledge concerning the health effects in question, and on whether the system needs to be used at the level of the individual or at the level of the population. It is quite possible that the same protocols or medical tests will be used by each of these different systems. The questions are which health system is most appropriate, how can it best be set up, and what are the relevant preconditions.

4.1 Screening

The primary aim of screening is to limit the development of a certain disease, preferably at a stage in which affected individuals have not yet developed any symptoms (early warning, targeted approach). Screening is about detecting treatable changes in the health status of an individual, and is characterised by

effective predictive tests that can be carried out quickly and easily. One such example is the screening of women for breast cancer, using mammography. Another is the specific hearing test given to workers who are at risk of developing noise-induced hearing loss.

No screening programmes are currently available, anywhere in the world, for individuals who work with nanoparticles. In the Netherlands, however, the periodic occupational health examination (PAGO) or preventive medical examination (PMO) could be seen as a type of screening. Employers are obliged to offer this to workers if, after all control measures have been taken, a health risk still remains. The PMO consists of questionnaires, a medical examination and possible follow-up tests, depending on the worker's job, the associated degree of exposure, and any associated risks that might be anticipated. The results of the PMO are subject to privacy rules and regulations, which means that they cannot automatically be used by third parties, or by employers. With some exceptions, workers cannot be obliged to take part in a PMO.

Screening is only useful if a number of basic criteria are met, such as:

- actual or potential exposure
- strong evidence that exposure can lead to certain harmful health effects
- the availability of medical tests that can detect health effects related to exposure, preferably at an asymptomatic and reversible stage.

In addition to the basic criteria there are a number of further considerations, such as information about the burden of disease in the working population; the effectiveness of early detection; potential harm caused by the screening; intervention options that cause the risk factors to disappear; whether the benefits that can be achieved outweigh the disadvantages; fostering support; the costs involved; risk perception, and effective communication.[106,205]

Point a) Is there any occupational exposure to nanoparticles?

Occupational exposure to nanoparticles occurs, but details are still lacking concerning the extent of such exposure, the working conditions in question, and the number of individuals involved. A future exposure registry could provide a more accurate picture of these issues.

Point b) Is occupational exposure to nanoparticles harmful to health?

Initial toxicological studies in experimental animals and parallels with fine and ultrafine particles that occur naturally or those that are created unintentionally due to human activities have aroused the Committee's concern (see Section 2.5).

These studies indicate that inhaling nanoparticles may cause health effects by damaging the airways, lungs, heart, blood vessels, and other structures. However, much is still unclear. The animal studies conducted to date have been limited to just a few types of nanoparticles. Nor has any systematic observational research yet been carried out. Similarly, there has been no research into long-term effects, for example.

Point c) Are any medical tests available that can be used to trace relevant nano-related health effects?

These include tests that provide information about the biological effects involved (biological effect monitoring), functional changes (health check), and ultimately about the disease itself (diagnosis). The PMO already involves tests such as blood and urine tests (such as sensitisation tests for allergens, and cytogenetic tests in the event of exposure to radiation) and hearing tests.[106]

Some researchers have suggested that exposure to nanoparticles may lead to respiratory and cardiovascular effects. Accordingly, they want to focus on tests that trace adverse changes in the organ system concerned (respiratory system, heart, and blood vessels) at an early a stage as possible. This could include measuring heart rate variability, analysing the blood for early indicators of inflammation and cardiovascular parameters.[152] One possible drawback, however, is that these effects occur frequently in the general population, and that they can result from various non-work-related causes. As a result, it is currently impossible to say whether the effects revealed by a positive test result for a given individual were caused by occupational exposure to nanoparticles.

The Committee concludes that the most important prerequisites for the successful implementation of a screening programme to limit the development of disease in individual workers have not yet been fulfilled. This is because the exposure side has not yet been fully identified, nor is there yet a complete picture of the potential harmful health effects involved. The Committee takes the view that limiting screening to respiratory and cardiovascular effects would serve little purpose, as these effects occur generally and a positive result at the individual level cannot be correlated with exposure to nanoparticles. In short, regarding exposure to nanoparticles, the Committee currently feels that it would not be particularly useful to screen individual workers (whether as part of the PMO or in some other context).

At international level, the Committee's conclusion is shared by health and safety experts who are actively engaged in assessing healthy and safe working practices for chemical substances and nanoparticles.[90,100,205-207] It emphasises

that screening is only useful if the hazards of certain nanoparticles have been identified and characterised. Only then will it possible to detect any preclinical changes in a targeted way with a medical examination. This is why periodic screening for individual nanoworkers is not used anywhere outside the Netherlands. In America, however, NIOSH feels that, in the near future, it will be possible to screen workers who handle carbon nanoparticles and titanium dioxide. This is because the health effects of these particles are much better understood than those associated with other such agents.[152]

4.2 Health monitoring

Health monitoring is the periodic measurement of health (or underlying determinants) to be able to establish changes in the health status of populations. It is used, for example, to determine the influence of interventions on certain health effects or to identify the long-term effects of disasters. Health monitoring can also be used as an instrument to detect the existence of a risk (or elevated risk) of a given health problem. Like screening, health monitoring for individuals who work with nanoparticles is not used anywhere in the world. In the Netherlands, however, there are instances of the use of health monitoring in connection with certain environmental factors. One example is the Gezondheidskundige Evaluatie Schiphol (health evaluation and monitoring programme for Schiphol airport) research programme, which is being carried out by RIVM. This involves an exploratory study into potential health and quality-of-life effects resulting from the environmental impacts of air traffic and airport activities.

Health monitoring is useful only if the health problem in question is sufficiently specific to be linked (to some extent) to nanoparticle exposure, and if this problem occurs with sufficient frequency (in relation to the anticipated risk) to indicate statistical certainty. As with screening, a complete picture of the potential health effects is still lacking. Furthermore, the anticipated respiratory and cardiovascular effects are multifactorial in nature and occur so generally that, at population level, it may be difficult to attribute small changes in incidence or prevalence to nanoparticle exposure with any certainty. For these reasons, the Committee takes the view that health monitoring, too, is not yet a suitable instrument for tracking the health of those who handle nanoparticles.

4.3 Medical surveillance

As with health monitoring, medical surveillance can be used as a detection system to identify trends in diseases and risk factors. The major difference between the two systems, however, is the frequency of measurement (periodic in the case of health monitoring, continuous in the case of medical surveillance) and the focus on certain health effects (more targeted in the case of health monitoring, less so in the case of medical surveillance). In fact, medical surveillance provides the data required for future assessments of the usefulness of screening or monitoring workers' health (either individually or as a group). The signals picked up by medical surveillance can also be used to formulate the specific research questions needed to initiate targeted toxicological and epidemiological research, for example.

Thus, unlike screening and health monitoring, medical surveillance does not require such a detailed knowledge of the anticipated health effects. This is because the latter embraces all of the possible health effects covered by health registries. Of course, if there are already well-founded suspicions about which area is involved, medical surveillance can be targeted specifically at these effects. In cases such as these, medical surveillance is already verging on health monitoring. With regard to nanoparticles, the Committee favours an examination of the entire range of potential health effects (both short-term and long-term). By avoiding a premature focus on a limited number of effects, such as respiratory and cardiovascular effects, this will ensure that nothing is missed. Indeed, if these specific effects were to occur, this would be revealed by general medical surveillance.

With this in mind, the Committee has focused more closely on the medical surveillance options for work involving the handling of nanoparticles.

4.3.1 Implementation and conditions

If medical surveillance is to be truly effective, data must be collected continuously and systematically. The data in question must be complete and reliable. Furthermore, there must be a high level of participation and such surveillance must cover as large a population as possible, preferably the entire country. In addition, given the current uncertainty about potential health risks, it is best if the early symptoms of disease development are picked up as soon as possible (early warning). Nonetheless, it is certainly also important not to lose sight of any potential long-term effects. The question, therefore, is how medical

surveillance can best be carried out under these preconditions. To this end, the Committee initially assessed the usefulness of data from existing health registries for the working population and the general population (passive surveillance).

Working population

The working population is served by the national registry of work-related diseases, and the special surveillance schemes of the Netherlands Centre for Occupational Illnesses (Nederlands Centrum van Beroepsziekten, NCvB). Occupational physicians and some medical specialists use these facilities to report cases of occupation-related illnesses. Most of the cases in the national registry relate to instances when workers are seen by occupational physicians, in connection with sickness absenteeism. In some instances, however, notification of cases may also occur following a PMO. The occupational physician determines whether the health condition in question is work related, and then reports to the NCvB. In the special surveillance schemes for work-related lung conditions and work-related skin diseases, pulmonary specialists and dermatologists submit monthly reports to the NCvB on new cases of work-related conditions. However, the NCvB systems are not without their drawbacks. For instance, in regular health care (general practitioners, medical specialists), work-related diseases may often be missed if no causal link is established between a patient's work and their symptoms (e.g. if they present with generally occurring symptoms). In cases such as these, no notifications will be submitted to the special surveillance schemes. As a result, there will be a high likelihood of under-reporting. Reports issued by the NCvB itself also show that by no means all company doctors report cases of occupational illness, which makes the likelihood of under-reporting even greater.[208]

General population

- Virtually every hospital in the country is affiliated to the Netherlands Medical Registration System (LMR), which contains data on hospital admissions and discharges.[209] All diagnoses are registered in the LMR (including respiratory tract conditions and cardiovascular illnesses) in accordance with a standard classification system. Until recently, the register was virtually complete, covering the whole of the country and containing data on diseases which develop both in the short term and the long term. One limitation, however, was that the LMR only contained details on patients who had been admitted to hospital for at least one day. As a result, outpatients

could have been missed. As yet, there are no details concerning future changes to the LMR. What is known is that, in 2014, the LMR and the National Ambulant Care Registry will be remodelled, modernised, and merged into a single integrated database, the National Base Registry for Hospital Care.

- The mandatory reporting of causes of death to Statistics Netherlands, by physicians. [209] This register is virtually complete. It contains data on diseases which can develop both in the short term or the long term.
- The Dutch Cancer Registry (NKR).[209] All cancer patients are registered in this system. The register is complete. However, cancer often has a long latency period, sometimes spanning several decades. Accordingly, the NKR only relates to exposure that took place decades ago, not to recent incidents. This system is therefore of little benefit to short term (early warning) events.
- EUROCAT (European Registry of Congenital Anomalies and Twins), and Dutch registration systems for congenital abnormalities.[209] EUROCAT is a dedicated registry for congenital abnormalities in live births and stillbirths, which uses a standard classification system. It registers relatively short-term effects. Data is provided on a voluntary basis, by physicians and obstetricians, who must first obtain the parents' permission. Unfortunately, this registry only covers the northern part of the Netherlands, which accounts for about 10 percent of the total number of births in the Netherlands. The National Obstetrics Registry (LVR) and the National Neonatology Registry (LNR), however, cover the whole of the country.
- Continuous Morbidity Registry Special Surveillance Schemes (CMR special surveillance schemes) and the National Information Network for General Practice (LINH).[209] These registries cover about one percent of all registered patients in the Netherlands. One of the main drawbacks of the CMR is that the list of diseases to be registered is reviewed annually by an advisory committee. Since its inception, the CMR has recorded cardiovascular diseases only sporadically, and respiratory diseases not at all.[210]

Despite the limitations of some of the above-mentioned systems, they can provide valuable information on short-term and long-term effects. This is a more cost-effective option than the establishment of a new active medical surveillance programme, given the level of investment involved. Accordingly, the Committee argues in favour of using data from existing health registries (passive medical surveillance). Moreover, the Committee is aware that a passive medical surveillance system in the Netherlands can only provide limited insights. This is due to the small size of the working population that may be subject to exposure,

and the rare nature of some of the disorders involved. For this reason, the best option would be to pool data with other countries in future.

4.3.2 *Linking up with an exposure registry*

Before conclusions be drawn about possible connections between exposure to nanoparticles and subsequent health effects, data from passive medical surveillance systems must somehow be linked to the exposure registry.

To be effective, such linkage must meet a number of conditions.[211] For example, registry holders must have the legal right to make their data available to institutes (in anonymised form). Reliable health data, valid exposure data, and general personal data (age and gender) should also be made available. There must also be effective harmonisation, options for the exchange of data, and a willingness to cooperate on the part of the various registry holders. This is in keeping with the growing international trend of concentrating expertise, data and analyses to facilitate faster responses to early indications of health effects.

In addition to its potential and to the requisite conditions, the Committee is also aware of the limitations that may stand in the way of effective linkage. For example, in addition to the legal ramifications (see next subsection), there are social, political, financial and methodological restrictions, as well as limitations with regard to the interpretation of data.

The Committee emphasises that linking health data from medical surveillance to the exposure registry is an absolute prerequisite if the system is to effectively identify changes in the health status of individuals who work with nanoparticles.

4.3.3 *Regulations for health registries*

One issue that may restrict the use of passive medical surveillance is the privacy of personal data (including medical data). This is protected by a number of laws, which limit the use of data traceable to individuals.[211] The main item of legislation in this area is the Personal Data Protection Act (Wet bescherming persoonsgegevens (WBP)), which is intended to protect the privacy of affected individuals. One of the Act's requirements is that, with regard to the purposes for which it was collected, data must not be retained any longer than necessary. The Medical Treatment Contracts Act (*Wet geneeskundige behandelingsovereenkomst*) is a supplement to the WBP. It regulates the handling of personal data (by imposing an obligation of confidentiality), the obligation to keep files, the obligation of retention, the right of inspection, the right of destruction, and rules

on the exchange of data. With a view to scientific research, the Act also regulates the transfer of personal data to separate registries. In general terms, the Act permits such transfers, provided that the data in question is anonymised, that it is not traceable to specific individuals, and that the individuals involved have expressed no objections.

The Medical Research (Human Subjects) Act (Wet medisch-wetenschappelijk onderzoek met mensen; WMO) is intended to provide protection for test subjects. There is also draft legislation dictating that donors have the right to determine how their body tissues are used, both now and in the future.

These laws limit the use of health registries and the storage of body tissues by third parties, or for purposes other than those for which the participants were originally asked to give their informed consent.

4.4 Epidemiological research as part of an early warning system

This advisory report specifically addresses the use of early warning systems in humans. The Committee also considers epidemiological research to be of great importance in this regard. Such research can provide valuable information, as passive medical surveillance alone may not permit reliable conclusions to be drawn about relationships between health effects and exposure. In fact, not only is epidemiological research complementary to medical surveillance, but it may actually help to sharpen the focus of future surveillance. Accordingly, the Committee considers epidemiological research to be an essential part of the early warning system.

