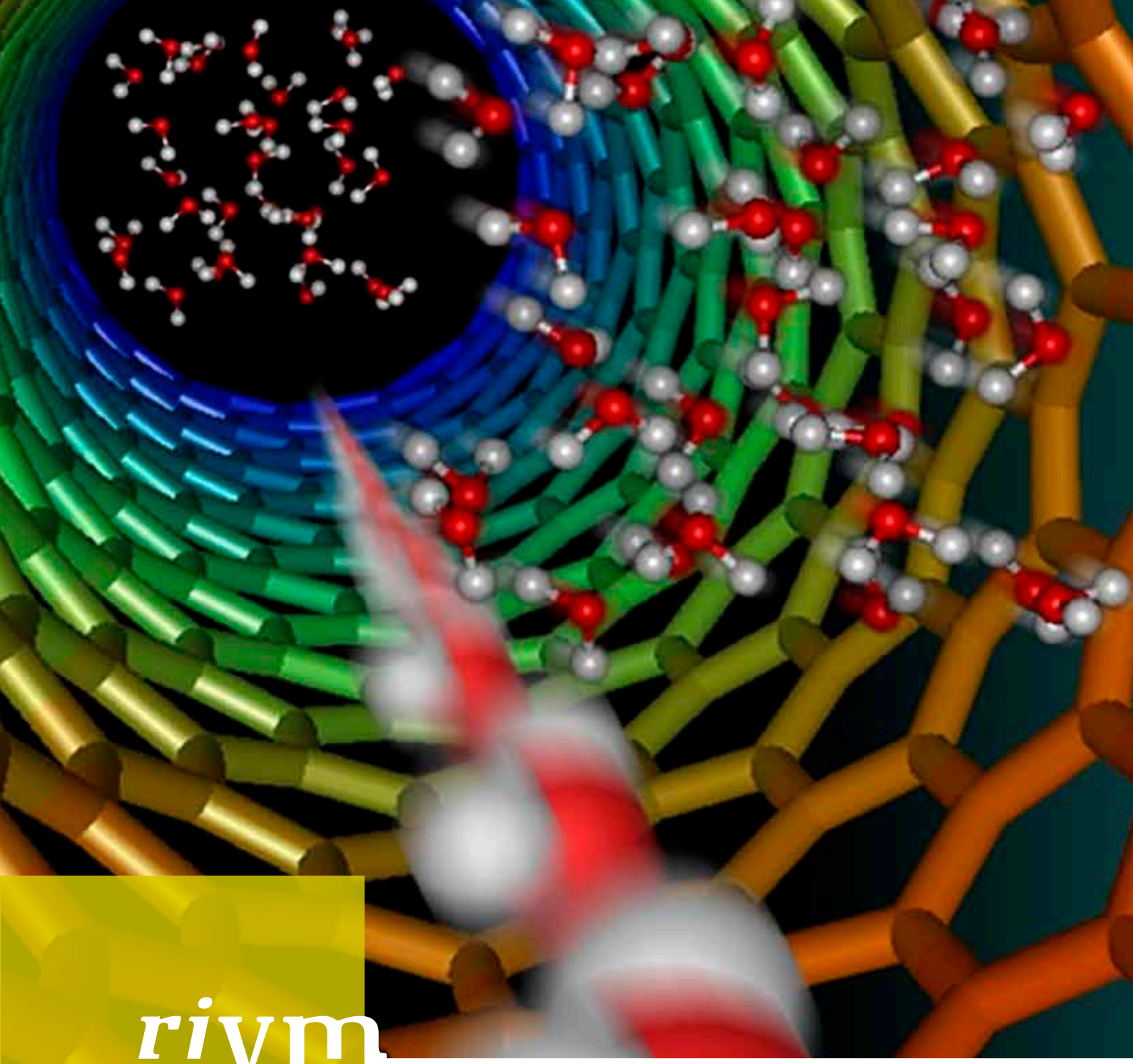

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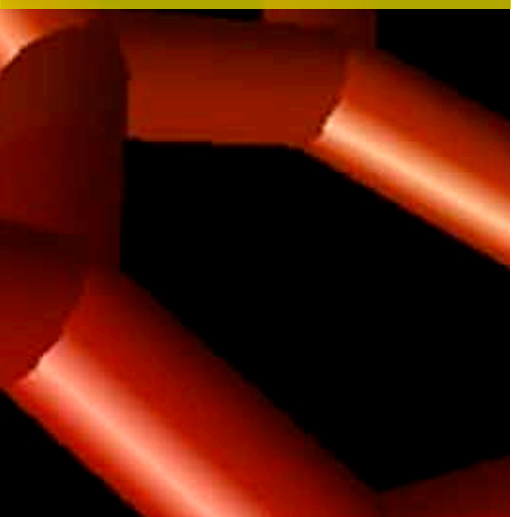
Report 601785003/2009

M. van Zijverden | A.J.A.M. Sips (ed.)

Nanotechnology in perspective

Risks to man and the environment



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RIVM Report 601785003/2009

Nanotechnology in perspective

Risks to man and the environment

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This study was carried out on behalf of the Netherlands Ministries of Housing, Spatial Planning and the Environment (VROM); Health, Welfare and Sport (VWS) and Social Affairs and Employment (SZW), by the Risks of Nanotechnology Knowledge and Information Centre (KIR nano).

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Foreword

Nanotechnology is seen as one of the most innovative and pioneering technologies of our time. This technology makes it possible to give existing chemical substances new properties. The potential applications appear to be inexhaustible and offer opportunities to improve the quality of life and reduce energy consumption or promote other aspects of sustainability.

This report focuses on the risks to man and the environment of manufactured, free, non-degradable and insoluble nanoparticles. Products which incorporate these particles are already on the market. They range from medical applications and cosmetics to electronics and cleaning agents. The result of this is that humans and the environment are exposed to these nanoparticles while their actual toxicological effects are not yet well known.

It is important to start to look at the safety aspects of new technologies at an early stage. In the Netherlands and other countries in Europe and elsewhere, the safety of nano products has received a lot of attention. For the assessment and management of the risks of nanotechnology knowledge gaps have been identified and research programmes drawn up. Filling these gaps will help with the development of safe products and simplify the implementation of the legislation on nanotechnology.

Further to the government paper ‘Kabinetsvisie nanotechnologieën - van klein naar groots’ [The Dutch government’s vision on nanotechnologies - from small to great] (Netherlands’ government, 2006) in which the Dutch government sets out its vision on nanotechnology, RIVM was asked to provide reliable information on an ongoing basis on the possible adverse consequences of nanotechnology for man and the environment.

This monitoring report also shows that RIVM is in favour of an active exchange of knowledge and information. Not just exchange between the various disciplines, but also between government authorities, the scientific community and trade and industry. RIVM will be at the vanguard of this nationally and internationally.

Dr. Marc Sprenger,
Director General, RIVM

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Abstract

Nanotechnology in perspective
Risks for man and the environment

The Risks of Nanotechnology Knowledge and Information Centre (KIR nano), a Dutch government-supported observation organisation based at RIVM, has provided an overview of the potential risks to both man and the environment of exposure to nanoparticles. The focus is on free, non-degradable and insoluble nanoparticles found in medical applications, food, consumer products and the environment.

Scientific data compiled to date demonstrate that adverse effects due to exposure to nanoparticles cannot be ruled out. However, much more information is required to be able to estimate the risks of nanoparticles equally as well as those of other non-nano chemicals. Nevertheless, hundreds of products containing nanomaterials are currently available commercially, a situation which clearly necessitates investigation of the exposure and toxicity of these materials in the near future. Unfortunately, the research questions to be answered are so numerous that it will take years to compile the relevant data.

KIR nano recommends that research be focused primarily on those questions that provide information critical to the assessment of risks to man and the environment. Depending on the perspective – worker, consumer, patient, or the environment – the starting points can then be defined for controlling or limiting the risks. Information generated in the strictly regulated world of medical applications (e.g., on methodology) could constitute a valuable asset in other areas of research and application, where the data and dossier requirements are not as exacting.

Key concepts in the coming years include expanding our knowledge of nanoparticles and making this knowledge readily available to avoid duplication of research; identifying and where necessary taking appropriate risk management measures, deciding on which areas of research the Netherlands wishes to contribute to this field, supporting research & development and promoting cooperation between government bodies and agencies, the scientific community and trade and industry.

Key words:
nanotechnology, risks, health, environment, consumer products, medical applications, food, worker safety

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Rapport in het kort

Nanotechnologie in perspectief
Risico's voor mens en milieu

Het Kennis- en Informatiepunt Risico's van Nanotechnologie (KIR-nano) van het RIVM heeft de potentiële risico's van blootstelling van gefabriceerde, vrije, onafbreekbare en onoplosbare nanodeeltjes in kaart gebracht. In dit rapport worden de risico's voor de mens als werknemer, patiënt en consument behandeld, evenals risico's voor het milieu. Drie toepassingsgebieden zijn daarbij relevant: geneesmiddelen en medische technologie, voedselproductie en consumentenproducten.

De huidige stand van zaken van de wetenschap laat zien dat risico's niet uit te sluiten zijn. Er ontbreekt echter nog veel kennis om de risico's even goed in te kunnen schatten als voor 'chemische stoffen niet in nanovorm'. Toch zijn er al vele honderden producten waarin nanomaterialen zijn verwerkt op de markt. Dit vereist op korte termijn veel onderzoek naar de blootstelling en toxiciteit van deze materialen. Helaas is het aantal onderzoeksvragen dusdanig groot en fundamenteel van aard dat het nog jaren zal duren voordat alle informatie is vergaard.

KIR-nano adviseert daarom het onderzoek vooral te richten op die vragen die cruciale informatie voor de risicobeoordeling voor mens en milieu bieden. Afhankelijk van het perspectief van werknemer, consument, patiënt of milieu zijn oplossingsrichtingen gedefinieerd voor het beheersen van de risico's. Informatie die in de streng gereguleerde wereld van medische toepassingen wordt gegenereerd kan met name vanuit methodologisch oogpunt zeer waardevol zijn voor andere toepassingsgebieden, waar de dossiervereisten en dus veelal ook de informatievergaring (veel) beperkter voor zijn.

Kernbegrippen voor de komende jaren zijn samen te vatten onder KOKOS: *K*ennis vergroten en uitwisselen om dubbeling van onderzoek te voorkomen, *O*plossingsrichtingen en risicomanagement, *K*euzes maken in bijdragen vanuit Nederland aan dit onderzoeksveld, *O*nderzoek & Ontwikkeling, en *S*amenwerking bevorderen tussen wet- en regelgevende kaders, wetenschap en bedrijfsleven.

Trefwoorden:
nanotechnologie, risico's, gezondheid, milieu, consumentenproducten, medische toepassingen, voeding, arbeidsveiligheid

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Summary

See RIVM report 601785004 for the full summary of this report.

Nanotechnology is the entirety of new, emerging technologies which uses substances or structures on a nanoscale. At these dimensions chemical substances sometimes acquire new, different properties, as a result of which they offer new possible applications. In the Netherlands and elsewhere people have high expectations with regard to the economic potential offered by nanotechnology and its benefits to society. In its paper entitled 'Kabinetsvisie nanotechnologieën - van klein naar groots' [The Dutch government's vision on nanotechnologies - from small to great] (Netherlands' government, 2006) the Netherlands' government sets out its vision. The view is expressed in this document that nanotechnologies could become a 'major driver' of our knowledge economy and society.