Initially, such studies might focus on a few selected nanoparticle types (carbon nanotubes, titanium dioxide, carbon black, amorphous silica), and on monitoring early signs of respiratory and cardiovascular conditions. This could include the use of biomarkers among certain groups of workers who routinely handle nanomaterials. Information from an exposure registry could provide valuable input in this regard. It is particularly important to study the respiratory and cardiovascular effects, as these are expected to develop within a relatively short period of time. The Committee has already indicated that these effects can have a range of causes, and that they occur frequently in the general population. This makes it difficult to identify causal relationships, at population level, between these effects and exposure to nanoparticles. However, it might be possible to overcome this problem to some extent by studying these effects in a research setting, using a specific exposed population. Various research groups outside the Netherlands are currently setting up studies of this kind.[92,97,212-215]

4.5 High-risk groups

Certain groups of people may be more susceptible, due to their personal characteristics (genetic factors, age and gender, comorbidity) and lifestyle (smoking). They will either tend to develop disease symptoms at an earlier stage, or any latent disease symptoms that they may have will more rapidly lead to clinically detectable diseases. As yet, it is unclear whether (and, if so, to what extent) such risk factors affect the development of disease symptoms in response to occupational exposure to nanoparticles. Additional scientific research will have to be carried out to determine this. Accordingly, the Committee is of the opinion that, at this stage, it would be premature to take specific risk groups into account in a medical surveillance programme.

4.6 Evaluation and conclusion

Depending on the purpose in question, screening, health monitoring or medical surveillance can be used. These systems differ in terms of the level of data collection involved (individual or population level), the frequency with which they are carried out (periodically or continuously), and their specificity for certain health effects (purposiveness). If the health effects in question occur quickly or at an early stage, then a health system can be seen as an early warning system.

The choice of system is largely determined by the type of health effects that are expected to result from exposure to nanoparticles. Although researchers suggest that these will mainly be respiratory and cardiovascular in nature, certainly in the short term, this is by no means the whole story. In addition, such effects occur frequently and have a range of causes, thus making it difficult to attribute changes in the health status of an individual (or small changes in a population), to nanoparticle exposure. Furthermore, a stronger focus on these particular effects may cause less obvious effects in other organs to be overlooked. Therefore, the Committee is of the opinion that the broadest possible range of health effects should be covered, which rules out the use of screening and health monitoring. This is because these methods are used for specific health effects in which there are clear links between risk factors and the occurrence of diseases.

The Committee has closely examined the options for medical surveillance, as this is less dependent on prior details concerning the anticipated health effects. Effective medical surveillance requires that the following conditions are met.

The data must be collected continuously and systematically, it must also be complete and reliable. Furthermore, a high degree of participation is required as the surveillance must include as large a population as possible. Under these conditions, relatively small changes in health status can be detected.

Some health registries in the Netherlands are designed for the continuous input of disease data. In view of this, the Committee initially assessed these registries to determine whether they were able to provide sufficient information. Despite the limitations of some of these systems, they do cover a great range of possible health effects. Accordingly, they are capable of providing valuable information in both the short and long term. Therefore, the Committee is of the opinion that a separate medical surveillance system for nanoworkers (active medical surveillance) would serve no useful purpose. There is still uncertainty about the nature and magnitude of the health risks involved, and the creation of such a system would require considerable financial investment. In addition, small sub-populations within the total working population pose real challenges, as they are very diverse and handle a wide range of nanoparticle types. The Committee, therefore, considers a passive system to be the best option for medical surveillance. In combination with endeavours such as scientific research and the monitoring of international activities, the Committee believes that passive medical surveillance can make a valuable contribution towards understanding the health risks associated with handling nanoparticles in the workplace.

Any attempts to identify links between exposure and disease are conditional upon the linkage of health data from medical surveillance to data from the exposure registry. Although anonymised data is sufficient to establish or rule out specific relationships, the databases in question can only be linked using data that can be traced back to individuals. The Committee is fully aware that privacy legislation imposes restrictions on the provision of personal data. Informed consent must first be obtained. Other health monitoring systems are also bound by the same restriction.

Chapter 5

Considerations and replies to the Minister

In this concluding chapter, the Committee discusses a few subjects that relate both to the exposure registry and to medical surveillance. The chapter concludes with specific answers to the Minister's two main questions. The Committee also identifies what it feels are the most important points for consideration regarding the effective implementation of both systems.

5.1 Considerations

5.1.1 International context

Problems concerning the handling of nanoparticles in the workplace are not confined to the Netherlands. Other countries, such as Germany, France, the United Kingdom and the United States, are currently discussing the potential use of exposure registries and health monitoring systems, as well as epidemiological and toxicological research. At international level, the Committee's findings are almost entirely in line with the views of those from the worlds of research and business.[100,106,207,216,217] It concluded that the use of the precautionary principle is currently the best option, and that control measures should be implemented wherever possible. The use of an exposure registry could also be considered. Health monitoring for specific health effects in nanoworkers cannot be considered until sufficient data is available from toxicological research, and a

better picture has been obtained of the possible harmful health effects involved.[106,152,218]

These developments should be followed closely. It might also be worthwhile to establish ties with those involved. After all, this is a worldwide phenomenon, and knowledge that is gained jointly, and on a shared basis, will help to clarify matters much sooner than would otherwise be the case.

5.1.2 *Precaution and the controlling of exposure*

Given the uncertainty about the nature and magnitude of the health risks associated with exposure to nanoparticles, it is best if employers and workers apply the precautionary principle. Having to admit that the health effects were less serious than expected is preferable to concluding that earlier intervention might have prevented a great deal of suffering. In addition, the Committee emphasises that the introduction of an exposure registry and medical surveillance should not be used as a reason for terminating control measures that are already in place, such as the evaluation of exposure against provisional nano reference values. All available means should be used to prevent exposure (or to keep it as low as possible), thereby limiting the potential health risks to individual nanoworkers. In view of the prevailing uncertainty, effective communication about the risks involved is essential, to prevent concern among employers and workers.[219]

5.1.3 *Scientific research*

In Section 4.4, the Committee discussed the importance of epidemiological research. However, this alone is not sufficient. Emission and exposure scenarios, the best way to measure levels of nanoparticles in the air, toxicokinetics, specific nano-toxicity, and toxic mechanisms of action are all poorly understood. This underscores the need for targeted investigation through technical research (e.g. the development of nano-specific measurement instruments), toxicological studies, and mechanistic research (e.g. setting up exposure models, animal experiments and in vitro research). Provided that the findings of such research (together with those from epidemiological research) indicate that there is a need to do so, health monitoring systems could be set up that are more specifically focussed on this issue. It might even be possible to limit these systems to specific target groups.

5.1.4 *Nanoparticles in the environment*

This advisory report examines the situation at work and the working population involved throughout the entire chain of use. However, nanomaterials are being incorporated into consumer products that are already commercially available. As a result, there is already a risk that the general population (users) and the environment (through waste, dissipation and wear) may come into contact with nanoparticles. Even though it is the working population that will first to come into contact with nanoparticles and suffer higher levels of exposure, due consideration should also be given to the above issue.

5.2 Replies to the Minister's questions

You will note, from the contents of this advisory report, that relatively little is known about the toxicity and potential adverse health effects of nanoparticles. From the health point of view, this means that all options have to be taken into account. Therefore, the Committee is of the opinion that this advisory report applies to all nanoparticles, regardless of their composition, form or physical state, with the exception of those nanoparticles that immediately disintegrate or dissolve on contact with water (or an aqueous environment), which would not then meet the EU's definition. In all probability, the risk analysis can deal with the latter in the same way as 'non-nano' substances.

5.2.1 *What are the requirements for a registry of occupational exposure to nanoparticles that could be used to establish or rule out links to any subsequent health effects?*

Three types of data are needed in order to obtain a good picture of the nature and level of exposure. These are: a) data on the chemical and physical properties of nanoparticles, b) data on the determinants of emission and exposure, and c) data on the exposure concentration involved (see Annex K). The exposure concentration should preferentially expressed as three different measures (mass concentration, number of particles, or particle surface area).

An exposure registry offers a solid set of data that can be subsequently used to establish or rule out possible links between exposure and health effects. Data should be supplied at company level, the registry should be updated if there is any change in the working situation, and as many companies or institutes as possible should take part. Moreover, the data should be registered in such a way

(for instance, per department or stage of production), that it can be subsequently linked to individual workers (whose records include details of the type of work involved, and the departments in which they have worked). Furthermore, it is very important that a systematic and uniform approach is guaranteed, so it would be preferable for such a registry to be managed centrally. It would then be a relatively simple matter to check the data for completeness and to combine it.

The Committee feels that there are relatively few options for linking up with the current RI&E and REACH registries. Both include data that would be required by the exposure registry, but the degree of overlap is very limited. Nevertheless, some of the data from these registries could be used directly for the exposure registry.

The Committee feels that the registration of exposure should be introduced in all companies, both large and small, where nanoparticles are handled repeatedly and at fixed times. The Committee is aware that keeping updated records of the data requested can be quite burdensome for small businesses. One reason for this is that the chemical and physical properties of some types of nanoparticles are still unknown, another is that some exposure measurement instruments are still in the test phase. There are, however, no scientific grounds for excluding certain companies or groups of workers. Moreover, reasonable estimates of exposure levels can be made using currently available instruments.

There are also a number of issues, beyond the remit of the Health Council, which could impede the establishment of an effective exposure registry. For instance, manufacturers and importers are not currently required to indicate on the label that their products contain nanoparticles, nor are they required to identify the nanoparticles in question. Therefore, it is unclear how many workers might potentially be exposed to nanoparticles. Nor, indeed, are all employers and workers aware that they are handling nanomaterials. Over the next few years, the number of companies handling nanomaterials is expected to rise, so complete information is becoming increasingly important.

5.2.2 *To what extent is it possible and useful when working with nanoparticles to set up a health monitoring system and/or early warning system? What conditions would such a system need to meet in order to work effectively?*

Depending on the purpose in question, screening, health monitoring or medical surveillance can be used. If the health effects in question occur rapidly or at an early stage, then a health system can be seen as an early warning system. The choice of system is largely determined by the type of health effects that are

expected to result from exposure. Although researchers suggest that these will mainly be respiratory and cardiovascular in nature, certainly in the short term, this is by no means the whole story. The Committee is of the opinion that the widest possible range of health effects should be covered. This would tend to rule out the use of systems such as screening and health monitoring. However, the Committee feels that medical surveillance is a viable option, as this is less dependent on prior details concerning the anticipated health effects.

Effective medical surveillance requires that the following conditions are met. The data must be collected continuously and systematically, it must also be complete and reliable. Furthermore, a high degree of participation is required, and the surveillance must include as large a population as possible. Under these conditions, relatively small changes in the health status of the working population can be detected.

Some medical surveillance systems in the Netherlands are designed for the continuous input of disease data. In view of this, the Committee has assessed these registries to determine whether they are able to provide sufficient information. Despite the limitations of some of these systems, they do cover a great range of possible health effects. Accordingly, they are capable of providing valuable information in both the short and long term. Therefore, the Committee is of the opinion that a separate medical surveillance system for nanoworkers (active surveillance) would serve no useful purpose. With regard to medical surveillance, the Committee considers the implementation of a passive system to be the best option for tracking changes in the health status of a population.

If passive medical surveillance is to be used effectively, it must be possible for health data to be linked to data in the exposure registry. This requires the use of personal data, and that in turn requires informed consent. The other health systems that might be used are also bound by the same restriction.

This advisory report specifically addresses early warning systems for use in humans. The Committee also feels that epidemiological research has an important past to play. This type of research can provide valuable information, as passive medical surveillance may not be able to support reliable conclusions about whether or not links exist between health effects and exposure. Indeed, epidemiological research is complementary to medical surveillance, and has the potential to enhance its focus. Accordingly, the Committee sees epidemiological research as an essential component of an early warning system.

References

1 Health Council of the Netherlands. Health significance of nanotechnologies. The Hague: Health Council of the Netherlands, 2006; publication no. 2006/06E

2 Sociaal-Economische Raad. Veilig omgaan met nanodeeltjes op de werkplek. Sociaal-Economische Raad, Den Haag, publicatie 09/01; 2009.

3 Health Council of the Netherlands. Nanomaterials in waste. The Hague: Health Council of the Netherlands, 2011; publication no. 2011/14E.

4 Oberdorster G, Oberdorster E, Oberdorster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect 2005; 113(7): 823-839.

5 Borm PJ, Robbins D, Haubold S, Kuhlbusch T, Fissan H, Donaldson K et al. The potential risks of nanomaterials: a review carried out for ECETOC. Part Fibre Toxicol 2006; 3: 11.

6 Oberdorster E, Stone V, Donaldson K. Toxicology of nanoparticles: A historical perspective. Nanotoxicology 2007; 1(1): 2-25.

7 Singh S, Nalwa HS. Nanotechnology and health safety--toxicity and risk assessments of nanostructured materials on human health. J Nanosci Nanotechnol 2007; 7(9): 3048-3070.

8 Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). Scientific basis for the definition of the term “nanomateria”. SCENIHR, European Union, 6 July 2010, http://ec.europa.eu/health/ph_risk/; 2010.

9 Powell MC, Kanarek MS. Nanomaterial health effects--part 1: background and current knowledge. WMJ 2006; 105(2): 16-20.

10 Maynard AD, Aitken RJ. Assessing exposure to airborne nanomaterials: Current abilities and future requirements. Nanotoxicology 2007; 1(1): 26-41.

11 Nel A, Xia T, Madler L, Li N. Toxic potential of materials at the nanolevel. Science 2006; 311(5761): 622-627.

12 The Royal Society & the Royal Academy of Engineering. Nanoscience and nanotechnologies: opportunities and uncertainties. The Royal Society, Science Policy Section, London, the UK; 2004.

13 Zijverden M van, Sips A. Nanotechnologie in perspectief. Risico's voor mens en milieu. RIVM, Bilthoven, Rapport 601785002/2008; 2008.

14 Cornelissen R, Van der Laan G, Hoeneveld D, Tweehuysen H. Dossier nanotechnologie. Kennisdossier Arbokennisnet; 2011.

15 Pronk A, Brouwer D, Op de Weegh-Nieboer M, Bekker C, Dekkers S, Tielemans E. Vervaardiging en gebruik van nano-eindproducten in Nederland. TNO, Zeist, rapport nr. V9300; 2011.

16 Borm P, Houba R, Linker F. Omgaan met nanodeeltjes op de werkvloer. Survey naar goede praktijken in omgaan met nanomaterialen in de Nederlandse industrie en kennisinstellingen. Hogeschool Zuyd, Centre of Expertise in Life Sciences, Heerlen; Arbo-Unie, Expertise Centrum Toxische Stoffen, Roermond; DSM Arbodienst, Geleen; 2008.

17 Bundesanstalt für Arbeitsschutz und Arbeitsmedizin. Exposure to nanomaterials in Germany. Results of the corporate survey of the Federal Institute for Occupational Health and Safety (BAuA) and the Association of the Chemical Industry (VCI) using questionnaires. BAuA, Dortmund, Germany, www.baua.de; 2008.

18 Helland A, Scheringer M, Siegrist M, Kastenholz HG, Wiek A, Scholz RW. Risk assessment of engineered nanomaterials: a survey of industrial approaches. Environ Sci Technol 2008; 42(2): 640-646.

19 Schmid K, Danuser B, Riediker M. Swiss Nano-Inventory. An assessment of the usage of nanoparticles in Swiss industry. Swiss Institute for Work and Health (IST), Lausanne, Switzerland; 2008.

20 HSE. Nanoparticles: An occupational hygiene review. 2004: RR274. Internet: http:// www.hse.gov.uk/research/rrhtm/rr274.htm.

21 Nordic Council of Ministers. Evaluation and control of occupational health risks from nanoparticles. Nordic Council of Ministers, Thomas Schneider et al., Copenhagen, Denmark, ThemaNord 2007:581; 2007.

22 Agence Francaise de Sécurité Sanitaire de l'Environnement et du Travail. Nanomaterials and occupational safety. Case No. 2006/006, Report of the Afsset Working Group on "physical agents, new technologies and development areas". Afsset, France; 2008.

23 Schubauer-Berigan MK, Dahm MM, Yencken MS. Engineered carbonaceous nanomaterials manufacturers in the United States: workforce size, characteristics, and feasibility of epidemiologic studies. J Occup Environ Med 2011; 53(6 Suppl): S62-S67.

24 Aschberger K, Johnston HJ, Stone V, Aitken RJ, Hankin SM, Peters SA et al. Review of carbon nanotubes toxicity and exposure--appraisal of human health risk assessment based on open literature. Crit Rev Toxicol 2010; 40(9): 759-790.

25 ENHRES. Engineered Nanoparticles - Review of Health & Environmental Safety. 2009. Internet: http://nmi.jrc.ec.europa.eu/project/ENRHES.htm.

26 Savolainen K, Alenius H, Norppa H, Pylkkanen L, Tuomi T, Kasper G. Risk assessment of engineered nanomaterials and nanotechnologies--a review. Toxicology 2010; 269(2-3): 92-104.

27 Hu YL, Gao JQ. Potential neurotoxicity of nanoparticles. Int J Pharm 2010; 394(1-2): 115-121.

28 Oberdorster G, Sharp Z, Atudorei V, Elder A, Gelein R, Kreyling W et al. Translocation of inhaled ultrafine particles to the brain. Inhal Toxicol 2004; 16(6-7): 437-445.

29 Win-Shwe TT, Fujimaki H. Nanoparticles and neurotoxicity. Int J Mol Sci 2011; 12(9): 6267-6280.

30 Madl AK, Pinkerton KE. Health effects of inhaled engineered and incidental nanoparticles. Crit Rev Toxicol 2009; 39(8): 629-658.

31 Oberdorster G, Elder A, Rinderknecht A. Nanoparticles and the brain: cause for concern? J Nanosci Nanotechnol 2009; 9(8): 4996-5007.

32 Crosera M, Bovenzi M, Maina G, Adami G, Zanette C, Florio C et al. Nanoparticle dermal absorption and toxicity: a review of the literature. Int Arch Occup Environ Health 2009; 82(9): 1043-1055.

33 Nohynek GJ, Dufour EK, Roberts MS. Nanotechnology, cosmetics and the skin: is there a health risk? Skin Pharmacol Physiol 2008; 21(3): 136-149.

34 Schneider M, Stracke F, Hansen S, Schaefer UF. Nanoparticles and their interactions with the dermal barrier. Dermatoendocrinol 2009; 1(4): 197-206.

35 Choksi AN, Poonawalla T, Wilkerson MG. Nanoparticles: a closer look at their dermal effects. J Drugs Dermatol 2010; 9(5): 475-481.

36 Rossi EM, Pylkkanen L, Koivisto AJ, Vippola M, Jensen KA, Miettinen M et al. Airway exposure to silica-coated TiO2 nanoparticles induces pulmonary neutrophilia in mice. Toxicol Sci 2010; 113(2): 422-433.

37 Johnston HJ, Hutchison G, Christensen FM, Peters S, Hankin S, Stone V. A review of the in vivo and in vitro toxicity of silver and gold particulates: particle attributes and biological mechanisms responsible for the observed toxicity. Crit Rev Toxicol 2010; 40(4): 328-346.

38 Papp T, Schiffmann D, Weiss D, Castranova V, Vallyathan V, Rahman Q. Human health implications of nanomaterial exposure. Nanotoxicology 2008; 2(1): 9-27.

39 Smijs TG, Bouwstra JA. Focus on skin as a possible port of entry for solid nanoparticles and the toxicological impact. J Biomed Nanotechnol 2010; 6(5): 469-484.

40 Prow TW, Monteiro-Riviere NA, Inman AO, Grice JE, Chen X, Zhao X et al. Quantum dot penetration into viable human skin. Nanotoxicology 2011;

41 Nabeshi H, Yoshikawa T, Matsuyama K, Nakazato Y, Matsuo K, Arimori A et al. Systemic distribution, nuclear entry and cytotoxicity of amorphous nanosilica following topical application. Biomaterials 2011; 32(11): 2713-2724.

42 IRSST, Ostiguy C, Roberge B, Ménard L, Endo C. Best Practices Guide to Synthetic Nanoparticle Risk Management. IRSST; 2009: R-599.

43 Yamashita K, Yoshioka Y, Higashisaka K, Mimura K, Morishita Y, Nozaki M et al. Silica and titanium dioxide nanoparticles cause pregnancy complications in mice. Nat Nanotechnol 2011; 6(5): 321-328.

44 Sharma HS, Ali SF, Hussain SM, Schlager JJ, Sharma A. Influence of engineered nanoparticles from metals on the blood-brain barrier permeability, cerebral blood flow, brain edema and neurotoxicity. An experimental study in the rat and mice using biochemical and morphological approaches. J Nanosci Nanotechnol 2009; 9(8): 5055-5072.

45 Sharma HS, Ali SF, Tian ZR, Hussain SM, Schlager JJ, Sjoquist PO et al. Chronic treatment with nanoparticles exacerbate hyperthermia induced blood-brain barrier breakdown, cognitive dysfunction and brain pathology in the rat. Neuroprotective effects of nanowired-antioxidant compound H-290/51. J Nanosci Nanotechnol 2009; 9(8): 5073-5090.

46 Genaidy A, Tolaymat T, Sequeira R, Rinder M, Dionysiou D. Health effects of exposure to carbon nanofibers: systematic review, critical appraisal, meta analysis and research to practice perspectives. Sci Total Environ 2009; 407(12): 3686-3701.

47 Helland A, Wick P, Koehler A, Schmid K, Som C. Reviewing the environmental and human health knowledge base of carbon nanotubes. Environ Health Perspect 2007; 115(8): 1125-1131.

48 Johnston H, Hutchison GR, Christensen FM, Peters S, Hankin S, Aschberger K et al. A critical review of the biological mechanisms underlying the in vivo and in vitro toxicity of carbon nanotubes. The contribution of physico-chemical characteristics. Nanotoxicology 2010; 4(2): 207-246.

49 Ma-Hock L, Treumann S, Strauss V, Brill S, Luizi F, Mertler M et al. Inhalation toxicity of multiwall carbon nanotubes in rats exposed for 3 months. Toxicol Sci 2009; 112(2): 468-481.

50 Muller J, Huaux F, Moreau N, Misson P, Heilier JF, Delos M et al. Respiratory toxicity of multi-wall carbon nanotubes. Toxicol Appl Pharmacol 2005; 207(3): 221-231.

51 Safe Work Australia. Engineered nanomaterials: a review of the toxicology and health hazards. Safe Work Australia, produced by Toxikos Pty Ltd (Drew, R), Australia; 2000.

52 Ryman-Rasmussen JP, Cesta MF, Brody AR, Shipley-Phillips JK, Everitt JI, Tewksbury EW et al. Inhaled carbon nanotubes reach the subpleural tissue in mice. Nat Nanotechnol 2009; 4(11): 747-751.

53 Murphy FA, Poland CA, Duffin R, Al-Jamal KT, li-Boucetta H, Nunes A et al. Length-dependent retention of carbon nanotubes in the pleural space of mice initiates sustained inflammation and progressive fibrosis on the parietal pleura. Am J Pathol 2011; 178(6): 2587-2600.

54 Shvedova AA, Kisin E, Murray AR, Johnson VJ, Gorelik O, Arepalli S et al. Inhalation vs. aspiration of single-walled carbon nanotubes in C57BL/6 mice: inflammation, fibrosis, oxidative stress, and mutagenesis. Am J Physiol Lung Cell Mol Physiol 2008; 295(4): L552-L565.

55 Pauluhn J. Subchronic 13-week inhalation exposure of rats to multiwalled carbon nanotubes: toxic effects are determined by density of agglomerate structures, not fibrillar structures. Toxicol Sci 2010; 113(1): 226-242.

56 Nielsen GD, Roursgaard M, Jensen KA, Poulsen SS, Larsen ST. In vivo biology and toxicology of fullerenes and their derivatives. Basic Clin Pharmacol Toxicol 2008; 103(3): 197-208.

57 Card JW, Zeldin DC, Bonner JC, Nestmann ER. Pulmonary applications and toxicity of engineered nanoparticles. Am J Physiol Lung Cell Mol Physiol 2008; 295(3): L400-L411.

58 Jang J, Lim DH, Choi IH. The impact of nanomaterials in immune system. Immune Netw 2010; 10(3): 85-91.

59 Santhanam P, Wagner JG, Elder A, Gelein R, Carter JM, Driscoll KE et al. Effects of subchronic inhalation exposure to carbon black nanoparticles in the nasa; airways of laboratory rats. Int J Nanotechnol 2008; 5(1): 30-54.

60 Heinrich U, Fuhst R, Rittinghausen S, Creutzenberg O, Bellman B, Koch W et al. Chronic inhalation exposure of Wistar rats and two different strains of mice to diesel engine exhaust, carbon black, and titanium dioxide. Inhal Toxicol 1995; 7: 533-556.

61 Sager TM, Kommineni C, Castranova V. Pulmonary response to intratracheal instillation of ultrafine versus fine titanium dioxide: role of particle surface area. Part Fibre Toxicol 2008; 5: 17.

62 Li Z, Hulderman T, Salmen R, Chapman R, Leonard SS, Young SH et al. Cardiovascular effects of pulmonary exposure to single-wall carbon nanotubes. Environ Health Perspect 2007; 115(3): 377-382.

63 Duffin R, Mills NL, Donaldson K. Nanoparticles-a thoracic toxicology perspective. Yonsei Med J 2007; 48(4): 561-572.

64 Geys J, Nemmar A, Verbeken E, Smolders E, Ratoi M, Hoylaerts MF et al. Acute toxicity and prothrombotic effects of quantum dots: impact of surface charge. Environ Health Perspect 2008; 116(12): 1607-1613.

65 Oszlanczi G, Vezer T, Sarkozi L, Horvath E, Konya Z, Papp A. Functional neurotoxicity of Mn-containing nanoparticles in rats. Ecotoxicol Environ Saf 2010; 73(8): 2004-2009.

66 Oszlanczi G, Papp A, Szabo A, Nagymajtenyi L, Sapi A, Konya Z et al. Nervous system effects in rats on subacute exposure by lead-containing nanoparticles via the airways. Inhal Toxicol 2011; 23(4): 173-181.

67 Zhang QL, Li MQ, Ji JW, Gao FP, Bai R, Chen CY et al. In vivo toxicity of nano-alumina on mice neurobehavioral profiles and the potential mechanisms. Int J Immunopathol Pharmacol 2011; 24(1 Suppl): 23S-29S.

68 Wu J, Wang C, Sun J, Xue Y. Neurotoxicity of silica nanoparticles: brain localization and dopaminergic neurons damage pathways. ACS Nano 2011; 5(6): 4476-4489.

69 Aoshima H, Saitoh Y, Ito S, Yamana S, Miwa N. Safety evaluation of highly purified fullerenes (HPFs): based on screening of eye and skin damage. J Toxicol Sci 2009; 34(5): 555-562.

70 Trop M, Novak M, Rodl S, Hellbom B, Kroell W, Goessler W. Silver-coated dressing acticoat caused raised liver enzymes and argyria-like symptoms in burn patient. J Trauma 2006; 60(3): 648-652.

71 Muller J, Delos M, Panin N, Rabolli V, Huaux F, Lison D. Absence of carcinogenic response to multiwall carbon nanotubes in a 2-year bioassay in the peritoneal cavity of the rat. Toxicol Sci 2009; 110(2): 442-448.

72 Poland CA, Duffin R, Kinloch I, Maynard A, Wallace WA, Seaton A et al. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. Nat Nanotechnol 2008; 3(7): 423-428.

73 Bonner JC. Nanoparticles as a potential cause of pleural and interstitial lung disease. Proc Am Thorac Soc 2010; 7(2): 138-141.

74 Elder A. Nanotoxicology: How do nanotubes suppress T cells? Nat Nanotechnol 2009; 4(7): 409-410.

75 Monteiller C, Tran L, Macnee W, Faux S, Jones A, Miller B et al. The pro-inflammatory effects of low-toxicity low-solubility particles, nanoparticles and fine particles, on epithelial cells in vitro: the role of surface area. Occup Environ Med 2007; 64(9): 609-615.

76 Cassee FR, van Balen EC, Singh C, Green D, Muijser H, Weinstein J et al. Exposure, Health and Ecological Effects Review of Engineered Nanoscale Cerium and Cerium Oxide Associated with its Use as a Fuel Additive. Crit Rev Toxicol 2011; 41(13): 213-229.

77 Hardman R. A toxicologic review of quantum dots: toxicity depends on physicochemical and environmental factors. Environ Health Perspect 2006; 114(2): 165-172.

78 Aitken R, Hankin S, Ross B, Tran CL, Stone V, Fernandes TF et al. EMERGNANO: A review of completed and near completed environment, health and safety research on nanomaterials and nanotechnology. Intitute of Occupational Medicine, Edinburgh, United Kingdom, report TM/09/01; 2009.

79 Gonzalez L, Lison D, Kirsch-Volders M. Genotoxicity of engineered nanomaterials: A critical review. Nanotoxicology 2008; 2(4): 252-273.