At the same time signals are coming from the scientific community that the application of these technologies could pose certain risks to man and the environment. These risks, however, are more difficult to determine than those of chemical substances that are not in a nano form, and are therefore to some extent still largely unknown. The basic principle of the Netherlands policy on managing the risks is therefore the substances policy in force and the risk policy as formulated in the VROM policy document 'Nuchter omgaan met risico's' [Coping rationally with risks] (VROM, 2004). In addition, the Risks of Nanotechnology Knowledge and Information Centre (KIR nano) was set up at RIVM at the request of the government.

Man and the environment can come into contact with the use of nanotechnology through a wide range of application areas. Some of these applications are produced only with the aid of nanotechnology, others will actually contain nanomaterial. From the perspective of risks, this second category is important, particularly when they contain the non-degradable, insoluble, freely available nanoparticles. For this category of products there are already a great many different areas of application, including medical applications, food, and consumer products as well as environmental and energy technology. These applications can improve the quality of life and the environment and can also lead to significantly more sustainable products.

There are already hundreds of nanotechnology applications on the market. For example, nanoparticles of titanium oxide and zinc oxide as UV reflectors in sunscreen creams. Nanotechnology is also used to make clothing crease and dirt-resistant and to make electronics ever smaller, faster and more multifunctional. But by far the most potential applications of nanotechnology are currently still in the research and development phase and are expected to appear on the market over the coming years.

The purpose of this preliminary monitoring report is to outline the current state-of-affairs and developments in the field of nanotechnology and to make an initial analysis of the potential risks to humans (as workers, consumers and patients) and the environment. The report focuses on three areas of application of nanotechnology where the greatest likelihood of exposure may be expected now or in the future: medical applications, agrofood and non-food consumer products.

It is generally expected that manufactured, free, non-degradable and insoluble nanoparticles are likely to pose the most risk to human health and the environment. There are indications, for example, that *some* of these nanoparticles can behave in the human body in the same way as fine particulates or asbestos.

The research to establish the risks of nanotechnology is particularly extensive and complex. Addressing this issue in the coming years will be largely defined by the following key concepts: increasing and exchanging information and knowledge to prevent duplication of research, identifying solution areas and possible measures to minimise the risks to humans and the environment, deciding what contributions can be made to this field of research by the Netherlands, promoting research & development, and cooperation between legislative bodies, the scientific community and trade and industry.

Given the benefits which nanotechnologies could bring to society, it is important that the various stakeholders subscribe to the same principle, i.e.: that *the implementation of nanotechnologies in society deserves to succeed, provided that the safety of man and the environment can be guaranteed.*

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1 Introduction

This is the first monitoring report 'Nanotechnology in Perspective' compiled by the Risks of Nanotechnology Knowledge and Information Centre (KIR nano). It describes the current situation and developments related to the risks of nanotechnology to humans and the environment. A full summary of this report has also been published as RIVM report 601785004.

1.1 Risks of Nanotechnology Knowledge and Information Centre (KIR nano)

1.1.1 Background

Nanotechnology is the entirety of new, emerging technologies which uses substances or structures on a nanoscale (for definitions see the list at the back of this report). In the Netherlands and elsewhere people have high expectations with regard to the economic potential offered by nanotechnology and its benefits to society. In the government paper entitled 'Kabinetsvisie nanotechnologieën - van klein naar groots' [The Dutch government's vision on nanotechnologies - from small to great] (Netherlands' government, 2006) the Dutch government sets out its vision on nanotechnology. In this document the view is expressed that nanotechnologies could become a 'major driver' of our knowledge economy and society.
It is forecast that the worldwide sales of products containing nanotechnologies will grow from €25 billion in 2004 to €450 billion in 2010. The Netherlands has a number of academic research groups and companies who are world leaders in the development of nanotechnologies. This is partly why a great deal is expected of the opportunities which nanotechnologies can offer the Netherlands. Apart from the economic benefits and the knowledge acquired, nanotechnologies could significantly improve the quality and efficiency of healthcare, increase the efficiency and sustainability of food production and lead to substantial energy savings, for example.
At the same time signals are also coming from the scientific community that the application of these technologies could pose certain risks to consumers, workers and the environment. These risks, however, are more difficult to determine than those of chemical substances that are not in a nano form, and are therefore still largely unknown. The position adopted in Europe (EC, 2007, see also Annex 3), and in the Netherlands (Netherlands' government, 2006) is that these risks should be treated with caution, care and common sense. This is in line with the report 'Betekenis van nanotechnologie voor de gezondheid. [Health significance of nanotechnologies] by the Health Council of the Netherlands (2006).

The current substances policy and risk policy in force, as formulated in the VROM policy document 'Nuchter omgaan met risico's' [Coping rationally with risks] (VROM, 2004), provides the framework for this. The following basic principles apply:

- transparent decision-making;
- defining responsibilities (authorities, citizens, manufacturers, scientific community);
- public consultation at an early stage in decision-making;
- balancing hazards and risks against costs and benefits to society;
- taking into account the accumulation of risks in decision-making (VROM policy document, 2004).

Annex 2 provides further details on nanotechnology and 'Coping rationally with risks'.

The government paper on nanotechnology recommended setting up an Observatory to monitor the potential risks of nanotechnology to humans and the environment. Against this background the Minister of Housing, Spatial Planning and the Environment (VROM) in 2007 asked RIVM to carry out the preliminary work to set up such an Observatory. The Risks of Nanotechnology Knowledge and Information Centre (KIR nano) was set up on 1 January 2008 with the Ministries of Health, Welfare and Sport (VWS) and Social Affairs and Employment (SZW) also commissioning the research.

1.1.2 What will KIR nano do?

KIR nano will look at the potential risks of nanotechnology to humans and the environment. In this way the Netherlands will be at the vanguard of Europe in specifically devoting attention to this subject.

KIR nano will concentrate on the following main activities: Observing, Advising, Participating and Informing (see Textbox 1). For this purpose it is important that the relevant research developments on risks are closely followed. But relevant policy developments and developments in society also need to be monitored. As a supplier and integrator of knowledge, KIR nano aims mainly to provide added value for policy-makers, supervisory bodies and professionals in the field.
The tasks of KIR nano are:

- OBSERVING AND IDENTIFYING: scientific advances in the field of nanotechnology and related risks to humans and the environment. National and international knowledge networks will be set up and maintained for this purpose. KIR nano gathers relevant information and issues regular reports on this to central government;
- ADVISING: central government on the assessment of risks to humans and the environment;
- PARTICIPATING: in national and international scientific fora, including in the area of standardisation and risk research. This task also underpins the other tasks. KIR nano will play a coordinating role in fora that are developing methods for the risk assessment of nanomaterials. In particular, the OECD Working Party for Manufactured Nanomaterials (WPMN) operates as a global centre for methodology development and harmonisation;
- INFORMING: primarily government authorities and professionals on the risks of nanotechnology based on independent and reliable information. This will make the available knowledge accessible in the best way and can serve for the implementation of policy. KIR nano will further contribute to the dialogue with industry and society at large.

Textbox 1: Tasks of KIR nano.

Information on KIR nano can be found on the Risks of Substances website: http://www.rivm.nl/rvs/ Information can also be found on this site about RIVM research on the risks of nanotechnology to humans and the environment.

Recently, in the context of the European 7th Framework Programme, a project was started to set up a European Observatory. This Observatory will be partly concerned with safety aspects, but also to a large extent with technological and economic analyses. KIR nano will actively take part in this project. In four years' time the project should result in the permanent establishment of the European Observatory (www.observatorynano.eu).

1.2 General background to this report

Over the last few years products with first generation nanomaterials have appeared on the market and that number will only increase in the near future (see Chapters 4-6 for current applications). At the same time new generations of nanotechnologies are about to appear. There are already four separate generations of nanotechnologies (Roco, 2007), these are:

First generation: nanostructures with passive, fixed structures and functions. These include chemical substances with particles on a nanoscale which are often applied as part of or as an ingredient in types of products which already exist.

Second generation: active nanostructures which further to a stimulus can exhibit a change in properties, such as dimension, form or conductivity. For example, nanoparticles which target drugs at a tumour in the body and under the influence of a radiation source release the pharmaceutical in the tumour.

Third generation: networks of nanosystems: three dimensional networks, bio and chemical assembly techniques and robotics on a nanoscale.

Fourth generation: molecular nanosystems which can be designed per particle, e.g., for advanced genetic therapies. Self-assembling structures on a nanoscale also fall under this fourth generation.

The second generation of nanotechnologies are currently at the point of applied research and market introduction. A few medical applications are already on the market. The third and fourth generation of nanotechnologies are still at the fundamental research phase. Applications of these generations may be expected only in the mid to long term (see also Annex 1: research on applications).

This monitoring report focuses mainly on the potential risks of the first generation of nanomaterials. These are chemical substances which are applied as particles in nano dimensions, i.e. dimensions of approximately 1 – 100 nanometres. At these dimensions chemical substances sometimes acquire new, different properties and they offer new potential applications.

This report considers the risks to man as workers (including researcher and professional), patients and consumers as well as the environment. There are three relevant areas of application in this context:

- pharmaceuticals and medical technology;
- food production;
- non-food consumer products.

1.3 General principles applied in the assessment of risks

The following approach is taken in the general system for assessing the risks of chemical substances not in nano form:

RISK = EXPOSURE x TOXICITY

This approach is also used for nanomaterials. A specific nanomaterial may be hazardous, but if the level of exposure is very small, the ultimate risk will always be limited. The intrinsic hazard, or toxicity of a nanomaterial is determined by a number of factors, such as the ability of a nanoparticle to pass through certain barriers in humans, plants or animals and cause damaging effects. The actual exposure is also determined by various factors such as the form in which the nanomaterial occurs (e.g., either bonded or as 'free' particles) and the likelihood of contact.
The way in which the risks of nanomaterials to humans and the environment are determined varies in certain respects. This will be examined in more detail in Chapter 3.

1.4 The purpose of this report

The purpose of this first monitoring report is to outline the current situation and developments in the field of nanotechnology and make an initial analysis of the acknowledged and potential risks to humans as workers, consumers and patients, and to the environment.

1.5 Scope

- Initial research has shown that following uptake the body has great difficulty in eliminating *deliberately manufactured, free, non-degradable and insoluble nanoparticles*. This report therefore concentrates on the potential risk posed by such particles. Particles which are unintentionally released (as fine dust) and particles which occur naturally (volcanic dust) will be left aside. This report will mainly consider the risks of nanoparticles (of three dimensions smaller than 100 nm), but where this involves not just nanoparticles, the broader term of nanomaterial (with at least one dimension smaller than 100 nm) will also be used;
- It is not the purpose of this report to make policy recommendations, but rather to identify some policy leads regarding the risks of nanotechnologies;
- This report deals with the toxicological and ecotoxicological risks of exposure to *first generation nanomaterials* which the population and the environment could *already come into contact with at the moment*. This is the case for *medical applications, food* and *consumer products*;
- The following target groups have been identified: workers, (this includes research workers and production workers, as well as those professionally involved in the application of nanomaterials), patients, consumers, the general population and the environment;
- The report provides a snapshot of the present moment in time. Rapid developments are taking place in both applications and risk research. Therefore parts of the report will eventually be overtaken by events. The picture outlined here will be updated in future reports;
- This report provides an overview of the potential risks of nanotechnologies by combining two factors: the degree to which humans and the environment are exposed to nanomaterials, and the toxicity of such nanomaterials. The combination of these two factors determines the ultimate risk;

- Societal aspects, such as risk perception (see Annex 5) and differences in the acceptance of risks, fall outside the immediate scope of this report.