80 Kreyling WG, Semmler-Behnke M, Möller W. Health implications of nanoparticles. J Nanopart Res 2006; 8: 543-562.

81 Li N, Xia T, Nel AE. The role of oxidative stress in ambient particulate matter-induced lung diseases and its implications in the toxicity of engineered nanoparticles. Free Radic Biol Med 2008; 44(9): 1689-1699.

82 Knaapen AM, Borm PJ, Albrecht C, Schins RP. Inhaled particles and lung cancer. Part A: Mechanisms. Int J Cancer 2004; 109(6): 799-809.

83 Mossman BT, Borm PJ, Castranova V, Costa DL, Donaldson K, Kleeberger SR. Mechanisms of action of inhaled fibers, particles and nanoparticles in lung and cardiovascular diseases. Part Fibre Toxicol 2007; 4: 4.

84 Stone V, Donaldson K. Nanotoxicology: signs of stress. Nat Nanotechnol 2006; 1(1): 23-24.

85 Marano F, Hussain S, Rodrigues-Lima F, Baeza-Squiban A, Boland S. Nanoparticles: molecular targets and cell signalling. Arch Toxicol 2011; 85(7): 733-741.

86 Landsiedel R, Kapp MD, Schulz M, Wiench K, Oesch F. Genotoxicity investigations on nanomaterials: methods, preparation and characterization of test material, potential artifacts and limitations--many questions, some answers. Mutat Res 2009; 681(2-3): 241-258.

87 Lindberg HK, Falck GC, Suhonen S, Vippola M, Vanhala E, Catalan J et al. Genotoxicity of nanomaterials: DNA damage and micronuclei induced by carbon nanotubes and graphite nanofibres in human bronchial epithelial cells in vitro. Toxicol Lett 2009; 186(3): 166-173.

88 Donaldson K, Aitken R, Tran L, Stone V, Duffin R, Forrest G et al. Carbon nanotubes: a review of their properties in relation to pulmonary toxicology and workplace safety. Toxicol Sci 2006; 92(1): 5-22.

89 Aillon KL, Xie Y, El-Gendy N, Berkland CJ, Forrest ML. Effects of nanomaterial physicochemical properties on in vivo toxicity. Adv Drug Deliv Rev 2009; 61(6): 457-466.

90 Schulte PA, Trout D, Zumwalde RD, Kuempel E, Geraci CL, Castranova V et al. Options for occupational health surveillance of workers potentially exposed to engineered nanoparticles: state of the science. J Occup Environ Med 2008; 50(5): 517-526.

91 Schulte PA, Trout DB. Nanomaterials and worker health: medical surveillance, exposure registries, and epidemiologic research. J Occup Environ Med 2011; 53(6 Suppl): S3-S7.

92 Laney AS, McCauley LA, Schubauer-Berigan MK. Workshop summary: epidemiologic design strategies for studies of nanomaterial workers. J Occup Environ Med 2011; 53(6 Suppl): S87-S90.

93 Liou S-H, Tsou T-C, Wang S-L, Li L-A, Chiang H-C, Li W-F et al. Epidemiological study of haelth hazards among workers handling engineered nanomaterials. J Nanopart Res 2012; 14: 878-893.

94 Boutou-Kempf O, Marchand JL, Radauceanu A, Witschger O, Imbernon E. Development of a French epidemiological surveillance system of workers producing or handling engineered nanomaterials in the workplace. J Occup Environ Med 2011; 53(6 Suppl): S103-S107.

95 Boutou-Kempf O. Eléments de faisabilité pour un dispositif de surveillance épidémiologique des travailleurs exposés aux nanomatériaux intentionnellement produits. Sant-Maurice: Institut de veille sanitaire, www.invs.sante.fr; 2011.

96 NIOSH. Approaches to safe nanotechnology. Managing the health and safety concerns associated with engineered nanomaterials. Department of Health and Human Services, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, OH, USA; 2009.

97 Eisen EA, Costello S, Chevrier J, Picciotto S. Epidemiologic challenges for studies of occupational exposure to engineered nanoparticles; a commentary. J Occup Environ Med 2011; 53(6 Suppl): S57-S61.

98 Elder A, Oberdorster G. Translocation and effects of ultrafine particles outside of the lung. Clin Occup Environ Med 2006; 5(4): 785-796.

99 Agence Francaise de Sécurité Sanitaire de l'Environnement et du Travail. Les nanomatériaux. Effets sur la santé de l'homme et sur l'environnement. AFSSET, Maisons-Alfort Cedex, France; 2006.

100 NIOSH. Current Intelligence Bulletin 60. Interim Guidance for Medical Screening and Hazard Surveillance for Workers Potentially Exposed to Engineered Nanoparticles. DHHS (NIOSH); 2009: 2009-116. Internet: http://www.cdc.gov/niosh/docs/2009-116/.

101 Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ et al. Long-term exposure to traffic-related air pollution and lung cancer risk. Epidemiology 2008; 19(5): 702-710.

102 Beelen R, Hoek G, Houthuijs D, van den Brandt PA, Goldbohm RA, Fischer P et al. The joint association of air pollution and noise from road traffic with cardiovascular mortality in a cohort study. Occup Environ Med 2009; 66(4): 243-250.
103 Mustafic H, Jabre P, Caussin C, Murad MH, Escolano S, Tafflet M et al. Main air pollutants and myocardial infarction: a systematic review and meta-analysis. JAMA 2012; 307(7): 713-721.
104 Wellenius GA, Burger MR, Coull BA, Schwartz J, Suh HH, Koutrakis P et al. Ambient air pollution and the risk of acute ischemic stroke. Arch Intern Med 2012; 172(3): 229-234.
105 Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. Exposure to particulate air pollution and cognitive decline in older women. Arch Intern Med 2012; 172(3): 219-227.
106 Nasterlack M, Zober A, Oberlinner C. Considerations on occupational medical surveillance in employees handling nanoparticles. Int Arch Occup Environ Health 2008; 81(6): 721-726.
107 Berlinger B, Benker N, Weinbruch S, L'Vov B, Ebert M, Koch W et al. Physicochemical characterisation of different welding aerosols. Anal Bioanal Chem 2011; 399(5): 1773-1780.
108 Buonanno G, Morawska L, Stabile L. Exposure to welding fumes in automotive plants. J Aerosol Sci 2011; 42(5): 295-304.
109 Elihn K, Berg P, Liden G. Correlation between airborne particle concentrations in seven industrial plants and estimated respiratory tract deposition by number, mass and elemental composition. J Aerosol Sci 2011; 42(2): 127-141.
110 Pelzer J, Lehnert A, Lotz C, Mohlmann R, Gelder van A, Goebel A et al. Measurements of the number concentrations of fine and ultrafine particles in welding fumes - Comparison with the gravimetrically obtained mass concentrations in connection with the WELDOX project. Gefahrstoffe Reinhalt Luft 2011; 71(9): 389-392.
111 Stephenson D, Seshadri G, Veranth JM. Workplace exposure to submicron particle mass and number concentrations from manual arc welding of carbon steel. AIHA J (Fairfax, Va) 2003; 64(4): 516-521.
112 Dutch Expert Committee on Occupational Standards. Health-based recommended occupational exposure limit for ARC welding fume particles not containing chromium and nickel. Directorate-General of Labour, The Hague, report no. RA 1/93; 1993.
113 International Organization for Standardization (ISO). Chromium, nickel and welding. IARC, Lyon, France, Monograph Volume 49; 1990.
114 Fang SC, Cassidy A, Christiani DC. A systematic review of occupational exposure to particulate matter and cardiovascular disease. Int J Environ Res Public Health 2010; 7(4): 1773-1806.
115 Ibfelt E, Bonde JP, Hansen J. Exposure to metal welding fume particles and risk for cardiovascular disease in Denmark: a prospective cohort study. Occup Environ Med 2010; 67(11): 772-777.
116 Donaldson K, Tran CL. An introduction to the short-term toxicology of respirable industrial fibres. Mutat Res 2004; 553(1-2): 5-9.
117 Kane AB, Hurt RH. Nanotoxicology: the asbestos analogy revisited. Nat Nanotechnol 2008; 3(7): 378-379.
118 Health Council of the Netherlands. Asbestos. Risks of environmental and occupational exposure. The Hague: Health Council of the Netherlands, publication no. 2010/10E.

119 Health Council of the Netherlands. Man-made mineral fibers, health-based recommended occupational exposure limits. Dutch Expert Committee on Occupational Standards, The Hague, Health Council of the Netherlands, 1995; publication no. 1995/02WGD.
120 Ayala P, Kauppinen E, Nov E, Chiriac H, Lupu N, Malanowski N et al. Recommendations for Legislation Policy Makers. IMPART, Contract number NMP4-CT-2005-013968; 2008. Internet: http://www.impart-nanotox.org/.
121 Hansen SF. A global view of regulations affecting nanomaterials. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2010; 2(5): 441-449.
122 Tweede Kamer der Staten Generaal. Arbeidsomstandigheden. Brief van de minister van Sociale Zaken en Werkgelegenheid, Tweede Kamer, vergaderjaar 2009-2010, 25 883, nr.161; 2009.
123 Tweede Kamer der Staten Generaal. Actieplan nanotechnologie. Tweede Kamer, vergaderjaar 2007-2008, 29 338, nr. 75; 2008.
124 Health Council of the Netherlands. Prudent precaution. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/18E.
125 Tyshenko MG, Farhat N, Lewis R, Shilnikova N, Krewski D. Applying a precautionary risk management strategy for regulation of nanotechnology. Int J Nanotechnol 2010; 7(2-3): 243-264.
126 Woskie S. Workplace practices for engineered nanomaterial manufacturers. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2010; 2(6): 685-692.
127 Brouwer DH. Control banding approaches for nanomaterials. Ann Occup Hyg 2012; 56(5): 506-514.
128 French Agency for Food EaOHaS. Development of a specific control banding tool for nanomaterials. ANSES, France, www.anses.fr; 2010.
129 Groso A, Petri-Fink A, Magrez A, Riediker M, Meyer T. Management of nanomaterials safety in research environment. Part Fibre Toxicol 2010; 7: 40.
130 Paik SY, Zalk DM, Swuste P. Application of a pilot control banding tool for risk level assessment and control of nanoparticle exposures. Ann Occup Hyg 2008; 52(6): 419-428.
131 Schulte P, Geraci C, Hodson L, Zumwalde R, Castranova V, Kuempel E et al. Nanotechnologies and nanomaterials in the occupational setting. Italian J Occupa Environ Hyg 2010; 1(2): 63-68.
132 Schulte PA, Murashov V, Zumwalde R, Kuempel E, Geraci C. Occupational exposure limits for nanomaterials: state of the art. J Nanopart Res 2010; 12: 1971-1987.
133 Zalk DM, Paik S, Swuste P. Evaluating the control banding nanotool: a qualitative risk assessment method for controlling nanoparticle exposures. J Nanopart Res 2009; 11: 1685-1704.
134 Zalk DM. Control banding. A simplified qualitative strategy for the assessment of occupational risks and selection of solutions. Thesis, Technical University Delft, The Netherlands; 2010.
135 Cornelissen R, Jongeneelen F, Van Broekhuizen P. Handleiding veilig werken met nanomaterialen en - producten. IVAM-Uva, Amsterdam, in opdracht van FNV, VNO-NCW en CNV. Documentnr. 1041 O ; 2010.
136 Nordberg GF, Fowler BA, Nordberg M, Friberg LT. Handbook on the toxicology of metals. Third Edition, Aitio A., Anderssson I., et al. (eds), Elsevier, the UK; 2008.

137 American Conference of Governmental Industrial Hygienists. Particulates (insoluble) not otherwise specified (PNOS), containing no asbestos and < 1% crystalline silica. The American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, the USA, Documentation of the TLVs and Beis, Vol: 7th edition, www.acgih.org; 2001.

138 American Conference of Governmental Industrial Hygienists. TLVs® and BEIs®. ACGIH, Cincinnati, Ohio, the USA, www.acgih.org; 2009.

139 Deutsche Forschungsgemeinschaft. General threshold limit value for dust. In: Occupational toxicants, critical data evaluation for MAK values and classification of carcinogens, Volume 12. Deutsche Forschungsgemeinschaft, Wiley-VCH Verlag GmbH, Weinheim, Germany, pp 239-270; 1999.

140 Deutsche Forschungsgemeinschaft (DFG). List of MAK and BAT values. DFG, Wiley-VCH Verlag GmbH, Weinheim, Germany, Report No. 46; 2010.

141 Kuempel ED. Carbon nanotube risk assessment: implications for exposure and medical monitoring. J Occup Environ Med 2011; 53(6 Suppl): S91-S97.

142 NIOSH. Current intelligence bulletin: Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide (draft). 2005.

143 Pauluhn J. Multi-walled carbon nanotubes (Baytubes(R)): Approach for derivation of occupational exposure limit. Regul Toxicol Pharmacol 2010; 57(1): 78-89.

144 Organisation for Economic Co-operation and Development. List of manufactured nanomaterials and list of endpoints for phase one of the OECD testing programme. OECD, series on the safety of manufactured nanomaterials: number 6, Report ENV/JM/MONO(2008)13/REV, Paris, France; 2007.

145 Organisation for Economic Co-operation and Development. Report on an OECD workshop on exposure assessment and exposure mitigation: manufactured nanomaterials. OECD, series on the safety of manufactured nanomaterials: number 13, Report ENV/JM/MONO(2009)18, Paris, France; 2009.

146 British Standards Institution. Nanotechnologies - Part 2: Guide to safe handling and disposal of manufactured nanomaterials. BSi Group, London, the UK, Report PD 6699-2; 2007.

147 Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA). Maßstäbe zur Beurteilung der Wirksamkeit von Schutzmaßnahmen. Grenzwerte in Deutschland. IFA, www.dguv.de/ifa/; 2010.

148 Dekkers S, Heer dC. Tijdelijke nano-referentiewaarden. Bruikbaarheid van het concept en van de gepubliceerde methoden. Rijksinstituut voor Volksgezondheid en Milieu (RIVM), Bilthoven, Rapport 601044001; 2010.

149 Sociaal-Economische Raad. Voorlopige nanoreferentiewaarden voor synthetische nanomaterialen. Sociaal-Economische Raad, Den Haag, advies 12/01; 2012.

150 Van Broekhuizen P, Van Broekhuizen F, Cornelissen R, Reijnders L. Workplace exposure to nanoparticles and the application of provisional nanoreference values in times of uncertain risks. J Nanopart Res 2012; 14: 770-794.

151 Schulte P, Geraci C, Zumwalde R, Hoover M, Castranova V, Kuempel E et al. Sharpening the focus on occupational safety and health in nanotechnology. Scand J Work Environ Health 2008; 34(6): 471-478.

152 Trout DB, Schulte PA. Medical surveillance, exposure registries, and epidemiologic research for workers exposed to nanomaterials. Toxicology 2010; 269(2-3): 128-135.