1.6 Note to reader

This report is intended to provide a wider readership with insight into what is currently known about the risks of nanotechnology to man and the environment. Therefore it has been attempted to provide a description from various perspectives. Chapters 1, 2, 3 and 9 are mainly aimed at readers looking for information on research and on activities concerning the risks of nanotechnology in general. Chapters 4, 5 and 6 consider specific areas of application. The chapters describe in outline the present and future applications, as well as the potential risks and, of course, the steps being taken in this context. Each chapter concludes with observations.
It is recommended to read Chapter 9 in any event, because this chapter contains observations which were arrived at further to an analysis of the entire range of application areas and fields of expertise.

2 Nanotechnology: terms and definitions

2.1 Nanoparticles and nanotechnology

Although there are, as yet, no officially recognized definitions, nanotechnology has been provisionally defined by the ISO (International Organization for Standardization) as follows (ISO draft business plan, 2007):

- *Understanding and control of matter and processes at the nanoscale, typically, but not exclusively, below 100 nanometres in one or more dimensions where the onset of size-dependent phenomena usually enables novel applications*.
- *Utilizing the properties of nanoscale materials that differ from the properties of individual atoms, molecules, and bulk matter, to create improved materials, devices, and systems that exploit these new properties.*

Working definitions of other nanotechnology-related terms have been drawn up by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) of the European Commission. These working definitions have been used in this report.
The diameter of a single atom is in the order of around 0.1 nanometres. Materials with dimensions between 0.1 and 100 nm exhibit properties which may differ from the same materials with larger dimensions. The different forms, such as tubes or spheres, also determine the properties of nanomaterials. Nanomaterials can have specific mechanical, optical, electrical and magnetic properties, for example (Health Council of the Netherlands, 2006). This means that different properties of nanomaterials may be relevant compared with other substances: both in the application, and in the assessment of the potential risks of using these materials.

Nanomaterials (soluble and insoluble, degradable and non-degradable) can be found in various forms in applications:

- Free nanoparticles;
- Aggregated nanoparticles;
- Agglomerated nanoparticles;
- Fixed nanoparticles (in a matrix);
- Coated nanoparticles;
- Colloid nanoparticles.

Nanotechnologies are occasionally referred to as ‘converging technologies’. This indicates that various scientific disciplines are brought together in nanotechnologies, such as physics, chemistry, information technology, medicine and biology. Where the integration of various disciplines leads to new and innovative developments this may be described as a converging technology. Nanotechnologies are also sometimes called ‘enabling technologies’, because nanotechnologies enable new scientific and technological developments in a wide range of disciplines and fields of application.

Two different approaches are taken in the development of nanotechnologies, i.e. bottom-up and top-down approaches. The bottom-up approach relates to the manipulation of individual atoms and molecules to build-up (nano) structures. The top-down approach relates to the size reduction of

structures, like electronic circuits (Health Council of the Netherlands, 2006). The top-down approach was most common in the first generation of nanotechnologies.

2.2 Definitions

Discussions are currently taking place in various national and international fora on definitions for nanoparticles, nanomaterials and related terms. Widely accepted accurate definitions are important for scientific research as well as for legislation and clear communication in general on nanotechnology.

Early 2008, SCENIHR adopted an opinion with regard to existing and proposed definitions related to the products of nanoscience and nanotechnology (SCENIHR, 2008). This opinion contains a conceptual framework for definitions in the area of nanoscience and nanotechnology. This framework is specifically intended for use in risk assessment procedures. SCENIHR states that the adoption of different definitions in different sectors should be avoided. Most of the concepts and behaviour patterns on the extremely small scale associated with nanotechnology are not new, and these can be described using the existing terminology for larger scales. According to SCENIHR it is vital that the scientific community does not unnecessarily adopt a new language, and if new terminology is necessary, this should be consistent with the established terminology.

In this context SCENIHR refers to a number of key points involved:

1. The size limits which are associated with the prefix ‘nano’ have been somewhat arbitrarily set. Because there is no abrupt change in the properties of substances once they reach a certain size. It is not likely, for example, that particles of 105 nm will behave differently than particles of 100 nm;
2. Many of the terms used in nanoscience are based on ordinary words that are generally used (substance, material). It is important that the development of terms in nanoscience is consistent with the general meaning of the words used as already defined in other scientific disciplines (which, for that matter, are also not always consistent!);
3. Certain (size and form-dependent) physico-chemical properties of the products of nanotechnology will probably have a major impact on fate and behaviour in the environment and thus on the exposure of humans and the environment. SCENIHR has taken this into account in the selection of a number of key terms;
4. Certain forms of substances with very small dimensions occur naturally in the environment, and exposure to these substances is unavoidable. The increase in manufactured nanotechnology products, however, may make it necessary to apply new words and definitions;
5. There are various reasons for making a distinction between different sizes of particles. However, an implied a priori connection between toxicological, health or environmental risks and a certain order of size cannot be made.

Among others, SCENIHR proposes the following definitions:

- Nanoscale: A feature characterised by dimensions of the order of 100 nm or less;
- Nanostructure: Any structure that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less;
- Nanomaterial: Any form of a material that is composed of discrete functional parts, many of which have one or more dimensions of the order of 100 nm or less;
- Engineered nanomaterial: Any material that is deliberately created such that it is composed of discrete functional parts, either internally or at the surface, many of which will have one or more dimensions of the order of 100 nm or less;
- Nanotube: A discrete hollow entity which has two dimensions of the order of 100 nm or less and one long dimension;
- Nanoparticle: A discrete entity which has three dimensions of the order of 100 nm or less;
- Nanoparticulate matter: A substance comprising of particles, the substantial majority of which have three dimensions of the order of 100 nm or less (SCENIHR, 2008).

According to SCENIHR, of all possible configurations of nano-structured materials, nanoparticles are the most important structures from the point of view of health and the environment. This report mainly considers the risks of nanoparticles, but where this concerns not only nanoparticles the broader term of nanomaterial is also used.
The following terms are important for the risk assessment of nanoparticles, not only to humans but more specifically, also to assess the fate and behaviour of nanoparticles in the environment:

- Agglomerate: A group of particles held together by weak forces such as Van der Waals forces, some electrostatic forces and the surface tension;
- Aggregate: A group of particles held together by strong forces such as those associated with covalent or metallic bonds;
- Degradation: A change in the chemical structure, physical properties or appearance of a material;
- Solubilisation: The process of dissolution (SCENIHR, 2008).

Due to the fact that the threshold of 100 nm in the definitions used is somewhat arbitrary, there is something to be said for the use of other definitions of nanoparticles, nanomaterials, et cetera. Alternative definitions are conceivable based on surface-volume ratios, for example, or on certain other specific nanoparticle properties compared with non-nanoparticles. Eventually, based on further insight into dose-effect relationships it may well turn out that the SCENIHR definitions cannot be fully applied in toxicological research. From the point of view of international harmonisation of definitions, however, it would be most practical for now to adopt the SCENIHR definitions.

In the context of OECD and ISO activities (see also below), there are discussions taking place on the definitions to be developed. ISO, OECD and SCENIHR are also in consultation with one another on this matter.

2.3 Standardisation

In the government paper on nanotechnology it states: ‘It is vitally important to arrive at a system of standards which makes the standardisation of production methods, products and risk assessment

possible'; and further 'this is essentially the requirement for adequate legislation which ensures a level playing field for all parties. Only then can the precautionary principle and chain liability be implemented in practice' (Netherlands' government, 2006).

Standardisation in the field of nanotechnology is being worked on in both the national (Dutch standards organisation: NEN) and international (CEN, ISO) contexts. The Dutch standards organisation, NEN, does not set independent Dutch standards for nanotechnology, but rather facilitates the input of the Netherlands' Dutch point of view in ISO and CEN. At ISO (International Organization for Standardization), Technical Committee 229 is concerned with standardisation in the area of nanotechnology. Within the TC 229, three working groups are working on the development of three categories of standards:

- Terminology and nomenclature: these standards must provide a common language for the purpose of scientific, technical, commercial and regulatory processes;
- Measurement and characterisation: these standards must provide an internationally recognized basis for quantitative scientific, commercial and regulatory activities;
- Health, safety and the environment: these standards improve occupational health and safety and protect consumers and the environment by promoting good practices in the areas of production, use and waste processing of nanomaterials, nanotechnology products and nanotechnology-enabled systems and products (ISO TC229, 2007).

The ISO standards in the field of nanotechnology are expected to be published in three years' time. In 2008 ISO will formulate a draft definition.

3 Risks of nanotechnology

3.1 The risks to man and the environment

Various analyses, such as those of the scientific committees of the EU (SCENIHR, SCCP) and the OECD, have shown that there are still many knowledge gaps in relation to the risks of nanomaterials to humans and the environment. The most important research topics will be identified and discussed in this chapter. A brief overview will be given of the current status with regard to what is known about exposure, toxicity and risk estimation of these materials.
The present status in relation to patients (medical applications), consumers (food and consumer products), workers and those professionally engaged in nanotechnology applications, as well as the environment (including indirect exposure of the general population from the environment) will be discussed in more detail in Chapters 4 to 8.

Estimation of the potential of nanomaterials can be approached in a similar manner as estimation of the potential risks of chemical substances not in nano form. Thus consideration needs to be given to:

- exposure of humans and the environment;
- toxicity (fate and behaviour, and effects) to humans and the environment;
- methods by which exposure and toxicity can be established.

This report is limited to the risks of manufactured, free, non-degradable and insoluble nanoparticles given that the most urgent issues are related to first generation nanotechnologies, where it is mainly these particular types of nanomaterials which are of concern.

It is the 'free' particles that increase the chance of human exposure. Where the particles are bonded in a hard coating, for example, there is little or no chance of exposure. However, in the event of wear or waste processing, nanoparticles could still be released. If the particles are then also non-degradable and insoluble, they could accumulate in organisms or humans and lead to harmful effects.

As stated in Section 1.3, the term 'risk' is seen as a combination of the toxicity *of* and exposure *to* a substance.

3.1.1 Components of toxicological risk assessment

In the assessment of risks to *humans* there are a number of separate elements on which information must be gathered. Depending on the application, set requirements are laid down in the legislation on what information must be collected (and to what extent) for the different components.
In general terms this can be divided into information on external exposure, internal exposure and toxic effects. On the basis of this scientific data an assessment can be made of the toxicological risks (see also Section 1.3).

The following factors are taken into account when determining the **external exposure**:

- **Source:** the source of exposure to nanoparticles, for example, a consumer product, a medicine, the environment or the workplace;
- **Occurrence / concentration:** the occurrence or presence of nanoparticles in a product, environmental compartment or working environment;
- **Behaviour:** the behaviour of nanoparticles in a product, environmental compartment or working environment. Also the behaviour of people with regard to a product or nanoparticles,

e.g., the form of ingestion or use of a product, or other form of activity which could lead to internal or external exposure. The term exposure scenarios is used in this context;
- **External dose** (external exposure): the dose (quantity of nanoparticles) which people come into contact with per time unit.

The following factors are taken into account when determining **internal exposure**:
- **Point of entry and behaviour in the body**: the place in the body where nanomaterials are taken up. When a substance passes a point of entry internal exposure or uptake has taken place. Possible points of entry include the airways (inhalatory), the skin (dermal) and the gastro-intestinal tract (oral). Information can also be gathered on the behaviour of the substance in the body. This behaviour determines the places in the body where the substance ends up and how long it can remain there;
- **Internal dose** (internal exposure): the dose (quantity of nanoparticles) actually taken up by the body per time unit.

Harmful Effects are taken into account after both short (acute) and long-lasting (chronic) exposure. What is important here is establishing both the nature of the harmful effect as well as the dose-effect relationship.

In assessing risks to *the environment* similar elements to the above are taken into account. The most differences compared with the assessment of risk for humans, lie in the area of ***external exposure.***
- **Source:** the source of exposure to nanoparticles, such as a production facility or waste;
- **Emission:** the release of nanoparticles into the environment during the various phases of the product's life cycle (i.e. research and development, production, use and waste processing);
- **Occurrence / concentration:** the occurrence or presence of nanoparticles in the compartments of air, water, soil or sediment;
- **Behaviour:** the behaviour of nanoparticles in one of the above compartments, such as degradation, distribution within and between the environmental compartments, absorption and aerosol formation;
- **External dose** (external exposure): the dose (quantity of nanoparticles) which an organism (in the environment) comes into contact with per time unit.

To establish internal exposure and harmful effects in the environment the same concepts are used as in the assessment of the risk to humans. Only different animal species are investigated.

3.1.2 Problems in toxicological risk assessment

Figures 3.1 and 3.2 provide an overview of the main knowledge gaps in assessing the risks of nanomaterials to humans and the environment. The red colour indicates that there is an urgent need for information which is currently only available to a very limited extent. The colour green means that not all the necessary information is to hand, but that there is enough for the time being to work with. As the figures show, the research questions that need to be addressed to estimate the risks of nanotechnology extend along the whole length of the chain.

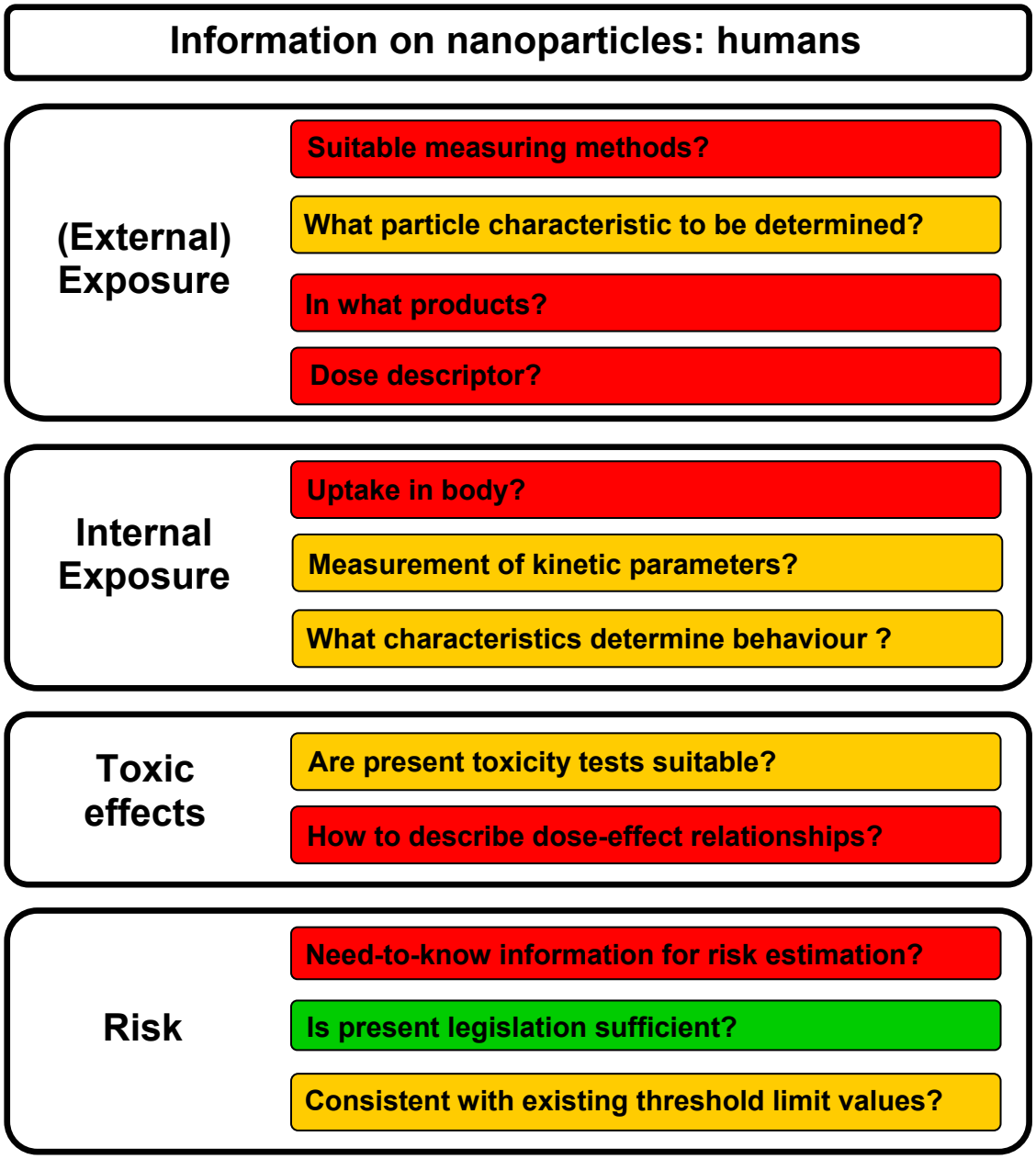

Figure 3.1 Overview of the most significant knowledge gaps in human risk estimation for exposure to nanoparticles. Red = little or no information available. Orange = little information or not the right information available. Green = information is sufficient (for the time being). The applicability of the legislation is shown (see also EC, 2008c).

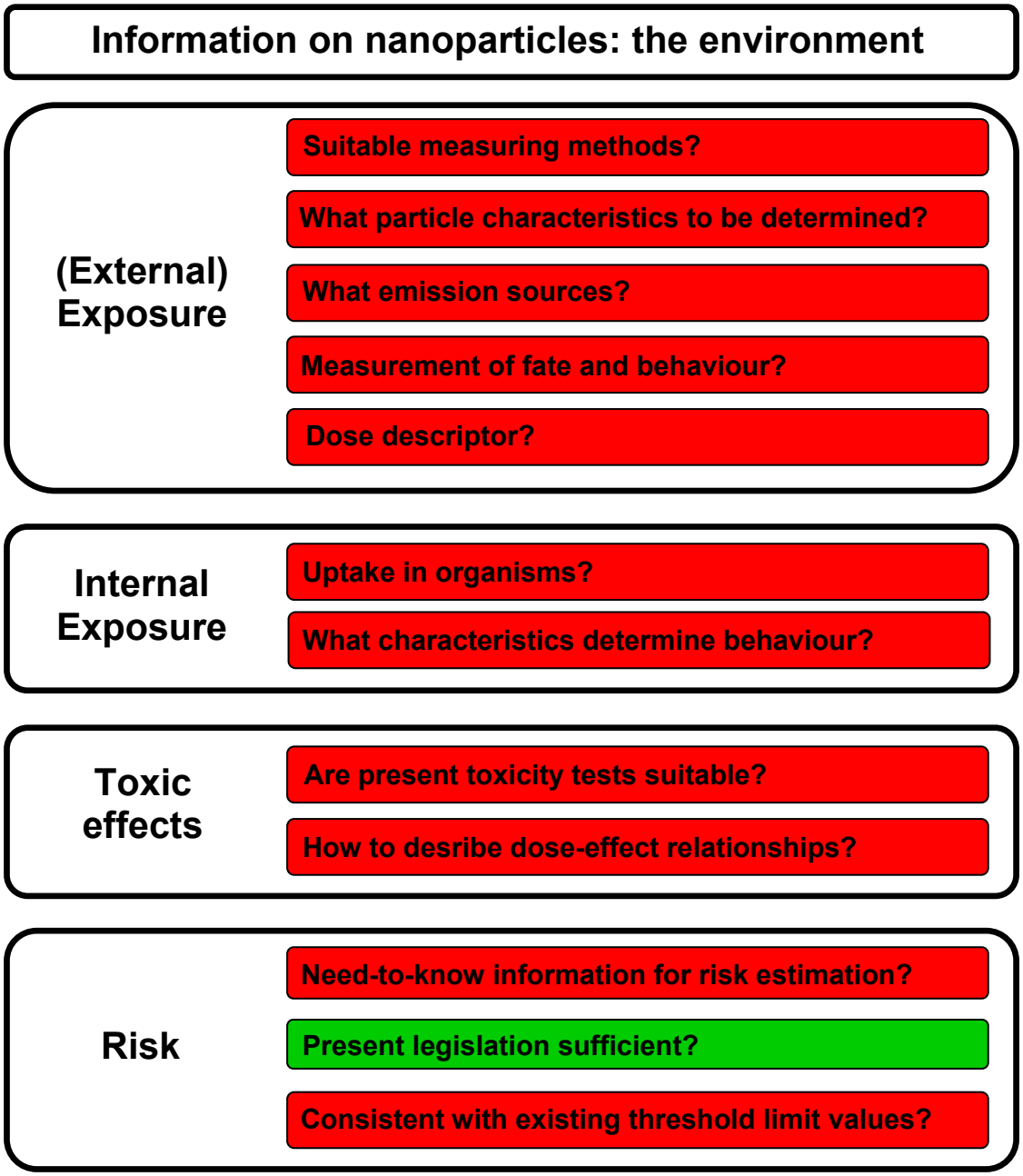

Figure 3.2 Overview of the most significant knowledge gaps in environmental risk assessment for exposure to nanoparticles. Red = little or no information available. Orange = too little information or not the right information available. Green = information is sufficient (for the time being). The applicability of the legislation is shown (see also EC, 2008c).

In view of the fact that nanomaterials are increasingly being used, it may be expected that the emissions of nanoparticles to the environment will also increase and therefore also their impact on ecosystems. There are at present, however, still a large number of knowledge gaps along the entire chain of causality from emissions to behaviour, and the effects of nanoparticles. This chapter will be limited to

the risks of exposure to nanoparticles to humans. The environmental aspects of nanoparticles will be dealt with in Chapter 8.

3.2 External exposure

Given the wide range of applications, humans may be exposed to nanomaterials in numerous ways. However, there is still insufficient information available about the products which incorporate nanoparticles to be able to make a proper estimate of the external exposure. Information is lacking in particular on the characteristics of the nanoparticles included in the products and in the ultimate form they take in the products. As a result we have almost no insight into the extent and the form in which nanoparticles occur in environmental compartments. One of the reasons for the lack of such information is the lack of reliable measuring methods which are simple to apply. The measuring methods which are available require specialist knowledge, are not suitable for processing large quantities of samples and are therefore also expensive.

Moreover, exposure can take place in various ways, for example while present at the workplace, through the consumption of food and drinking water, through the use of cosmetic products such as creams, and through the ingestion and administering of nanotechnology-based medicines. Furthermore exposure can take place from the environment through contact with soil, surface water or air, and through the consumption of drinking water and food in the form of agricultural produce.
People can also be exposed to nanoparticles in various stages of the life cycle of nanoparticles or products containing nanoparticles, i.e., in the development, production, application or use phases and the waste phase. People working in laboratories and production facilities, et cetera, appear to run the greatest risk of exposure to free nanoparticles, particularly if the measures taken to manage the risk of exposure are insufficient (Health Council of the Netherlands, 2006).