153 DEFRA. Characterising the Potential Risks posed by Engineered Nanoparticles. A Second UK Government Research Report. 2007. Internet: http://www.nanowerk.com/nanotechnology/reports/Characterising_the_Potential_Risks_posed_by_Engineered_Nanoparticles_2nd_report.html.

154 DEFRA. Nanomaterials: Hazards and risks to health and the environment. A supplementary guide for the UK Voluntary reporting scheme. Department for Environment Food and Rural Affairs (DEFRA), London, the UK; 2008.

155 U.S.Environmental Protection Agency. Meeting summary report: Material characterization of nanoscale materials. U.S. EPA, Office of Prevention, Pesticides and Toxic Substances, Washington D.C., www.epa.gov; 2007.

156 U.S.Environmental Protection Agency. Nanoscale materials stewardship program interim report. U.S. EPA, Office of Pollution Prevention and Toxics, Washington D.C., www.epa.gov; 2009.

157 Kreider T, Halperin W. Engineered nanomaterials: learning from the past, planning for the future. J Occup Environ Med 2011; 53(6 Suppl): S108-S112.

158 Card JW, Magnuson BA. A method to assess the quality of studies that examine the toxicity of engineered nanomaterials. Int J Toxicol 2010; 29(4): 402-410.

159 Hamilton RF, Wu N, Porter D, Buford M, Wolfarth M, Holian A. Particle length-dependent titanium dioxide nanomaterials toxicity and bioactivity. Part Fibre Toxicol 2009; 6: 35.

160 Powers KW, Palazuelos M, Moudgil BM, Roberts SM. Characterization of the size, shape, and state of dispersion of nanoparticles for toxicological studies. Nanotoxicology 2007; 1(1): 42-51.

161 Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). The appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies. SCENIHR; 2006: SCENIHR 002/05. Internet: http://ec.europa.eu/health/ph_risk/committees/04_scenihr/scenihr_cons_01_en.htm.

162 Warheit DB, Borm PJ, Hennes C, Lademann J. Testing strategies to establish the safety of nanomaterials: conclusions of an ECETOC workshop. Inhal Toxicol 2007; 19(8): 631-643.

163 Warheit DB, Sayes CM, Reed KL, Swain KA. Health effects related to nanoparticle exposures: environmental, health and safety considerations for assessing hazards and risks. Pharmacol Ther 2008; 120(1): 35-42.

164 Warheit DB. How meaningful are the results of nanotoxicity studies in the absence of adequate material characterization? Toxicol Sci 2008; 101(2): 183-185.

165 International Organization for Standardization (ISO). Nanotechnologies - Guidance on physicochemical characterization for manufactured nano-objects submitted for toxicological testing. Report No. ISO TC 229/SC N, date 2011-01-28; 2011.

166 Elder A, Vidyasagar S, DeLouise L. Physicochemical factors that affect metal and metal oxide nanoparticle passage across epithelial barriers. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2009; 1(4): 434-450.

167 Hameri K, Lahde T, Hussein T, Koivisto J, Savolainen K. Facing the key workplace challenge: assessing and preventing exposure to nanoparticles at source. Inhal Toxicol 2009; 21 Suppl 1: 17-24.

168 International Organization for Standardization (ISO). Workplace atmospheres - ultrafine, nanoparticle and nano-structured aerosols - inhalation exposure characterization and assessment. Technical committee ISO/TC 146 (Air quality), Subcommittee SC2 (workplace atmospheres), ISO, Technical report ISO/TR 27628:2007; 2007.

169 Seipenbusch M, Binder A, Kasper G. Temporal evolution of nanoparticle aerosols in workplace exposure. Ann Occup Hyg 2008; 52(8): 707-716.

170 Asati A, Santra S, Kaittanis C, Perez JM. Surface-charge-dependent cell localization and cytotoxicity of cerium oxide nanoparticles. ACS Nano 2010; 4(9): 5321-5331.

171 Bhattacharjee S, de Haan LH, Evers NM, Jiang X, Marcelis AT, Zuilhof H et al. Role of surface charge and oxidative stress in cytotoxicity of organic monolayer-coated silicon nanoparticles towards macrophage NR8383 cells. Part Fibre Toxicol 2010; 7: 25.

172 El Badawy AM, Silva RG, Morris B, Scheckel KG, Suidan MT, Tolaymat TM. Surface charge-dependent toxicity of silver nanoparticles. Environ Sci Technol 2011; 45(1): 283-287.

173 Kroll A, Pillukat MH, Hahn D, Schnekenburger J. Current in vitro methods in nanoparticle risk assessment: limitations and challenges. Eur J Pharm Biopharm 2009; 72(2): 370-377.

174 Schaeublin NM, Braydich-Stolle LK, Schrand AM, Miller JM, Hutchison J, Schlager JJ et al. Surface charge of gold nanoparticles mediates mechanism of toxicity. Nanoscale 2011; 3(2): 410-420.

175 Veronesi B, de HC, Lee L, Oortgiesen M. The surface charge of visible particulate matter predicts biological activation in human bronchial epithelial cells. Toxicol Appl Pharmacol 2002; 178(3): 144-154.

176 Zhang LW, Monteiro-Riviere NA. Mechanisms of quantum dot nanoparticle cellular uptake. Toxicol Sci 2009; 110(1): 138-155.

177 Swuste, Drimmelen D, Burdorf. Pneumatic chippers design analysis and solution generation. Safety Science 1997; 27: 85-98.

178 Kroonenberg Hvd. Keuzetechnieken bij methodisch ontwerpen. De Constructeur 1986; 3: 24-32.

179 Kroonenberg Hvd. De dreigende teloorgang van het werktuigbouwkundig ontwerp. De Ingenieur 1990; 11: 25-28.

180 Schneider T, Brouwer DH, Koponen IK, Jensen KA, Fransman W, Van Duuren-Stuurman B et al. Conceptual model for assessment of inhalation exposure to manufactured nanoparticles. J Expo Sci Environ Epidemiol 2011; 21(5): 450-463.

181 Tielemans E, Schneider T, Goede H, Tischer M, Warren N, Kromhout H et al. Conceptual model for assessment of inhalation exposure: defining modifying factors. Ann Occup Hyg 2008; 52(7): 577-586.

182 Fissan H, Neumann S, Trampe A, Pui DYH, Shin WG. Rationale and principle of an instrument measuring lung deposited nanoparticle surface area. J Nanopart Res 2007; 9: 53-59.

183 Oberdorster G, Finkelstein J, Ferin J, Godleski J, Chang LY, Gelein R et al. Ultrafine particles as a potential environmental health hazard. Studies with model particles. Chest 1996; 109(3 Suppl): 68S-69S.

184 Tran CL, Buchanan D, Cullen RT, Searl A, Jones AD, Donaldson K. Inhalation of poorly soluble particles. II. Influence Of particle surface area on inflammation and clearance. Inhal Toxicol 2000; 12(12): 1113-1126.

185 Organisation for Economic Co-operation and Development (OECD). Preliminary analysis of exposure measurement and exposure mitigation in occupational settings: manufactured nanomaterials. OECD, series on the safety of manufactured nanomaterials: number 8, Report ENV/JM/MONO(2009)6, Paris, France; 2009.

186 Methner M, Hodson L, Dames A, Geraci C. Nanoparticle Emission Assessment Technique (NEAT) for the identification and measurement of potential inhalation exposure to engineered nanomaterials--Part B: Results from 12 field studies. J Occup Environ Hyg 2010; 7(3): 163-176.

187 Methner M, Hodson L, Geraci C. Nanoparticle emission assessment technique (NEAT) for the identification and measurement of potential inhalation exposure to engineered nanomaterials--part A. J Occup Environ Hyg 2010; 7(3): 127-132.

188 Brouwer D, Duuren-Stuurman van B, Berges M, Jankowska E, Bard D, Mark D. From workplace air measurement results toward estimates of exposure? Development of a strategy to assess exposure to manufactured nano-objects. J Nanopart Res 2009; 11: 1867-1881.

189 Brouwer DH, Gijsbers JH, Lurvink MW. Personal exposure to ultrafine particles in the workplace: exploring sampling techniques and strategies. Ann Occup Hyg 2004; 48(5): 439-453.

190 Tiered approach to an exposure measurement and assessment of nanoscale aerosols released from engineered nanomaterials in workplace operations. Presented by (in alphabetical order): Air Quality and Sustainable Nanotechnology of Energy and Environmental Technology e.V. (UTA), Federal Institute for Occupational Safety and Health (BAuA), German Social Accident Insurance Institution for the Raw materials and Chemical Industry (BG RCI), German Chemical Industry (VCI), Institute for Occupational Safety and Health of the DGUV (IFA), Research Group Mechanical Process Engineering, Institute of Process Engineering and Environmental Technology, Technical University Dresden (TUD). Germany; 2011.

191 Brunauer S, Emmett PH, Teller E. Adsorption of gases in multimolecular layers. J Am Chem Soc 1938; 60(2): 309-319.

192 Schmidt-Ott A, Baltensperger U, Gäggeler HW, Jost DT. Scaling behaviour of physical parameters describing agglomerates. J Aerosol Sci 1990; 21(6): 711-717.

193 Oberdorster G. Significance of particle parameters in the evaluation of exposure-dose-response relationships of inhaled particles. Inhal Toxicol 1996; 8 Suppl: 73-89.

194 Sager TM, Castranova V. Surface area of particle administered versus mass in determining the pulmonary toxicity of ultrafine and fine carbon black: comparison to ultrafine titanium dioxide. Part Fibre Toxicol 2009; 6: 15.
195 Cena LG, Anthony TR, Peters TM. A Personal Nanoparticle Respiratory Deposition (NRD) Sampler. Environ Sci Technol 2011; 45(15): 6483-6490.
196 Asbach C, Kaminski H, von BD, Kuhlbusch TA, Monz C, Dziurowitz N et al. Comparability of portable nanoparticle exposure monitors. Ann Occup Hyg 2012; 56(5): 606-621.
197 Methner MM, Birch ME, Evans DE, Ku BK, Crouch K, Hoover MD. Identification and characterization of potential sources of worker exposure to carbon nanofibers during polymer composite laboratory operations. J Occup Environ Hyg 2007; 4(12): D125-D130.
198 Dahm MM, Evans DE, Schubauer-Berigan MK, Birch ME, Fernback JE. Occupational exposure assessment in carbon nanotube and nanofiber primary and secondary manufacturers. Ann Occup Hyg 2012; 56(5): 542-556.
199 Broekhuizen F van, Van Broekhuizen JC, Cornelissen RTM, Terwoert J. Gebruik van nanoproducten in de Nederlandse bouwnijverheid. Stichting Arbouw, Harderwijk, rapport nr. 11-154; 2011.
200 Brouwer D. Exposure to manufactured nanoparticles in different workplaces. Toxicology 2010; 269(2-3): 120-127.
201 European Agency for Safety and Health at Work. Workplace exposure to nanoparticles. 2009.
202 Kuhlbusch TA, Asbach C, Fissan H, Gohler D, Stintz M. Nanoparticle exposure at nanotechnology workplaces: A review. Part Fibre Toxicol 2011; 8(1): 22.
203 Nazarenko Y, Han TW, Lioy PJ, Mainelis G. Potential for exposure to engineered nanoparticles from nanotechnology-based consumer spray products. J Expo Sci Environ Epidemiol 2011; 21(5): 515-528.
204 Schneider T. Evaluation and control of occupational health risks from nanoparticles. 2007: 581. Internet: http://www.norden.org/en/publications/publications/2007-581?set_language=en.
205 Trout DB. General principles of medical surveillance: implications for workers potentially exposed to nanomaterials. J Occup Environ Med 2011; 53(6 Suppl): S22-S24.
206 Fischman M, Storey E, McCunney RJ, Kosnett M. National Institute for Occupational Safety and Health nanomaterials and worker health conference--medical surveillance session summary report. J Occup Environ Med 2011; 53(6 Suppl): S35-S37.
207 Nasterlack M. Role of medical surveillance in risk management. J Occup Environ Med 2011; 53(6 Suppl): S18-S21.
208 Lenderink.A. Het melden van beroepsziekten: weten, willen, kunnen en mogen. Nederlands Centrum voor Beroepsziekten, Amsterdam; 2012.
209 Gezondheidsraad. Monitoring van milieu- en gezondheidsindicatoren. Een inventarisatie en evaluatie van milieufactoren, indicatoren en registratiesystemen. Den Haag: Gezondheidsraad, 2003; publication no. A03/07.
210 Donker GA. Continue Morbiditeits Registratie Peilstations Nederland 2010. Nederlands instituut voor onderzoek van de gezondheidszorg (NIVEL), Utrecht; 2011.

211 Gezondheidsraad. Gezondheid en milieu: mogelijkheden van monitoring. Den Haag: Gezondheidsraad; 2003: 2003/13.

212 Boutou-Kempf O, Marchand JL, Imbernon E. Feasibility of an epidemiological surveillance system for workers occupationally exposed to engineered nanomaterials. French Institute for Public Health Surveillance, France; 2012.

213 Erdely A, Liston A, Salmen-Muniz R, Hulderman T, Young SH, Zeidler-Erdely PC et al. Identification of systemic markers from a pulmonary carbon nanotube exposure. J Occup Environ Med 2011; 53(6 Suppl): S80-S86.

214 Li N, Nel AE. Feasibility of biomarker studies for engineered nanoparticles: what can be learned from air pollution research. J Occup Environ Med 2011; 53(6 Suppl): S74-S79.

215 Simeonova PP, Erdely A. Engineered nanoparticle respiratory exposure and potential risks for cardiovascular toxicity: predictive tests and biomarkers. Inhal Toxicol 2009; 21 Suppl 1: 68-73.

216 Bayer. Bayer code of good practice on the production and on-site-use of nanomaterials. 2007: Bayer AG, Lerverkussen, Duitsland.

217 David RM, Nasterlack M, Engel S, Conner PR. Developing a registry of workers involved in nanotechnology: BASF experiences. J Occup Environ Med 2011; 53(6 Suppl): S32-S34.

218 Schulte PA, Schubauer-Berigan MK, Mayweather C, Geraci CL, Zumwalde R, McKernan JL. Issues in the development of epidemiologic studies of workers exposed to engineered nanoparticles. J Occup Environ Med 2009; 51(3): 323-335.

219 European Agency for Safety and Health at Work. Risk perception and risk communication with regard to nanomaterials in the workplace. European Risk Observatory. EASHW, Luxembourg; 2012.