Humans can therefore be exposed to nanomaterials through various routes. The exposure through various products and environmental compartments means that the nanomaterials will encounter various barriers before they can be taken up by the body. In this context it may be useful to investigate the following exposure routes:

- inhalatory exposure (via the lungs);
- dermal exposure (via the skin);
- oral exposure (via the gastro-intestinal tract);
- parenteral exposure (introduced into the body by a means other than through the gastro-intestinal tract, e.g., by injection into the bloodstream (intravenous) or a muscle (intramuscular) or from implants) (SCENIHR, 2007);
- ocular exposure (via the eye).

From research on fine particulate matter there is already relatively a lot known about exposure to small particles through inhalation. Where possible the knowledge gleaned from this area is already used to estimate inhalatory exposure to nanomaterials. It appears that this knowledge is mainly suitable for setting up good methods and that the existing knowledge can in any event be used to make an initial qualitative estimate of inhalatory exposure to nanomaterials. Of course, the substance-specific data per nanomaterial will still have to be generated. Recently, there has also been more focus on other exposure routes.

3.2.1 Dosimetry: a new measure of dose?

The dose of a chemical substance not in nano form is traditionally described on the basis of weight, e.g., per gram chemical substance or active chemical substance per kilogram body weight or per kilogram dry matter of soil, et cetera. Over the years this type of dose descriptor has served as a good measure for describing effects. Various studies have shown that this is not the case for nanoparticles (SCENIHR, 2006; Brown et al., 2002; Oberdörster et al., 2000; Höhr et al., 2002). Characteristics such as surface and numbers of particles, for the time being, appear to be a better measure.

In its opinion document SCENIHR (SCENIHR, 2007) has already indicated that when assessing the risks of nanoparticles various physico-chemical properties should be taken into account, including:

- Dimension;
- Particle size and particles size distribution;
- Surface area;
- Composition of the surface layer (e.g., coating, charge);
- Elementary composition;
- Density;
- Crystalline structure;
- Solubility;
- Charge, polarity;
- Conductivity;
- Melting point;
- Hardness;
- Optic and magnetic properties;
- Morphology.

It is not yet known which of the above properties are critical to the behaviour and toxicity of nanoparticles. Until that time it is recommended to gather as much information as possible on the above characteristics for the administered dose in every study.

In most toxicological publications there appears to be a tendency to plot one of the above characteristics against the measured effects and then to see whether or not this leads to a good correlation with the measured effects. Given that a good dose descriptor is essential for risk assessment, more systematic research on the dosimetry is recommended. A hypothesis-driven approach would be most suitable in this case, e.g., where particle size, charge, et cetera, are indicative of the threshold of toxic effects. This could lead to a dose descriptor which is multifactored, i.e., a dose descriptor for which information on more than one variable is required. The development of such a dose descriptor will require a multidisciplinary approach.

3.3 Internal exposure

Nanomaterials can have fundamentally different physical and chemical properties than the same substances in non-nano form (Preining, 1998). It is therefore reasonable to assume that these different properties could also result in a different toxicological profile (Oberdörster et al., 2005a) and to a different distribution within the body (De Jong et al., 2008).
In comparison with the dossier requirements for chemical substances not in nano form, it is possible that additional information will be necessary for nanoparticles on absorption, distribution, metabolism and excretion (ADME). In this way extrapolations can be made from one exposure route to another or

from one particle size to another. Based on years of experience it is already possible to make better extrapolations for chemicals not in nano form on the basis of physico-chemical properties. However, for nanoparticles it is not yet clear what particle characteristics influence the kinetics and in what way. The potential risks of nanoparticles will thus for the time being have to be investigated on a case-by-case basis. Even then, the risk assessment of nanoparticles will be surrounded by major uncertainties.

In the same way as for chemicals not in nano form, it also applies to nanoparticles that the dose in a particular place in the body will determine the potential toxic effects. To be able to obtain information on the dose of nanoparticles (in the body), validated (real-time) detection and characterisation methods are urgently needed to detect nanoparticles in a biological matrix.
In the long term the efforts to establish the kinetic properties of nanoparticles will make a vital contribution to the safety and reliable application of nanotechnology.

3.3.1 Detection methods for toxicological research

Widely varying detection methods are used to describe the physico-chemical properties of nanoparticles. This makes it difficult to compare study results (Hagens et al., 2007) because there are no uniform agreements or a recognized approach for measuring nanoparticles (Oberdörster et al., 2005b; Tsuji et al., 2006).
For a solid risk assessment it is very important that it can be demonstrated that the form of the nanoparticles to which people are exposed and the form of the nanoparticles actually taken up by the body is the same. Therefore there is a need for techniques which can be used to demonstrate the presence of nanoparticles in tissues and organs, on the one hand, and to determine the quantity and characteristics of nanoparticles (and in what dimension), on the other. This could include measuring methods in the field of electron microscopy and quantitative extraction methods for nanoparticles in tissues and organs, followed by detection methods. The development of such measuring methods requires specialist knowledge and relatively large investments in equipment. On the basis of reviews by Hagens et al. (2007) on the toxicokinetics of nanoparticles and by Wijnhoven et al. (2009) on nanosilver, it may be concluded that the internal dose was rarely characterised and quantified in kinetic studies carried out so far. Often levels of a certain substance were measured in the body but the amount of that substance which was actually present in nano form was not measured.

3.3.2 Absorption

Inhalation. Various epidemiological studies have looked at fine particulates (including ultrafine particles) and the adverse (local and systemic) effects on health (Vermylen et al., 2005; Peters et al., 2006). At present it is not clear whether these adverse effects are caused by the absorbed particles themselves, or by a series of processes initiated by the particles in the lungs. Additional animal studies have shown a small, but detectable absorption of inhaled nanoparticles over the lungs and distribution to other organs (Geiser et al., 2005; Kreyling et al., 2002; Oberdörster et al., 2002). The results of inhalation studies with labelled nanoparticles (i.e., particles with a built-in radioactive atom which can be used to localise or measure the molecule in the test person) however do not conclusively reach the same conclusion (Brown et al., 2002; Mills et al., 2006; Nemmar et al., 2002; Wiebert et al., 2006). The differences between the animal experiments and the human studies are subscribed, among other things, to the fact that in animal studies higher and possibly more toxic doses can be administered. These higher doses could lead to a certain degree of overload, as a result of which particles could still pass over the lung wall. Besides this, the lower detection limit in animal studies, because of the fact that organs and tissues can be examined ex vivo (outside the body), could play an important part in the discrepancy between the animal and human studies.

The olfactory nerve (N. Olfactorius) is also an absorption route along which inhaled nanoparticles can reach the central nervous system (Oberdörster et al., 2004). Via this route they can reach the brain without crossing the blood-brain barrier (Oberdörster et al., 2005a). This neuronal absorption route has been demonstrated in animal studies but not yet in man. It is however reasonable to assume that this route also exists in humans, although the olfactory nerve in the rat is better developed than in humans and therefore has a relatively larger surface area for absorption in the rat.

Gastro-intestinal absorption. There are already various products on the market which could lead to oral exposure to nanoparticles (Lomer et al., 2002; Maynard and Michelson, 2005). It is therefore important that research is also carried out on absorption via the gastro-intestinal tract. There are indications that the size of the particles has an influence on the degree of absorption. It has been shown, for example, that the absorption of 100 nm polystyrene nanoparticles was 250 times greater than for larger particles (500 nm, 1 and 10 μm) (Desai et al., 1996). The differences appear to be smaller for particles of less than 100 nm; polystyrene nanoparticles of 50 and 100 nm showed absorption rates of 34% and 26% respectively (Jani et al., 1990). In humans no uptake of nanoparticles through the gastro-intestinal tract has so far been demonstrated.

Dermal absorption. The uptake of nanoparticles through the skin is the last important exposure route. This applies both to the intact skin (through clothing and cosmetics which may contain nanoparticles) as well as damaged skin (burn treatment creams with nanoparticles, sunscreen creams on sunburned skin) (Lee et al., 2003; Roszek et al., 2005).
Several studies have been carried out on absorption through the intact skin. Some studies report no dermal absorption of various nanoparticles (iron [Fe; 5 nm]; maghemite [γ-Fe_2O_3; 6 nm] and titanium dioxide [TiO_2]) through the intact skin (Baroli et al., 2007; Kiss et al., 2008; Nohynek, 2007).
However, in a recent study two sorts of quantum dots (5 nm and 12 nm with various neutral, positive and negative charged coatings) could indeed be transported through the skin (Ryman-Rasmussen et al., 2006). The same observation has been made for beryllium particles (500 nm and 1 μm; Tinkle et al., 2003), and fullerenes too (Rouse et al., 2007) could be transported over the epidermis (upper layer of skin) when moving skin was simulated.
Wound dressings containing nanosilver (e.g., Acticoat) are already being used in clinics to provide a local antibacterial treatment of the skin further to burns and other injuries. Various clinical studies show that further to wound treatment with nano forms of silver, higher concentrations of silver are found in plasma and urine than after treatment with other forms of silver (Vlachou et al., 2007; Trop et al., 2006). Because of the detection methods used it remains unclear whether it is the silver ions released or the silver nanoparticles themselves which are absorbed through the skin (Wijnhoven et al., 2009).

Parenteral exposure. Nanoparticles can also be introduced into the body through advanced medical applications. For medical imaging purposes nanoparticles with the desired physico-chemical properties can be directly injected into the body. The presence of nanoparticles in the body can also be caused by wear of implanted nanoparticles containing biomaterials (a material that is compatible with living organisms) (Gatti and Rivasi, 2002).

In **summary**, it can be stated that the present studies on the uptake of nanomaterials by the body indicate that uptake by the body can take place. However studies which show whether it is the nano forms of chemicals that are absorbed or the actually the ions, are lacking. This information is of vital importance for risk assessment.

3.3.3 Distribution

After nanoparticles have entered the body by one of the possible routes of exposure, the blood circulation distributes them further to the organs and tissues. During this process interactions can also take place with plasma proteins, clotting factors, blood platelets and blood cells. These interactions can have a major influence on the distribution and excretion of nanoparticles.
The presence of nanoparticles in blood has been demonstrated in various studies (Gatti et al., 2004; Hillyer and Albrecht., 2001). An inhalation study with radioactively charged nanoparticles in rats showed a small (but detectable) distribution of nanoparticles over various organs, including the liver, heart, kidneys, spleen and brain. These findings suggest that nanoparticles are distributed via the blood circulation (Oberdörster et al., 2002). In a recent distribution study with nanogold, intravenous administration of 10 nm gold particles in rats resulted in distribution of gold particles over the blood, liver, spleen, testes, kidney, thymus, heart, lungs and brain. Larger particles (50, 100 and 250 nm) were only found in the blood, liver and spleen (De Jong et al., 2008). These results indicate a (particle) size-dependent distribution in the body. A similar relationship between size and distribution pattern is already known for particles such as liposomes (De Jong et al., 2008; Hillyer and Albrecht, 2001).
From implanted biomaterials information has already been obtained about the distribution of nanoparticles released in the body as a result of wear to the implant. Such nanoparticles (PVC, TiO_2, SiO_2, Co, Ni) have been found in the blood, liver, kidneys and intestines of patients with an implant (Gatti and Rivasi, 2002; Gatti, 2004; Gatti et al., 2004; Revell et al., 1997). In vitro tests have shown that these particles can cause inflammatory reactions in the endothelium (cells lining blood vessels) (Peters et al., 2004).
Information is currently scarce on the distribution of nanoparticles to the reproductive organs and cells, about transport from the placenta to the foetus and passage over the blood-brain barrier. Scientists are, however, aware of the need for research on transport across these barriers.