220 DuPont. Nano Risk Framework (draft). Environmental Defense - DuPont Nano Partnership. February 26; 2007.

221 Tongeren M van, Aitken R, Brouwer D, Christensen F, Clark K, Friedrichs S et al. Development of generic exposure scenario descriptions. Development of exposure scenarios for manufactures nanomaterials. Work Package 2, Nanex, European Union; 2010.

222 Brouwer D, Gerritsen-Ebben R, Duuren-Stuurman vB, Puijk I, Uzu G, Golimowski J et al. Occupational exposure scenarios. Development of exposure scenarios for manufactures nanomaterials. Work Package 3, Nanex, European Union; 2010.

223 Duuren-Stuurman B, Vink SR, Brouwer D, Kroese D, Heussen H, Verbist K et al. Stoffenmanager Nano: description of the conceptual control banding model. TNO report V9216 TNO, ArboUnie; 2011.

224 HSE. The assessment of different metrics of the concentration of nano (ultrafine) particles in existing and new industries. 2006: RR513. Internet: http://www.hse.gov.uk/research/rrhtm/rr513.htm.

225 Majestic BJ, Erdakos GB, Lewandowski M, Oliver KD, Willis RD, Kleindienst TE et al. A review of selected engineered nanoparticles in the atmosphere. Sources, transformations, and techniques for sampling and analysis. Int J Occup Environ Health 2010; 16: 488-507.

226 Tardif F, Sicard Y, Shakesheff A, Moehlmann C, Backman U. Is it possible to easily measure the engineered nanoparticles at workplaces? Nanosafe; 2008: D115/D121. Internet: http://www.nanosafe.org/scripts/home/publigen/content/templates/show.asp?P=63&L=EN.

Annexes

Annex **A**

Request for advice

[Ministry of Social Affairs and Employment; reference G&VW/GW/2009/18420]

Dear Prof. Knottnerus,

I hereby ask the Health Council to produce an advisory report on an exposure registry and health monitoring when working with nanoparticles.

The background to my request

Nanotechnology and nanoparticles are becoming increasingly important. This is because of the economic and social opportunities that nanotechnology offers. But it is also because of the uncertain risks associated with it. Attention is focused above all on the risks that might be associated with free, synthetic, insoluble nanoparticles. There is a great need for more knowledge about the risks from these particles, both on exposure and also on any possible toxicological effects. Although a great deal of research is being carried out into this all over the world, it is likely that there will still continue to be gaps in our knowledge for some considerable time.

In its approach to nanotechnology, and the uncertain risks from nanoparticles in particular, the Government chooses an approach for dealing with nanoparticles responsibly in accordance with a precautionary approach.

At the end of March this year the SER Committee on Working Conditions reported on how precaution could be applied when working with nanoparticles*. As part of the precautionary approach, the SER asserts that there is a need for an "early warning system in the context of health monitoring, as the possibility cannot be ruled out that harm to health may manifest itself in employees only after many years of exposure". The Committee therefore recommends submitting a specific request for an advisory report to the Health Council of the Netherlands, "in view of the many uncertainties that still exist on the expected health effects and therefore also on the possibilities and use of an early warning system".

Another part of the recommendation of the SER, concerning this, is the setting up of an exposure registry in companies that work with nanoparticles or certain categories of nanoparticles. With a more extensive exposure registry such as this, in future for example it will be possible to establish more quickly the connection between exposure and any health effects that may occur, which in turn can contribute to an "early warning".

I have decided to ask you for an advisory report on this. To this end I submit the following questions to you.

The request for advice

How should a registry of occupational exposure to nanoparticles be set up (at the least), so that a connection can be made with any health effects which appear later (or such a connection can be ruled out)?

I would ask you in any event to devote attention to:

- The properties of the nanoparticles that are to be registered
- The best parameters for expressing the degree of exposure
- To achieve this, the possibility of applying a distinction into categories of nanoparticles as advised by the SER (page 41 and subsection 4.3.1. of the SER advisory report)
- The possibility of a clear definition/delimiting of what should be registered
- A registry at the level of the individual employee or at group level
- High-risk groups among employees
- The usability of, or additional requirements on, existing databases and instruments for an exposure registry
- Basic conditions for implementation

---

* Veilig omgaan met nanodeeltjes op de werkplek (Dealing with nanoparticles safely in the workplace), SER 2009, ISBN 90-6587-984-6

To what extent is it possible and useful when working with nanoparticles to set up a health monitoring system and/or early warning system? What conditions would such a system need to meet in order to work effectively?

I would ask you in any event to devote attention to:

- The health effects that might be expected from exposure to nanoparticles
- The parameters that can be monitored in order to be able to establish any effects of nanoparticles
- High-risk groups
- The relationship with the nanoparticle exposure registry
- The usability of, or additional requirements on, existing databases, horizon scanning systems, and instruments for periodic examination
- Organisation of a system of health monitoring at company level, and/or at national level.

In view of the international nature of the problem of working with nanoparticles on the shop floor, I would ask you in your advisory process to build in scope for holding international consultations. I would also ask you in close discussions to establish a method for consulting experts from industry and the trade unions.

The starting point for your advisory process is the knowledge that is available now on nanoparticles and the risks they bring. If possible, I would also ask you in your advisory process to take into account the developments in research into nanoparticles, and the way in which in future use could be made of it.

I would ask you to issue your advisory report at the beginning of 2011, or earlier if possible.

Yours sincerely,
The Minister for Social Affairs and Employment,

J.P.H. Donner

Annex **B**

The Committee

- Prof. W.E. Bijker, *chairman*
  Professor of Technology and Society, Maastricht University
- Prof. A. Burdorf
  Professor in Determinants of Public Health, Erasmus Medical Centre, Rotterdam
- Dr. R. Houba
  Occupational Hygienist, Nederlands Kenniscentrum Arbeid en Longaandoeningen, Utrecht
- Dr. T.M. Pal
  Occupational Physician, Nederlands Centrum voor Beroepsziekten, Amsterdam
- Prof. A. Schmidt-Ott
  Professor of Particle Technology, Technical University Delft
- Dr. P.H.J.J. Swuste
  Safety Manager/Occupational Hygienist, Technical University Delft
- Dr. E. Tielemans
  Business Line Manager ‘Safe handling of innovative substances and technologies’, TNO, Zeist
- Dr. R.C.H. Vermeulen
  Occupational Epidemiologist, Institute for Risk Assessment Sciences, University Utrecht

- Prof. F.R. Cassee, *advisor*
  National Institute for Public Health and the Environment, Bilthoven;
  Professor of Inhalation Toxicology, Institute for Risk Assessment Sciences, University Utrecht
- Drs. E.C. van de Aker, *observer*
  Ministry of Social Affairs and Employment, The Hague
- Dr. J.M. Rijnkels, *secretary*
  Health Council of the Netherlands, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Working Conference

On 25 January 2012, the Health Council, in the presence of the members of the Committee that produced this advisory report, held a conference to consult with experts (with experience) in Dutch industry, researchers and organisations involved in health and safety in the workplace. The conference was chaired by the chairman of the Committee, Prof. W.E. Bijker. The aim was to obtain more information and to listen to the experiences on starting and maintaining of an exposure registry and a system of health monitoring and/or early warning in the workplace. The participants at the conference are not responsible for the text and the content of this advisory report.

The information, ideas and also the concerns that the Committee gathered at the conference provided above all some understanding of the application of an exposure registry and a system of health monitoring, by health and safety experts (occupational hygienists, occupational physicians), and possibilities for implementation in business. There was barely any new scientific information. The Committee included the comments from the conference as a supplement to and in broad terms in its considerations.

Participants

- R. Van Beek, Vereniging FME-CMW, Zoetermeer
- K.G. Beaumont, Ministry of Public Health, Welfare and Sport, The Hague
- Dr. J. Boonstra, Expert centre Inspectorate SZW, The Hague
- P. Van Broekhuizen, IVAM - University of Amsterdam

- D. Bruinvels, Nederlandse Vereniging voor Arbeids- en Bedrijfsgeneeskunde, Utrecht
- R.T.M. Cornelissen, Stichting voor Fundamenteel Onderzoek der Materie, Utrecht
- S. Dekkers, Centrum voor Stoffen en Integrale Risicoschatting, RIVM, Bilthoven
- G. Dijkstra, Vereniging van Verf- en Drukinktfabrikanten, Leidschendam
- D. Hoeneveld, Arbozaken, Technical University Delft
- H. Holtman, Koninklijke Vereniging FOSAG, Waddinxveen
- F.J. Jongeneelen, Industox Consult, Nijmegen
- F. Linker, DSM Expert Center, Product Safety Toxicology & Industrial Hygiene, Heerlen
- A. Pronk, TNO Research Group Quality and Safety, Zeist
- H.E. Schram, Centrum voor Milieu Gezondheidsonderzoek, National Institute for Public Health and Environment, Bilthoven
- Dr. K. Verbist, Expertise Centrum Toxische Stoffen, Arbo Unie BV, Utrecht
- S.P. Verloove-Vanhorick, Leiden University Medical Centre en TNO Child Health, Leiden
- G. Visser, Innovation Center Corporate Technologies DSM, Heerlen
- A.P. van Wezel, KWR Watercycle Research Institute, Nieuwegein
- P.B. Wulp, Expert centre Inspectorate SZW, The Hague

Annex **D**

Comments on the public advisory report

A draft of the present advisory report was released in 2012 for public review. The following organisations and persons have commented on the draft document:

- G. Andrievsky, Insitute of Physiological Active Compounds, LLC, Kharkov, Oekraïne
- R. van Beek, FME-CWM, Zoetermeer
- P.J.A. Borm, Nano4imaging BV, Geleen
- P. van Broekhuijzen, IVAM University of Amsterdam, Amsterdam
- R.T.M. Cornelissen, FOM, Utrecht
- P.J. Fraanje, NVTB, Nieuwegein
- Ms. Gálvez-Pérez, CNNT-INSHT, Ministerio de Empleo y Seguridad Social, Madrid, Spain
- D. Hoeneveld, VSNU, The Hague
- F.L.M. Kok, WVOI, The Hague
- T.J. Lentz and dr. M. Schubauer-Rerigan, National Institute for Occupational Health and Safety, Cincinnati, United States
- M. Nasterlack, BASF SE, Ludwigshaven, Germany
- G. de Rooij, FNLI, Rijswijk
- S.P. Verloove-Vanhorick, Oegstgeest
- G. Visser and F. Linker, DSM Innovation Centre, Geleen
- A.P. van Wezel, KWR Watercycle Research Institute, Nieuwegein
- P.B. Wulp, Inspectie SZW, Utrecht
- E. van Zuilekom, RIVM, TWO Compliants, Bilthoven

The comments and the replies by the Committee can be inspected at the website of the Health Council: www.healthcouncil.nl

Annex **E**

Voluntary Reporting Scheme (Defra, UK)

Source: Nanomaterials: Hazards and risks to health and the environment. A supplementary guide for the UK Voluntary Reporting Scheme. Www.defra.gov.uk

2 Identity of the engineered nanoscale material

- CAS number and name (if available) and any other names, including trade names or synonyms
- Composition and structural formula
- Degree of purity (%)
- Nature of impurities, including isomers and by-products
- Percentage of main impurities
- Presence of a stabilising agent, inhibitor or other additive
- Spectral data (e.g. IR, UV, NMR, mass spectrum)
- Chromatographic data (e.g. HPLC, GC)
- Analytical methods of detection and determination
- Additional information (e.g. anticipated changes in properties that would impact on the identity of the material; analytical quality assurance procedures)

3 Information on the engineered nanoscale material

- Physical dimensions and shape, including the measurement technique employed
- Manufacturing process

- Source of the material (to be completed by those not manufacturing the reported nanoscale material)
- Intended use
- Potential human and environmental exposure pathways and likelihood of exposure
- Benefits of the uses of the material
- Agglomeration and aggregation properties

4 Physico-chemical properties of the engineered nanoscale material

- Physical form at 20ºC and 101.3kPa
- Melting point
- Boiling point
- Relative density
- Vapour pressure
- Surface tension
- Water solubility
- Partition coefficient (octanol-water)
- Flash point
- Flammability
- Explosive properties
- Self-ignition temperature
- Oxidising properties
- Particle size distribution

5 Toxicological Data

- Acute toxicity (following oral administration)
- Acute toxicity (following inhalation)
- Acute toxicity (following skin application)
- Skin irritation
- Eye irritation
- Skin sensitisation
- Repeated dose toxicity (28 days)
- Mutagenicity
- Reproductive toxicity
- Toxicokinetic behaviour
- Non-animal toxicity test results

6 Ecotoxicological Data

- Acute toxicity for fish
- Acute toxicity for daphnia

- Growth inhibition of algae
- Bacteriological inhibition
- Biotic degradation
- Abiotic degradation
- Absorption/desorption
- Bioaccumulation
- Distribution among environmental media

7 Risk management practices

- Recycling
- Neutralisation of unfavourable effects
- Destruction
- Other means of managing risk

Annex **F**

Voluntary Nanoscale Materials Stewardship Program (US EPA)

Source: NSMP Information Collection Request. Www.epa.gov/oppt/nano/stewardship.htm

1 Company name and other identifying information, address of company and site, technical contact and related information.

2 Common or trade name of chemical.

- Chemical identity and molecular structure of substance.

3 The following physical and environmental fate properties and information would be helpful to characterize the nanoscale material where relevant and reasonably ascertainable:

- Physical state
- Density
- Melting temperature
- Spectra
- Particle size distribution
- Henry's Law constant
- pH
- Flammability
- Adsorption coefficient
- Agglomeration state/dispersion state
- Vapour pressure
- Solubility in water or other solvents
- Boiling/sublimation temperature
- Dissociation constant
- Octanol/water partition coefficient
- Volatilisation from water
- Volatilisation from soil
- Explodability
- Shape
- Crystal structure
- Chemical composition – including spatially averaged (bulk) and spatially resolved

- heterogeneous composition
- Surface area
- Surface charge
- Surface chemistry
- Porosity

4 Description of all uses including expected consumer uses.

5 Estimate of the total amount of substance to be manufactured/imported including the amounts for each use category.

6 Description of byproduct resulting from manufacture, process, use or disposal of chemical.

7 For each type of workplace in the lifecycle, the same information requested on pp. 8-10 of the EPA PMN form (7710-25) would be helpful for releases and exposures, with the following additions.

8 In addition to the above properties and information the following physical properties would be helpful for understanding and assessing exposures and releases:

- surface reactivity
- average particle surface area
- aggregation
- wet and dry transport
- bioaccumulation/biomagnifications
- particle count
- surface/volume ratio
- mobility through soil
- average particle weight
- rate of sorption
- rate of diffusion
- rate of gravitational settling
- biodegradation
- rate of deposition
- average aerodynamic diameter
- influence of Redox and photochemical reaction

9 A brief overview of the lifecycle including all workplaces that manufacture, process, or use the nanoscale chemical and all expected consumer uses.

10 For each release point for which control technology is used, rationale for selecting the control, and, if available, data and measurement methods of waste treatment or purification efficiency studies for the nanoscale material.

11 Regarding worker exposure information, personal or area monitoring data (in mass concentrations, surface area per mass, number of particles, etc.) for the nanoscale material, including the measurement method(s) used to generate the data.

12 For each protective equipment or engineering control listed as worker protection, rationale for selecting the protective equipment or engineering controls, and data (and methods used to generate the data) that were used in making the selection or that may help to indicate the effectiveness of the protective equipment or engineering controls.

13 Information on cleaning/ reuse/ disposal of used protective equipment (gloves, respirator cartridges, etc.).

14 Additional procedures or other equipment intended to mitigate exposures to the nanoscale material.

15 Description of worker training and hazard communication (MSDS, other) specific to the nanoscale material.

16 Estimate of the total number of individuals other than workers exposed to the chemical and duration of exposure.

17 Manner or method of disposal for consumer use of products containing the nanoscale material.

18 Any test data in the submitter's possession regarding information on health/ environmental effects, environmental fate, worker safety, and material characterisation, including any data related to characterisation of the nanoscale material in the subject organism and test medium.

Annex **G**

Nano-specific individual exposure form (CEA, France)

Source: Commissariat à l'ènergie atomique (CEA), France, Daniël Bloch, presentation for NIOSH workshop on exposure registries of nanoparticles in the workplace (Keystone, June 2010)

FICHE PROCEDE NANOMATERIAUX N° Date rédaction:

Centre: UO: … Dep.: … Service: … Labo: …

Bâtiment: … Pièce: … Responsable de l'équipement: …

Nom de l'équipement: … Nom de procédé: …

CLS N°: … Mode opératoire: □ oui □ non

Personnes travaillant dur la manip: …

PROCEDE

Intitulé: … Description: …

MATIERES PREMIERES

Nature chimique: … **Quantités consommées / manip**: …

Si NANOMATERIAUX

Nature physique: Dimensions (nm) ø: … Longueur: …

□ nanofils □ nanotubes

□ nanopoudres □ nanocristaux % de la charge totale: …

Nature chimique: … **Quantités consommées par manip**: …

MATERIAU FINAL

Nature chimique: …

Nature physique:
☐ nanofils ☐ nanotubes
☐ nanopoudres ☐ nanocristaux
☐ couches minces

Dimensions (nm) ø: … Longueur: …

Conditionnement final:
☐ sec ☐ liquide ☐ aérosols

Epaisseur: …

Si déposé sur **substrat**, lequel: …

Quantités fabriquées/manip: …
Fréquence des manips: …

Impuretés, catalyseurs, produits associés:
Nature: …% en masse: …

PHASES CRITIQUES

				Moyens de prévention		
	Durée	Fréquence	Dustiness (1 á 10)	Collectifs	Masques	Gants et tenues
Chargements:	… …	… …	… …	… …	… …	… …
Collecte du matériau:	… …	… …	… …	… …	… …	… …
Ouvertures:	… …	… …	… …	… …	… …	… …
Nettoyage:	… …	… …	… …	… …	… …	… …
Maintenance:	… …	… …	… …	… …	… …	… …
Autre:	… …	… …	… …	… …	… …	… …

Codification des moyens de prévention

Collectifs:	**Masques:**	**Gants et tenues:**
1. BAG	1. Papier	1. Latex
2. Sorbonne	2. P2	2. Nitrile
3. Aspirations	3. P3	3. Vinyl
4. Aspirateurs T.H.E.	4. Adduction d'air	4. Tenue TYVEK
5. Filtres HEPA		5. Autre

Annex **H**

Form exposure scenarios (NANEX-WP2, EU)

Source: www.nanex-project.eu

Format for description of exposure scenarios: standard exposure scenario format for uses of substances by workers:

Title of Exposure Scenario
List of all use descriptors related to the life cycle stage and all the uses under it; include market sector (by PC) if relevant
Name of contributing environmental scenario (1) and corresponding ERC
List of names of contributing worker scenarios (2-n) and corresponding PROCs
Further explanations (if needed)
1 Exposure Scenario
2.1 Contributing exposure scenario (1) controlling environmental exposure for ...
Name of contributing exposure scenario
Further specification
Product characteristics
Product related conditions, e.g. the concentration of the substance in a mixture; viscosity of product; package design affecting exposure
Amounts used
Daily and annual amount per site (for uses in industrial setting) or daily and annual amount for wide disperse uses
Frequency and duration of use
Intermittent (used < 12 times per year for not more than 24 h) or continuous use/release

Environment factors not influenced by risk management

Flow rate of receiving surface water (m³/d) (usually 18,000 m³/d by default for the standard town); **please note**: the default flow rate will be rarely changeable for downstream uses*;*

Other given operational conditions affecting environmental exposure

Other given operational conditions: e.g. technology or process techniques determining the initial release of substance from process (via air and waste water); dry or water based processes; conditions related to temperature and pressure; indoor or outdoor use of products; work in confined area or open air

Technical conditions and measures at process level (source) to prevent release

Process design aiming to prevent releases and hence exposure to the environment; this includes in particular conditions ensuring rigorous containment; performance of the containment to be specified (e.g. by quantification of a release factor)

Technical onsite conditions and measures to reduce or limit discharges, air emissions and releases to soil

Technical measures, e.g. on-site waste water and waste treatment techniques, scrubbers, filters and other technical measures aiming at reducing releases to air, sewage system, surface water or soil; this includes strictly controlled conditions(procedural and control technology) to minimise emissions; specify effectiveness of measures; specify the size of industrial sewage treatment plant (m³/d), degradation effectiveness and sludge treatment (if applicable);

Organisational measures to prevent/limit release from site

Specific organisational measures or measures needed to support the functioning of particular technical measures. Those measures need to be reported in particular for demonstrating strictly controlled conditions

Conditions and measures related to municipal sewage treatment plant

Size of municipal sewage system/treatment plant (m³/d); specify degradation effectiveness; sludge treatment technique (disposal or recovery); measures to limit air emissions from sewage treatment (if applicable); please note: the default size of the municipal STP (2,000 m³/d) will be rarely changeable for downstream uses.

Conditions and measures related to external treatment of waste for disposal

Fraction of used amount transferred to external waste treatment for disposal; Type of suitable treatment for waste generated by workers uses, e.g. hazardous waste incineration, chemical-physical treatment for emulsions, chemical oxidation of aqueous waste,: specify effectiveness of treatment;

Conditions and measures related to external recovery of waste

Fraction of used amount transferred to external waste treatment for recovery: specify type of suitable recovery operations for waste generated by workers uses, e.g. re-distillation of solvents, refinery process for lubricant waste, recovery of slag: heat recovery outside waste incinerators; specify effectiveness of measure;

Additional good practice advice (for environment) beyond the REACH CSA Note: The measures reported in this section have not been taken into account in the exposure estimates related to the exposure scenario above. They are not subject to obligation laid down in Article 37 (4) of REACH, Thus, the downstream user is not obliged to i) carry out an own CSA and ii) to notify the use to the Agency, if he does not implement these measures.

Use specific measures expected to reduce the predicted exposure beyond the level estimated based on the exposure scenario.

2.2 Contributing exposure scenario (2-n) controlling worker exposure for ...

Name of contributing exposure scenario 2

Further specification:

Product characteristics

Product related conditions, e.g. the concentration of the substance in a mixture, the physical state of that mixture (solid, liquid; if solid: level of dustiness), package design affecting exposure)

Amounts used

Amounts used at a workplace (per task or per shift); note: sometimes this information is not needed for assessment of worker's exposure

Frequency and duration of use/exposure

Duration per task/activity (e.g. hours per shift) and frequency (e.g. single events or repeated) of exposure

Human factors not influenced by risk management

Particular conditions of use, e.g. body parts potentially exposed as a result of the nature of the activity

Other given operational conditions affecting workers exposure

Other given operational conditions: e.g. technology or process techniques determining the initial release of substance from process into workers environment; room volume, whether the work is carried out outdoors/indoors, process conditions related to temperature and pressure

Technical conditions and measures at process level (source) to prevent release

Process design aiming to prevent releases and hence exposure of workers; this in particular includes conditions ensuring rigorous containment; effectiveness of containment to be specified (e.g. by quantification of residual losses or exposure)

Technical conditions and measures to control dispersion from source towards the worker

Engineering controls, e.g. exhaust ventilation, general ventilation; specify effectiveness of measure

Organisational measures to prevent /limit releases, dispersion and exposure

Specific organisational measures or measures needed to support the functioning of particular technical measures. Those measures need to be reported in particular for demonstrating strictly controlled conditions (to justify exposure based waiving)

Conditions and measures related to personal protection, hygiene and health evaluation

Personal protection, e.g. wearing of gloves, face protection, full body dermal protection, goggles, respirator; specify effectiveness of measure; specify the suitable material for the PPE (where relevant) and advise how long the protective equipment can be used before replacement (if relevant)

Additional good practice advice beyond the REACH CSA Note: The measures reported in this section have not been taken into account in the exposure estimates related to the exposure scenario above. They are not subject to obligation laid down in Article 37 (4) of REACH, Thus, the downstream user is not obliged to i) carry out an own CSA and ii) to notify the use to the Agency, if he does not implement these measures.

Use specific measures expected to reduce the predicted exposure beyond the level estimated based on the exposure scenario.

3 Exposure estimation and reference to its source

Estimation of exposure and risk characterisation ratios (for all route of exposure for consumer and all compartment for the environment) resulting from the conditions described above (entries 2.1 and 2.2) and the substance properties; make reference to the exposure assessment method applied (specify for the routes if relevant);

Alternatively: Include a link to a website from where the information described above can be retrieved:

4 Guidance to DU to evaluate whether he works inside the boundaries set by the ES

Guidance how the DUs can evaluate whether they operate within the conditions set in the exposure scenario. This may be based on a set of determinants (and a suitable algorithm) which together ensure control of risk, but which have some flexibility in the respective values for each determinant. This section may also include a link to a suitable calculation tool. Where relevant: Other methods for DU to check whether they work within the boundaries set by the ES may be included here.

Example: Titanium dioxide

Please note this exposure sheet was not developed as part of a full risk assessment process, and may not necessarily describe exposure conditions for which there are no risks to human health and the environment.

Standard Exposure Scenario Format 1: For Uses of Substances by Workers

Title	Production of titanium dioxide by laser ablation	Date	08/07/2010
Substance type	TiO2	Entered by	TNO
Internal reference ID	ES 9		

List of all use descriptions related to the life cycle stage and all the uses under it; include market sector (by PC) if relevant:

SU 3; PC 7; PROC 15, 26

List of names of contributing exposure scenarios and corresponding PROCs/PCs

CES 1: Laser ablation (PROC 15, 26)

CES 1: Name of contributing exposure

Laser ablation (PROC 16, 26)

Further specification

Laboratory is part of the Laser Engineering Department and is situated next to a busy main road. In this workshop-like laboratory high energy cutting lasers (1kW) are used for research into the ablation of metals and the welding and cutting of metals. In the laser ablation process, plates of pure titanium dioxide are placed in a dish under deionised water. Spherical nanoparticles of titanium dioxide in the size range 20 – 80 nm are produced when the titanium plate is irradiated with a laser set at about 250 Watts. This scenario involves tests.

Production characteristics

Particles in liquid, viscosity unknown.

Amounts used

Production 3 g/hour

Frequency and duration of use/exposure

Duration task 8 minutes

Human factors not influenced by risk management

Not reported

Other given operational conditions affecting workers exposure

Laboratory volume 150 m3 (temperature and RH not reported)

Technical conditions and measures at process level (source) to prevent release

Task performed in screened off area made from a 2x2 m timber framework covered with plastificised fabric and accessed via an open wire mesh door. Laser normally was operated remotely, and nobody is allowed inside the enclosed area during laser operation.

Technical conditions and measures to control dispersion from source towards the worker

LEV (movable capture hood, natural ventilation)

Organisational measures to prevent/limit releases, dispersion and exposure

Not reported

Conditions and measures related to personal protection, hygiene and health evaluation

Disposable nitrite gloves

Additional good practice advice (for environment) beyond the REACH CSA

Not reported

Exposure estimation

SMPS:	particles < 100 nm during activity: 11699 #/cm3 (AM)
	particles < 100 nm during non-activity: 11974 #/cm3 (AM)
	particles > 100 nm during activity: 1575 #/cm3 (AM)
	particles > 100 nm during non-activity: 1675 #/cm3 (AM)

References

Ref Title: D2.2 Report of results and implications of main study to measure nanoparticles concentrations in workplaces – Part 1: Main summary; Author: NANOSH; Journal: -; Ref Year: 2010

Annex I

Data from the literature on processes involving nanomaterials

Tabel I.1 Data from industries.

Production function	Production principle	Production form	Reference
Material sourcing			Dupont, 2007[221]
Manufacturing		Carbon electrodes, laser beam, gas over heated surface	
Product manufacturing	Matrix incorporation, grinding, smoothing		
Filling/Packaging			
Use/reuse/maintenance			
Recycle/waste management			
	Refining, smelting, galvanizing, welding, gouging, cutting, coating, cooking, hot wax application	Hot processes	ISO, 2007[168]
Mechanical processes	Grinding, drilling	High speed, energy	
Material handling		Powders, dry colloidal deposits	
Manufacturing			Schulte et al., 2008/ 2010[90,131]
Maintenance			
Process equipment breakdown			
	Pouring, mixing		NIOSH, 2009[96]
		Open system	
Handling powders	Weighing, blending, spraying		
Maintenance		Cleaning equipment	

Cleaning		Dust collecting systems	
	Machining, drilling, sanding		
Synthesis		Tube furnace, lev	Zalk et al., 2009[133]
Maintenance		Tube furnace, containment	
Processing	Depositioning	Electric fields, ventilation	
	Sample preparation, cutting, slicing, grinding, lapping, etching, polishing	Ventilation	
	Pouring	Container, wet process, lev	
	Mixing, etching	Ventilation	
	Turning, milling	Lev	
	Sampling	Lev	
Start-up/scale up, transport, warehousing, maintenance			Trout et al., 2010[152]
Manufacturing/production, transport, warehousing, maintenance, waste handling			
Incorporation in products, maintenance, manipulation, application			
Manufacturing	Sampling, bagging	Reactor, closed system, tube	Tongeren et al., 2010[222]
	Opening, drying, grinding	Closed reactor, hatch, lev, closed dryer, lev, closed grinder, lev	
	Ablation	Laser, wet process, enclosure, lev	
Handling nanomaterials	Weighting, pouring, mixing	Bench, lev	
Maintenance reactor	Scratching	Reactor, scalpel, vacuum	
Production inks	emptying	Bags, filling station, lev	
		Closed process	Brouwer et al., 2010[223]
Maintenance, process disturbances	Continuous process, sampling,	Closed process	
	Batch process, charging, sampling	Closed/open process	
Processing	Mixing, blending	Solid/liquid, closed/open systems	.
	Calendering,		
	Spraying	Air dispersion	
	Rolling application, brushing		
	Dipping, pouring, immersing, soaking, washing		
	Tableting, compressing, extruding, pelletizing		
	Lubricating, greasing	Open process	
	Atomisation, dispersion, electrolysis	Hot process, wet process	
Transport of materials	(dis)charging, sampling, loading, filling, dumping, bagging, cleaning	Vessel, container,	
Manipulation of materials	Manual cutting, cold rolling, assembling		
Synthesis		Valves, pipe connections, seals	Duuren et al., 2011[224]

	Injecting	Flame, filter plate	Schneider et al., 2011[181]
Handling products	Bagging, dumping, cleaning, scooping, weighing	Big/small bags	
	Transporting	Containers, barrels, bottles, bags	
Processing	Spraying, fogging		
	Fracturing, abrasing, grinding		
	Turning, milling		
	Ablation	Laser	
	Mixing, adding, stirring, pouring	Wet process, container	
	Cutting, slicing, grinding, lapping, polishing, etching,		
	Sintering	Quartz tube	

Table I.2 Data from research laboratories.