3.3.4 Metabolism and elimination

After nanoparticles are taken up into the body they can be potentially eliminated through various routes. In general, the following routes are distinguished:

- via the liver;
- via the reticulo-endothelial system (RES, mainly phagocytic cells in the blood, liver and spleen, these are cells which digest bacteria, pieces of dead tissue and harmful substances);
- via the kidneys;
- via less obvious routes such as sweat, saliva, breast milk, hair and nails.

The liver is actively able to remove substances from the blood circulation. It is reasonable to assume that the liver is also capable of getting nanoparticles out of the blood by means of phagocytic cells (Kupfer cells, part of the RES). It is not clear, however, to what degree this process supports the excretion of nanoparticles from the body.
The metallic core of quantum dots and metal oxides could bind to metallothioneins. Metallothioneins are proteins found mainly in liver and kidney cells which are specifically capable of binding a metal to maintain the homeostasis (the ability of an organism to keep its internal environment constant) of free metal concentration in a cell (Coyle et al., 2002).
Nanoparticles with functional groups could be metabolised in this way. This route is not likely however for insoluble or non-degradable nanoparticles. The uptake of nanoparticles by the liver followed by excretion in the bile has been shown for nanoparticles (of polystyrene) in the rat (Ogawara et al., 1999a,b).

Renal clearance through the kidneys has been demonstrated for fullerenes and single-walled carbon nanotubes in rats (Rajagopalan et al., 1996; Singh et al., 2006). There is no data presently available on elimination via less obvious excretion routes such as sweat glands, saliva, breast milk, hair and nails.

There is also not yet much quantitative information on the rate at which nanomaterials are excreted. It would seem reasonable to assume that the elimination half-life for nano and other particles will be long. In a study in which mice were intravenously injected with various coated (zinc sulphide cadmium selenide) quantum dots, these particles were still detectable in the lymph nodes and bone marrow after 133 days (Ballou et al., 2004). This suggests that the half-life of such quantum dots could be in the order of months or even years (Hardman, 2006). With repeated exposure to these particles it can therefore be assumed that the nanoparticles will accumulate in the body. In the event of chronic exposure, even at relatively low doses, this could lead to toxic effects. Unfortunately there is little information available on the accumulation of nanoparticles in the body.

3.3.5 Conclusions on the toxicokinetics of nanomaterials

Various studies have been conducted on the toxicokinetics of a number of nanoparticles. Unfortunately, it is not (yet) possible to extrapolate the results from one particle size to another, or to carry out other types of kinetic extrapolations. This immediately makes clear the need for a characterisation of the nanoparticle dosage as broad as possible. From the literature it appears that the doses are only summarily described. This also makes it almost impossible to compare study results.
The studies show, however, that some particles can pass the point of entry and thus become available within the body. In kinetic research, initial attention should be given on research on the factors which determine which particles can pass the point of entry and under what circumstances. If no absorption takes place and there is thus no internal exposure, research on systemic toxicity will also be less relevant.

3.4 Toxicological effects

Non-degradable and insoluble nanoparticles require a different approach than particles which are degradable. This is the domain of *particle toxicology*, a field of expertise in which not much experience has yet been gained. The present knowledge is mainly obtained from fine particulates research. Research on liposomes is also often referred to. Liposomes, however, are ultimately degradable and soluble, which influences both the toxicokinetics and the toxic effects.

3.4.1 Fine and ultrafine particulates

There are safety standards in place on the concentration of fine particulates (PM_{10}, particles <10 μm) in the outdoor environment. PM_{10} contains a fraction of particles smaller than 1 μm, known as ultrafine particles. This ultrafine fraction also include particles of <100 nm, i.e., in the nano region. Although this fraction comprises particles which have not been deliberately produced (e.g., as a combustion product of diesel), the knowledge obtained from ultrafine particulate matter research will be very useful in directing research on the risks of nanoparticles produced by nanotechnologies. Studies with test animals show that exposure to traffic emissions, in which ultrafine particulates is an important component, for a few weeks can lead to effects in the brain. Increased concentrations of substances have been observed in the brain, which play a role in both signal transduction and inflammation (Campbell et al., 2005). Various studies have been published which also suggest that nanoparticles can reach the brain and the systemic blood circulation (Elder and Oberdörster, 2006; Nemmar et al., 2005),

but possible harmful effects (certainly in the longer term) are not known. This may be due to the fact that there are only limited detection methods in biological systems available (Mills et al., 2006). Oberdörster et al. (2000) showed that the toxicity following inhalation of titanium dioxide can be predicted by the surface area of the particles. Titanium dioxide is a substance used to colour toothpaste white, but which is transparent in its nano formulation and is used for the absorption of UV light in sunscreen creams. In studies with volunteers it appears that the ultrafine particles also play a role in the worsening of cardiovascular complaints such as arteriosclerosis, thrombosis and contraction of the blood vessels (Frampton, 2007; Mills et al., 2007; Araujo et al., 2008) and they have an impact on brain function (Cruts et al., 2008; Suglia et al., 2008).

3.4.2 Nanoparticles

The body of knowledge on the acute toxicity of inhaled nanoparticles is rapidly growing. Due to the limited availability of well characterised nanoparticles hardly any in-vivo studies have been carried out. Most publications therefore deal with effects on isolated cells. Oxidative stress and the formation of inflammatory factors would appear to play a key role in the mechanism of many toxic effects (e.g., inflammation and tumour development) in various organs. Less is known about the toxicity of nanoparticles further to long-term exposure and from other exposure routes than via inhalation.

The amount of literature on oral toxicity studies is limited. For various nanoparticles (zinc, copper, titanium dioxide) toxic effects in the kidneys, liver, spleen and other organs have been observed in rodents further to a short period of exposure of 48 hours to 2 weeks.
Inflammation and tumours have been demonstrated in rodents following intraperitoneal (i.p.) injection of carbon nanotubes in the stomach cavity (Takagi et al., 2008). Reservations can be made about the set up and approach of these and other studies (Lam et al., 2004; Warheit et al., 2004) on carcinogenicity, and thus also about the conclusions of these studies. The recently published study by Poland et al. (2008) however does provide clear evidence for the typical early stages of mesothelioma (asbestos carcinogenicity) due to carbon nanotubes in an animal model.
The effects of nanoparticles on certain organs/organ systems are described below (Borm et al., 2006a). Effects on other organs and organ systems, such as the gastro-intestinal tract and the skin have not so far been demonstrated.

Airways. Nanoparticles can cause inflammation in the lungs, a process in which their number and surface area appear to play a crucial role. Lung tumours are described in the literature only for rodents which have had excessive amounts of nanoparticles administered. The characteristic early stages of mesothelioma have been described however for carbon nanotubes further to i.p. injection (Poland et al., 2008). The lung fibrosis described for rats appears to occur to a lesser extent in humans (Borm et al., 2006a). Due to their small size the nanoparticles largely escape the cleaning mechanism of the lungs and due to penetration of the lung epithelium (the uppermost layer of cells lining the lungs) part of the inhaled dose can enter the body where it can spread to various organs where it may cause effects. Size is not by definition the crucial property which determines lung toxicity, other properties such as surface properties, may also be decisive.

Liver and spleen. The liver and spleen have always been considered part of the reticulo-endothelial system (RES). One of the tasks of the RES is to remove agents (including particles) from the bloodstream. When looked at the location where nanoparticles end up in the body then it can be concluded that a large part end up in the phagocytic cells (macrophages and Kuppfer cells) in the spleen and liver (Oberdörster et al., 2002; De Jong et al., 2008; Fabian et al., 2008). In principle, the RES can deal with the agents picked up and offer them to the immune system so that for instance after

the uptake of bacteria, an immune response is created. What happens to the nanoparticles and other particles which find their way into the RES is unknown. That will depend on the properties of the nanoparticles, in which solubility is an important factor (Borm et al., 2006a). With the accumulation of nanoparticles, the consequences will depend on the dose, the properties and where the accumulation occurs. It is reasonable to assume that in the event that non-degradable and insoluble nanoparticles accumulate, inflammation will occur.

Heart and blood vessels. Epidemiological studies have shown that exposure via the airways to fine and ultrafine particulates can have adverse effects on the heart and blood vessels (blood coagulation, plaque formation). The underlying mechanism is not yet fully understood. It is possible that migration of nanoparticles from the lungs occurs which then end up at weak spots in the bloodstream (atherosclerotic plaques), or inflammatory factors are induced in the lungs due to the presence of the nanoparticles which have an effect via the bloodstream.

Central nervous system and brain. Nanoparticles can reach the brain in test animals via the olfactory nerve (with inhalatory exposure) and also via the bloodstream after passing the blood-brain barrier. It has not been demonstrated that nanoparticles can unintentionally enter the brain of humans, but it has been shown that exposure to ultrafine particulate matter can affect the functioning of the brain.

3.5 Research on the risks of nanotechnology

A great deal is expected of the opportunities that nanotechnologies have to offer, both globally and to the Netherlands specifically. Apart from the economic benefits and greater knowledge, nanotechnologies can have a positive effect on the comfort and quality of people's lives and the environment. In the government paper which sets out the government's vision on nanotechnologies (Netherlands' government, 2006) it was already noted that besides consideration of the opportunities which these technologies offer, consideration should also be given to the potential risks of these technologies. In this way the products can be made available to society in a responsible manner. This vision is also subscribed to in the EU and around the world.

It is observed in the government that the investments in risk research lag behind those made in the development of nanotechnology. It is concluded that in the coming years, in order to take the right measures to manage the risks of nanotechnology, more needs to be invested in risk research both by government and industry (Netherlands' government, 2006). In the meantime, various research projects have been set up by the government, a dialogue between industry and government has been started and researchers and policy-makers are taking part in international research projects and debates.

3.5.1 Dutch research activities

The Dutch government takes part in international bodies (mainly ISO, EU and OECD) aimed at the international coordination of research, methodology development and standardisation. The Dutch government further invests in research activities, including:

- National surveys, such as in the area of working with nanoparticles (protective measures and good practices). In June 2008 this study will be completed;
- Pilot projects (possibly together with the private sector) to generate more information on the human and environmental risks of nanotechnologies, such as research on:
    - nano cerium oxide in diesel;
    - carbon nanotubes in car tyres;

- the development and optimisation of research methods for risk assessment using nano-silver as the model substance (RIVM);
- the environmental consequences of nanotechnology applications;
- oral exposure and possible toxic effects of nanoparticles in the context of food-related applications (Institute of Food Safety (RIKILT)) (Lower House of Netherlands'Parliament, 2008).

As the successor to NanoNed, in the government paper the Netherlands Nano Initiative (NNI, in preparation) is requested to draw up a research agenda for the Netherlands for the next ten years. Significant attention will be devoted to risk research on this agenda. Important areas for consideration under this part of the agenda include:

- measuring methods to determine both the characteristics of nanoparticles and the relevant dose descriptor (dosimetry);
- dosimetry, to investigate which particle characteristics can best be used to describe the dose;
- toxicokinetics/ behaviour of substances, including the uptake and distribution of particles in the body and the environment;
- dose-effect relationships for humans and the environment;
- risk assessment and implementation in the regulatory framework.

Research on the risk of nanoparticles is carried out in the Netherlands by various institutes such as Hogeschool Zuyd (Zuyd University), KIWA (quality assurance institute)/ RIZA (Institute for Inland Water Management and Waste Water Treatment), RIKILT (Institute of Food Safety)/WUR (Wageningen University and Research Centre), RIVM, TI (Top Institute)-Pharma, TNO Quality of Life, Delft University of Technology, University of Tilburg (mainly legal aspects), and University of Utrecht (Pharmacy), et cetera.