Production function	Production principle	Production form	Reference
Synthesis	Weighing, mixing, transporting	Vial, furnace, glove box, containment, container	Paik et al. (2008)[130]
	Injection	Flame, filter plate, lev	
		Tube furnace, carrier gas, containment.	
Handling products	Consolidating, weighing,	Powder, solvent, tube furnace, container, lev	
	Drying	Powder, canister, containment.	
Machining composites	Cutting	Dry/wet process, band-saw, cutting wheel, lev.	Tongeren et al. (2010)[222]
Manufacturing	Dissolving, depositioning	Syringe, tube furnace, glass tube, carrier gas, vial, fume cupboard, cutter, ventilation.	
Activity with nanomaterials		Dry/wet, open/closed process.	Groso et al. (2010)[129]

Annex **J**

Monitoring and measuring techniques

Available monitoring and measuring techniques for aerosols of nanoparticles.[10,96,168,186-189,224-226]

Method	Remarks
Size selective personal sampler.	Personal filter sampling via suction pump or via impactor samples. After this, gravimetric and chemical analysis of the filter samples necessary. There are no filters specifically receiving particles under 100 nm in size.
Size selective static sampler.	Fixed filter sampling via suction pump or impact samples. After this, gravimetric and chemical analysis of the filter samples necessary. Some impactors can receive particles with a diameter of less than 100 nm (among others Berner Low Pressure Impactor (LPI) and Micro Orifice Impactor (MOI).
Tapered Element Oscillating Microbalance (TEOM®).	Real-time monitoring of mass concentration. With special intakes, the size of the particles can be selected.
Electric Low Pressure Impactor (ELPI™).	Real-time monitoring. Particles are aspirated using a vacuum pump and then given an electrical charge. It measures the active surface area of the particle, sub-divided into size distribution. Mass concentration can be calculated if the particle charge and the density are known. ELPI is to be adjusted to the aerodynamic diameter of the aerosols. Aerosols can also be captured for further analysis.
Micro-Orifice Uniform Deposit Impactor (MOUDI).	Real-time monitoring. Is to be adjusted to the aerodynamic diameter of the particles.
Aerosol particle Mass Analyser (APM)	Samples aerosols with a particle density of around 1 g/cm^3. Sensitivity: 30 – 580 nm; gives only mass concentration and does not depend on particle size or shape.
Condensation Nuclei or Particle Counter (CNC or CPC).	Real-time monitoring (fixed and portable models). The CNC/CPC directs aspirated air into a saturated alcohol vapour. The alcohol condenses on the nanoparticles, on account of which they acquire a larger diameter. These larger particles can be counted with an optical detector. The instrument counts all particles sized from < 10 nm to 1,000 nm. It does not differentiate between larger and smaller particles and therefore does not show any distribution in particle size.
Optical Particle Counter (OPC).	Real-time monitoring (fixed and portable models). The OPC uses a laser scattering technique and measures the number of particles per litre of air with a diameter of from 300 nm and larger. In combination with a CPC, even particles with a smaller diameter can be measured.

Differential Mobility Analyser (DMA)	Near real-time aerosol monitoring of the distribution of the particle size based on a *mobility* diameter (≈5 – 800 nm). Mass concentration can be calculated if the particle load and the density are known. It can be combined with other techniques such as DMPS.
Scanning Mobility Particle Sizer (SMPS)	Measures in aerosols. Sensitivity: 3 – 1,000 nm; uses an electrostatic arrangement and a CPC. Can be connected to a DMA.
Fast Mobility Particle Sizer (FMPS)	Real-time fixed monitoring. See DMAS and SMPS.
Electron microscopy	Off-line. Particle samples are collected on a filter and, after processing, are placed in the electron microscope.
(Aerosol) Diffusion Charger ((A)DC).	Real-time monitoring of active surface area aerosols. Not all chargers can measure particles with an 'active surface area' of less than 100 nm. Examples are: The portable Aerotrak™ 9000 Nanoparticle Aerosol Monitor (does not distinguish particles > 100 nm). The portable Grimm Nano-Check™ 1.320 (measures particle concentration and mean *mobility* diameter, on account of which it is possible to estimate the geometric surface area of the particle; lower limit of detection limit is 25 nm). The portable Philips Aerasense Nanotracer and Nanomonitor (measures particle concentration and mean particle diameter, on account of which it is possible to estimate the geometric surface area of the particle; detection 10 and 300 nm). Matter Diffusion Size Classifier. LO1-DC.
Nanoparticle Surface Area Monitor (NSAM)	Real-time fixed monitoring. Is sensitive to particles larger than 10 nm in aerosols. Comparable action as the Electrical Aerosol Detector (EAD).
DMAS linked to ELPI™	Difference in measured aerodynamic and *mobility* diameter can be used for calculating particle surface area.
Transmission electron microscopy	Off-line analysis; sensitive to 1 nm; more than 1 microgram of sample is necessary for analysis. It is also suitable for other characterisation (aggregates, shape).
Scanning electron microscopy	Off-line analysis; sensitive to 1 nm. Is also suitable for other characterisation (aggregates, shape).
Atomic Force Microscopy (AFM)	Off-line analysis; sensitivity: 1 nm – 8 micrometres; is a form of scanning Probe Microscopy. Air and liquid sampling possible. Is also suitable for other characterisation (aggregates, shape).
Photon Correlation Spectroscopy (PCS)	Off-line analysis; sensitivity 1 nm – 10 micrometres; based on Dynamic Light Scattering (DLS).
Nanoparticle Tracking Analysis (NTA)	Measures in suspensions. Sensitivity: 10 – 1,000 nm; is used in combination with DLS and PCS.
X-Ray Diffraction (XRD)	Off-line analysis; Can identify individual crystals; sensitive to 1 nm; at least 1 mg of sample needed.
Aerosol Time of Flight Mass Spectrometry	Measures in aerosols; sensitivity 100 – 3,000 nm; the smaller the particles, the less efficient the analysis.

Monitoring and measuring techniques classified by parameters.

Parameter	Method(s)
Mass concentration	Aerosol particle Mass Analyser (APM) Electric Low Pressure Impactor (ELPI™) Micro-Orifice Uniform Deposit Impactor (MOUDI) Size selective personal sampler Size selective static sampler Tapered Element Oscillating Microbalance (TEOM®)
Particle concentration	Condensation Nuclei or Particle Counter (CNC or CPC) Differential Mobility Analyser (DMA) Electron microscopy Fast Mobility Particle Sizer (FMPS) Optical Particle Counter (OPC) Scanning Mobility Particle Sizer (SMPS)
Surface area concentration	(Aerosol) Diffusion Charger ((A)DC) DMAS linked to ELPI™ Electric Low Pressure Impactor (ELPI™) Electron microscopy Nanoparticle Surface Area Monitor (NSAM)
Particle characteristics: particle size	Aerosol Time of Flight Mass Spectrometry Atomic Force Microscopy (AFM) Nanoparticle Tracking Analysis (NTA) Photon Correlation Spectroscopy (PCS) Scanning electron microscopy Transmission electron microscopy X-Ray Diffraction (XRD) Cascade impactor
Particle characteristics: distribution of the particle size	Nanoparticle Tracking Analysis (NTA) Photon Correlation Spectroscopy (PCS) Scanning Mobility Particle Sizer (SMPS)

Annex **K**

Summary of data to be registered

In this annex, the Committee outlines what data is important for a successful registration. The data display an overlap with the data asked for in various foreign registry projects (see Annexes E to H). See Subsections 3.1, 3.3 and 3.5 for an explanation of the choices that the Committee has made.

In the overview a distinction is made between the data (for each substance or nanomaterial) which can be filled in once (A) and data which may have to be filled in on several occasions, because several emission and exposure scenarios are possible within a company, each of which must be registered (B). As soon as the scenario changes the data in the registration need to be updated.

Part of the physical and chemical data, which are mentioned in table A, will sometimes be difficult to obtain. However, such data is necessary to get a good picture of the toxic properties of nanoparticles.

A – General data

	Explanation/examples
General	
Type of company or institution	Development, manufacturing, production, use, waste or recycling
Number of employees who can potentially be exposed to nanoparticles	
Production or volume of use	Estimated amount used or produced annually
Identity of nanomaterial (if applicable)	
CAS number	If available
Product name	
Synonyms, including trade names	
Identification and percentage of nanoparticles	
Identity of nanoparticles	
CAS number	If available
Name	
Synonyms, including trade names	
Chemical and physical properties of nanoparticles	
See the proposed guideline by ISO.[165] See also the three REACH Implementation Projects for Nanomaterials (RIP-oNs). Guidelines on identifying nanomaterials are laid down in these projects (RIP-oN1), information requirements (RIP-oN2) and on exposure assessment and danger and risk characterisation (RIP-oN3). They are developed for companies and are indeed used as aids in, for example, setting up an RI&E and for the REACH registry. Other possible sources of information are the safety information sheets (EU-REACH), International Chemical Safety Card (WHO) and the Material Safety Data Sheet (USA).	
Particle size and size distribution, fibre length and diameter	Description of the physical dimensions (diameter, length) and particle size distribution.
Agglomeration and aggregation properties	Number of aggregate particles compared to the total number of primary particles in an agglomerate of aggregate; distribution of these particles.
Particle shape	For example homogeneous or heterogeneous balls, fullerenes, tubes, and sheets.
Chemical composition	This includes a description of the crystal and molecular structure, and data on identification and percentage of contamination or by-products.
Surface chemistry	Description of the chemical composition at the surface of the particle.
Electrical charge at the surface	Measure of the electrical charge at the surface of a particle (zeta potential).
Solubility and dispergation	Description of the solubility of a particle in a solution, or a description on how the particle is distributed in a medium (for instance, colloid, emulsion or suspension).

B – Emission and exposure scenarios (several scenarios are possible)

	Explanation/examples
General data	
Date/period	The date of the scenario described below, and total period of the scenario.
Department/workplace	Department or workplace which apply to the scenario described below.
Job taks workers	Job tasks of workers which apply to the scenario described below.
Emission determinants (see extended explanation under this table)	
Production function	Supply, storage, transport, manufacture, use, waste treatment, cleaning and maintenance
Production principle	Mixing, separating, surface treatment (sanding, drilling, etc.)
	Manual, mechanical, automatic
Type of production	Open or closed systems, such as cubicles
Physical state	Solid, liquid, suspension, gas
Exposure determinants	
Position of the worker in relation to the source of emissions	Sources close to the employee have a greater effect on exposure in the area where the employee breathes than comparable sources at a distance.
Dilution due to air distribution	From the source of emissions to the immediate work environment, and from the work environment to working areas further away to the outdoor air
Control measures used	Work hygiene strategy: insulation/protection, general ventilation, local ventilation, working methods and personal protective measures
Inventory of surface contamination	Contaminated work clothing, apparatus, tables or equipment
Duration of exposure scenario	
Exposure measurements	
See also the Dutch standards NEN-EN 689 and NEN-EN 482 as guidelines for determining exposure to particles in the workplace. See also examples from abroad, such as: Precautionary matrix for engineered nanomaterials (Switzerland, www.bag.admin.ch/nanotechnologie), the ISO standards (www.iso.org) and the Assessment strategy of ORC Worldwide (US, www.orc-dc.com). Annex J shows a list of available instruments.	
Type of measurement	Eight-hour measurements, peak or task-related measurements; real-time; fixed or personal measurements in the area where the employee breathes?
Measure of exposure	Mass concentration, number of particles and surface area of particles. Preferably use several measures.
Method	See examples in Annex J.
Background exposure	

Explanation of emission determinants: The production function is an abstract description of the aim of the production process and describes the basic steps of the process. Examples of production functions are: supply of raw materials, storage of raw materials, transportation of raw materials and intermediate/end products, processing the raw materials and shaping the end product, finishing the end product, treating the waste, maintaining installations and repairing breakdowns. These seven production functions describe the vast majority of all production and other processes. These production processes can be carried out via various principles.

The production principles specify the general process (continuous versus batch-by-batch), including the mechanical engineering principle and the operating principle. Examples of mechanical engineering principles of the production function' processing raw materials' are: shaping, mixing, separating, combining, surface-treating, etc. The second principle, the operating principle, is an indication of the distance from a worker to an installation. This is short in manual and mechanically-operated functions and large in remote-controlled and automated functions. The production principles give the variations which are possible per production function. The ultimate design has not yet been established with the production function and the production principle. Choices are still possible there at the level of the type of production.

The type of production is the ultimate design of the installation. This relates to the detailed design with which the principle is given shape. This detailed design also determines whether an installation is operated according to an open or a closed system and which technical measures are used to reduce exposure.

The production of nanomaterials and nanomaterials is to be described as having ten or fewer than ten production functions. It is estimated that each production function will possibly have five to ten different principles and several forms of production are possible per principle. The emission and exposure to nanoparticles takes place at the level of the type of production. Logically, to control exposure via so-called add-on technical measures, attention is mainly directed at the type of production. But the source of emission and exposure are mainly determined by the production principle. A batch-by-batch approach, carried out manually, open process of mixing of raw materials will result in higher exposure than if this process is carried out continuously, is remote-controlled and is closed. In the last case, emission and exposure take place during maintenance activities and when rectifying process breakdowns.