It is recommended that in the first instance research should be focused on gathering information which can ultimately be used to set up a good system for risk assessment. This means that the focus should mainly be on the 'need-to-know' questions for risk assessment.
The risk assessment must ultimately provide valid test methods and information on the risks of exposure to nanomaterials. This is relevant for manufacturers and in the context of policy and supervision.

In the context of supervision the Food and Consumer Product Safety Authority (VWA) is actively focusing on how to deal with the risks of food and consumer products in which nanoparticles are present. For example, on behalf of the Food and Consumer Product Safety Authority (VWA), RIVM and Institute of Food Safety (RIKILT) have drawn up a report on nano food safety (Bouwmeester et al., 2007) and the Food and Consumer Product Safety Authority (VWA) has published its recommendations to the Ministers of Agriculture, Nature and Food Quality (LNV) and Health, Welfare and Sport (VWS) about what is necessary to guarantee the safety of nanomaterials in food applications and consumer products (http://www.vwa.nl). Furthermore the Food and Consumer Product Safety Authority (VWA) has set up a board of experts for food and non-food products. This body will be concerned with knowledge transfer on nanotechnologies in the broadest sense, but this is still being developed, and is working on the development of expertise in the field. The aim is that this board of experts will provide interested parties with relevant information on the risks of nanotechnology in the areas of food and non-food products.
Other supervisory bodies, such as the Health and Safety Inspectorate (ArbeidsInspectie), Environmental Inspectorate (MilieuInspectie) and the Netherlands Health Care Inspectorate (Inspectie

voor Volksgezondheid) are still more at the exploratory phase on how best to deal with the risks of nanotechnology and its products.

KIR nano also intends to set up such bodies for other areas, including the environment. These bodies must encourage the exchange of knowledge and information, wherever possible to lead and facilitate the coordination of research and the integration of knowledge from various studies. At the same time KIR nano will facilitate the communication between the various bodies.

3.5.2 International developments and activities

Worldwide a great many research institutes are conducting research on the risks on nanotechnologies. It is not possible to provide a complete overview of the worldwide risk research in the area of nanotechnology. An online inventory of risk research (Environmental and Health Safety (HSE) research) is maintained in the context of the Project on Emerging Nanotechnology by the Woodrow Wilson International Center for Scholars (http://www.nanotechproject.org/inventories/ehs). This inventory gives a worldwide overview of government funded risk research but it is not (yet) complete. At present some 550 research projects are included in the inventory, carried out in more than 15 different countries.

KIR nano takes part in various international fora. Below we will mainly discuss research carried out in Europe in the context of the EU and OECD. KIR nano is also a steering group member of ICON (the International Council on Nanotechnology) which is a renowned international organisation that brings together various stakeholders to arrive at a joint approach to the responsible use of nanotechnology.

EU

The European Commission has set up a working group among the members states' consultation of REACH (Registration, Evaluation, Authorization and restriction of Chemicals), which will be involved with the interpretation of REACH to include nanomaterials. KIR nano supports the Ministry of Housing, Spatial Planning and the Environment (VROM), which represents the Netherlands, with scientific information.

The EU SCENIHR scientific committee is concerned with emerging and newly-identified health risks, including the risks of nanotechnology. SCENIHR formulates opinions on which EU aspirations and standpoints are based. SCENIHR takes a methodological and risk assessment approach for this. SCENIHR activities in the area of nanotechnology are supplementary. The committee is occupied with:

- the development of definitions, mainly for the purpose of risk assessment. In February 2008 SCENIHR published an opinion with regard to the existing and proposed definitions in the areas of nanoscience and nanotechnology (see Chapter 4; SCENIHR, 2008);
- the development of methods and techniques for risk assessment (SCENIHR, 2006, 2007);
- carrying out case studies.

Besides SCENIHR the EU Scientific Committee on Consumer Products (SCCP) has also published an opinion on nanotechnology but specifically on its use in cosmetic products (SCCP, 2007). The European Food Safety Authority (http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_home.htm) has been asked by the European Commission to draw up an opinion on the safety of the use of nanotechnology in food and food production chains. For humans the risk due to direct exposure to food products 'with nano' must be assessed, as well as potential indirect exposure through foodstuffs of animal origin where food 'with nano' has been fed to the animals. Aspects of food technology and the packaging of food also need to be considered in the opinion.

In the 5th, 6th and 7th EU Framework Programmes (FP5, FP6 and FP7) attention is increasingly devoted to the risk aspects of nanotechnology in relation to humans and the environment (HSE). Research projects and networking activities are being carried out in the context of these framework programmes (http://ec.europa.eu/research).

Besides the EU-funded research, most of the EU member states are conducting their own research projects related to the HSE aspects of nanotechnology. From time to time, the European Parliament has also commissioned small research projects, usually of an inventarizing nature (e.g., Dekkers et al., 2007a).

OECD
The OECD programme in the area of nanotechnology risks began in 2007 and is expected to continue for some time. Various working groups have been set up within the WPMN (Working Party on Manufactured Nanomaterials) to undertake projects which fall under the work programme of the WPMN. The overall goal is to arrive at a global knowledge agenda for assessment methods.

Eight working groups have been formed in WPMN:
1. Development of OECD Nanosafety database;
2. HSE research strategies;
3. Safety research on a representative group of nanomaterials;
4. Nanomaterials and testing guidelines;
5. Cooperation in the areas of voluntary schemes and regulatory programmes;
6. Cooperation in the areas of risk assessment and exposure measurement;
7. Alternatives to animal testing;
8. Cooperation in the area of exposure.

Working group 3 will gather data on the toxicity and ecotoxicity of 15 different nanomaterials (including gold, zinc, cerium oxide, nanotubes, titanium dioxide and silver). These particles will be tested for all relevant toxicological and ecotoxicological properties and endpoints (read-out parameters of a test). Participating countries and parties will be asked to supply complete and partial dossiers for this research. Here it should be noted that the toxicity and ecotoxicity of various sizes and forms will have to be tested per nanomaterial, which will therefore require a huge research effort!

Besides the WPMN there is also a WPN (Working Party on Nanotechnology) within the OECD. The WPN concentrates more on the applications of nanotechnology. The aim of the WPN is to promote international cooperation for the purpose of research and development and ‘responsible commercialisation’.

4 Nanotechnology in medical applications

It is expected that innovative medical applications of nanotechnology will have a major impact on healthcare in the future. These new nanotechnology applications relate to both medicines and medical technologies.

Partly because of the strict safety requirements which medical applications of nanotechnology are subject to, there are at present only a relatively small number of such applications available. There are nevertheless high expectations for the future prospects of this application area (Netherlands' government, 2006). The scientific and technological developments may well eventually make it possible to treat disease and hereditary disorders on a cellular level.

Certain medical applications of nanotechnology are converging technologies. As a result, in some applications, the dividing line between medicines and medical technology is not always clear. For the medical field, the collective term 'nanomedicine' is used, which encompasses the application of nanotechnology in both medicines and medical technology. Where possible, a distinction will be made between these two fields in this chapter.

4.1 Applications

Nanomedicines are medicines made from new or existing substances which are applied on a nanometre scale. These nanomedicines may consist of nanoparticles of the active ingredient, nanoparticles as a carrier material or porous material from which the active ingredient is released in a controlled manner. It is particularly this controlled release system, sometimes in very specific places within the body, which represents the great strength of nanomedicines. The nanoparticles can contain or carry all kinds of active ingredients: chemical substances, proteins or genetic material. The surface of nanoparticles can be modified to adjust the release mechanism, to target specific organs or tissues in the body or to prolong the circulation time in blood (known as the 'stealth effect'). In this way the effectiveness of the uptake of the active ingredient by the target organ/tissues (organ/tissue where a substance has its effect) is increased. Nanomedicines are expected to make a positive contribution to the prevention, diagnosis and treatment of diseases such as cancer, infections, auto-immune diseases and inflammations. Nanomedicines may also be suitable to treat diseases which at present can only be treated with drugs that have many adverse effects. It is expected that nanomedicines have less adverse effects because the drug can be more accurately targeted at its destination. It is also expected that less of the drug will have to be administered (http://www.rivm.nl/rvs/075_nanotechnologie/risicos_mens/geneesmiddelen/).

Nanotechnology makes it possible to control substances at the atomic and molecular levels and thus has the potential to create materials with new properties. This can speed up the rate of development thus leading to a new generation of medical products and technologies. The influence of nanotechnology on the diagnosis, treatment and prevention of diseases is already apparent. It has brought early diagnosis, precision and effective treatment methods within reach (http://www.rivm.nl/rvs/075_nanotechnologie/risicos_mens/medische_technologie/).

4.1.1 Present applications

The following applications of nanotechnology in medical technology are currently available (Roszek et al., 2005; Health Council of the Netherlands, 2006; Geertsma, 2007):

- Surgery. The surface of surgical scalpels and the composition of surgical suture needles can be modified to give them better properties, such as a better cutting edge. Textiles used in the operating theatre can also be furnished with better antibacterial properties.
  Examples include:
  - diamond-coated surgical scalpels (surface roughness 20-40 nm);
  - surgical suture needles containing steel nanoparticles (1-10 nm);
  - operating room textiles containing nanosilver;
- Medical imaging techniques. With new imaging techniques, in vivo diagnoses can be made earlier. These new contrast substances are subjected to the medicinal products legislation. The equipment for imaging techniques falls under medical technology. Imaging is thus an example of converging technologies.
  Examples include:
  - Contrast media:
    - Superparamagnetic iron oxide nanoparticles (50-500 nm) for magnetic resonance imaging (MRI).
    - Micro and nanobubbles for ultrasonic imaging.
  - X-ray tube with carbon nanotubes which act as a cathode;
- Biosensors and biodetection for the diagnosis of diabetes, cancer, bacteria and viruses;
- Implantable materials and equipment.
  Examples include:
  - Bone cement / bone replacement materials:
    - Hydroxyapatite and tricalcium phosphate: nanoparticles which facilitate rapid integration with the bone of the patient.
  - Surface coatings. The surface of implants can be modified with the aid of nanotechnologies to enable them to integrate better in the body (improved biocompatibility):
    - Joint prosthetics (hip, knee) with nanohydroxyapatite coating;
    - Coronary stents with a diamond-like nano composite coating made of ultrathin polymer;
    - Catheters with a nanosilver coating for bladder drainage, haemodialysis and local administering of anaesthesia;
  - Spintronic technology (in spintronics the quantum mechanical ‘spin’ of electrons is used to make smaller and faster circuits and storage media) for implant equipment, such as pacemakers and hearing aids;
  - Battery components which contain nanomaterials for implant equipment;
- Wound treatment.
  Examples include:
  - Wound treatment products (wound dressings) containing nanocrystalline silver particles which are used for improved antibacterial and anti-fungal activity;
- Smaller and more refined analytical instruments and cheap disposable components;
- DNA/protein micro-arrays (set of miniature test wells on a chip) and lab-on-a-chip devices for molecular in vitro diagnostics, point-of-care applications;
- Micro-cantilevers used in molecular in vitro diagnostics;
- Systems with micro-needles for minimally invasive drug administration or for monitoring blood values such that minimal tissue damage occurs and little pain is experienced.

With the aid of nanotechnology, more effective medicines are being developed with fewer adverse effects. In the area of medicines, a distinction is made between the following nanotechnology applications:

- Medicines in a nanocrystal form. These are regularly used for ingredients which do not dissolve easily. These nanocrystals often show a more rapid uptake and distribution in the body compared with the same ingredients in another form;
- Carrier materials and tools for delivery of medicines. A great deal of research is being performed on this topic. Simple applications are already on the market (Health Council of the Netherlands, 2006).

4.1.1.1 Research and development

Research groups working on the medical applications of nanotechnology are mainly occupied with nanobiology and biophysics, nanofluids, physics, (bio)chemistry of functional nanoparticles, pharmaceutics, material science, and cell biology. This research is taking place in most of the Dutch universities and the FOM Institute for Atomic and Molecular Physics (AMOLF).

There are many companies in the Netherlands which are involved with medical applications of nanotechnology. Dutch companies are active in diagnostics, imaging and drug delivery systems, among other areas. Large companies as well as small innovative enterprises are working with the applications of nanotechnology in medicines and medical technology.
In the field of nanotechnology, companies are faced with the dilemma of 'waiting or investing'. Companies want to avoid the initial phase with its attendant teething problems, while on the other hand not end up lagging too far behind. It is therefore a matter of finding the right moment to join the race. In practice it appears that starting up a separate nanotechnology division does not always work well because of the multi-disciplinary nature of nanotechnology. An umbrella group with representatives from all the present divisions however does give added value.

IoN (Institute of Nanotechnology, UK), which also plays an important role in the European Observatory (ObservatoryNano), has set up Nanomednet. Nanomednet is an international organisation whose objective is to bring industry, clinicians, universities, government authorities and other stakeholders together for the purpose of exchanging information, and to facilitate education and training (http://www.nano.org.uk/nanomednet/). Industry often develops products on its own initiative without taking into account the demand from the clinical side. There are many benefits to be gained in this area. Improving the link between academic and other scientific research and the government authorities is also important. KIR nano supplies an expert on medical applications who advises IoN and at the same time is also kept abreast of developments in this field of application.

4.1.1.2 Patents

Between 1996 and 2006 the following numbers of patents were issued in the field of nanomedicine (Keller, 2007):

- therapeutic applications: 775 patents (drug delivery, vaccine delivery, tissue engineering);
- diagnostic applications: 270 patents (sensors, biomarkers);
- consumer health: 449 patents (cosmetics, sunscreen products and water treatment systems). (The applications in this last category are covered in this report in Chapters 6 and 8 on consumer products and environmental applications, respectively.)

Patents are valid for 20 years. For a drug, the development pathway plus the pathway for registration takes about 9 years. The development of new forms of administration can increase the patent period.

For this purpose, new formulations are also developed under the 'nano' label. In this way, a company can prolong the profitable period of a drug. An example of this is a treatment against breast cancer which has been brought onto the market in a new (nano)formulation .
The development period for medical technologies is shorter than that for medicinal products. New generations of medical equipment ever more quickly succeed one another.

4.1.2 Future applications

The following applications of nanotechnology in medical technology are currently in development:

- Surgery:
  - Nanosurgery:
    - Optical tweezers for the manipulation and immobilisation of cells, cell organelles and biomolecules;
    - Femtosecond laser systems for neurosurgery, ophthalmology and dermatology;
  - Minimally invasive surgery:
    - Catheters strengthened with carbon nanotubes;
- Imaging techniques for in vivo diagnostics:
  - Contrast media for MRI:
    - Ultrasmall superparamagnetic iron oxide nanoparticles (<50 nm);
    - Monocrystalline iron oxide nanoparticles (3 nm) ;
    - Dextran cross-linked iron oxide nanoparticles;
    - Carbon nanotubes loaded with gadolinium clusters;
    - Fullerenes containing gadolinium;
    - Fullerenes containing metallonitride;
    - Gadolinium-conjugated dendrimers;
  - Radiological contrast media for computer tomography:
    - Iodine-containing fullerenes and holmium fullerenes;
    - Iodine-filled carbon nanotubes;
    - Polymer-coated bismuth sulphide nanoparticles;
  - Contrast medium for ultrasonic imaging:
    - Nanobubbles;
  - Contrast medium for optical imaging:
    - Quantum dots;
  - Contrast medium for opto-accoustic tomography:
    - Bio-conjugated gold nanoparticles;
- In vitro diagnostics:
  - Biosensors based on superparamagnetic nanoparticles ('magnetic relaxation switches') for mobile magnetic resonance diagnostics;
  - Biosensors based on nanotubes, nanowires, nanoarrays of nano-electromechanical systems (NEMS) for the diagnosis of diabetes or cancer and for the detection of bacteria, fungi or viruses. It is expected that in the future cheap, portable sensors will be available which will enable a diagnosis to be made at the patient's bedside or GP's practice;
  - '*Lab-on-a-chip*' instruments combining one or more sensor functions and software for the interpretation of the measured data with facilities for processing blood or saliva samples. This will make it possible to simply and easily screen patients for dozens of disorders without the need for a large clinical laboratory;

- Therapy:
  With the aid of nanotechnology, tumours can be more accurately targeted and treated. Particles can be introduced into tumours which can then be radiated from outside. This is a highly targeted form of therapy. Depending on the mechanism used by the particles to destroy the tumour, it is debatable whether the product should be classified as a drug or a medical device.
  - Heat therapy with superparamagnetic iron oxide nanoparticles;
  - Heat ablation with gold nanoparticles;
  - Light therapy;
  - Boron neutron capture therapy;
- Theranostics (therapy combined with diagnostics):
  - Combination of diagnostics and heat therapy with the aid of superparamagnetic iron oxide nanoparticles;
- Implantable materials and equipment:
  - Bone cement/ bone replacement products containing nanomaterials:
    - Nanosilver as an antimicrobial additive;
  - Micro-electromechanical systems:
    - Neuroprosthetics, e.g., for 'deep brain' stimulation;
    - Retina prostheses for the blind;
    - '*Stentenna*', stents as antenna for wireless monitoring of implanted sensors;
  - Coatings and surface modifications:
    - Coronary stents with nanocoatings of aluminium oxide, glycoproteins, hydroxyapatite, platinum or titanium dioxide;
    - Silver nanocoatings for various catheters, orthopaedic implants, contact lenses, endotrachial tubes and mesh implants;
    - Orthopaedic implants with nanocrystalline metallo-ceramic coatings;
    - Electrodes with laminin nanocoating through layer-on-layer self-assembly to improve electrode-tissue interface;
    - Surface modification of neural micro-electrodes with polymer nanotubes for a low impedance electrode-tissue interface;
    - Nanoporous micro-electrodes for a brain-machine interface;
    - Modification of the surface roughness of an implant which influences the function of bone-forming and bone-degenerating cells;
  - Carrier material ('scaffold') for *tissue engineering products* with a nanoporous structure and surface properties which facilitate the growth of living cells and enable the transport of nutrients and waste products. The purpose of these types of products is to replace, repair or regenerate tissues and, ultimately, even organs.

In the medicines field there are currently many developments taking place mainly in the area of drug delivery. Dozens of products are in development. Estimates indicate that by 2015 about half the drug delivery systems which will then be in development will be based on nanotechnology. At the moment research is being carried out on the use of many different types of nanoparticles for drug delivery, among other things. This applies to dendrimers, nanotubes, liposomes, nanocrystals, quantum dots, spheres or rods of substances such as gold, silica and albumin. The nanoparticles may be in the form in which the drug itself is delivered (e.g., nanocrystals) or serve as a carrier for the actual drug. The use of nanoparticles can improve solubility and increase bioavailability and thus more efficient dosing. But also the deliverery to less accessible places such as across the blood-brain barrier and the more precise targeting and circumventing of the immune system are being potential benefits.
Work is also being done on combined products which bring together several functional modalities. Applications include imaging techniques, therapy, monitoring or a platform with various substances for

the recognition of structures to make a tumour-specific drug. Such applications are examples of converging technologies.

4.1.2.1 Future generations

The nano applications already available and those that will become available in the near future fall under the first generation (e.g., coatings and joint replacements) and the second generation (e.g., targeted drugs, sensors for in vivo monitoring) (Roco, 2007). The medical applications to follow in the third and fourth generations of nanotechnology are still in development (Roco, 2007):

Third generation:

- Artificial organs;
- Improved cell-material interactions;
- 'Scaffolds' for tissue engineering;
- Localised drug delivery;
- Rapid diagnostic techniques;
- Closed loop systems, such as applications in anaesthesia, in which a stable level of sedation can be maintained with the aid of sensors.

Fourth generation:

- Genetic changes;
- Stem cell therapies;
- Tackling the ageing of cells;
- Devices for gene therapy;
- Self-assembling molecular structures.

The Netherlands can make an important contribution to the following future developments:

- Nanotechnology for diagnostics (including lab-on-a-chip biosensing systems);
- Identifying the cause and development of diseases;
- Molecular medical imaging techniques;
- Drug and protein delivery and vaccination;
- Reconstructive and regenerative medicine, including the use of intelligent biomaterials for in vitro and in vivo control, 'smart' implants (with electronics) and synthetic biology, among other things, to change the functions of cells (NNI, in preparation).

4.2 Potential risks

4.2.1 Present understanding of risks

During the use of nanomedicines, exposure to nanoparticles are specifically part of the intended effect of the drugs. This in contrast to 'unintentional' exposure when nanoparticles are used in other products, such as paint. The risks of the use of nanomedicines could, among other things, lie in a different distribution of the particles in the body compared to medicines not in a nano form. This is because the particles are often far smaller and could penetrate the blood-brain barrier or cell membranes, or remain lodged in capillaries. Nanoparticles could also have an impact on the immune system and be consumed by macrophages. Further toxicological risks of nanomedicines are as yet unknown (De Jong and Borm, 2008). For free nanoparticles in medical applications such as drug delivery systems, it is very important that the toxicological properties are investigated (Geertsma, 2007). If a nanoparticle is fixed on or in a medical device, e.g., an implant, then it is expected that the health risk will be minimal. However, if the

particles are released due to wear or a chemical reaction, for example, then these free particles could constitute a risk. There are also medical technologies which actually make use of free nanoparticles, for example, in certain cancer therapies. The specific toxicological risks of these still have to be investigated, but the present regulatory framework already requires a comprehensive dossier on the safety aspects of medical applications (http://www.rivm.nl/rvs/075_nanotechnologie/risicos_mens/medische_technologie/). To gain access to the market a risk-benefit analysis must be carried out for every medical application. This involves a balancing of the risks of substances against the benefits of proposed risk management measures in which socio-economic factors also play a role, and which should show whether the risk is acceptable or not.

In general, the toxicological risks of nanoparticles in medical applications (Geertsma, 2007) depend on:

- Material properties (composition, toxicity, degradability, hydrophilicity (i.e., the degree to which substances are inclined to dissolve in water), size, and form);
- Exposure route (implant, injection, dermal, oral, inhalation);
- Dose.

There are also technological risks involved, such as the risk that a certain product does not function or the risk of material faults. There may also be other risks involved in the use of nanotechnology, such as radiation. Besides the possible toxicological risks, in its report the Health Council of the Netherlands also identifies a number of social implications and moral issues related to nanotechnology (Health Council of the Netherlands, 2006). These relate to matters such as the distribution of wealth and the protection of privacy, but also:

- Change in the patient-doctor relationship: treatment will increasingly be carried out by nursing staff. This raises questions about good nursing care and the provision of information;
- Gap between diagnostics and therapy: the ability to discover and treat disorders at an early stage is steadily growing. The arrival of new techniques will put pressure on the basic principle of screening people for treatable diseases;
- Fundamental questions surrounding the ‘improvement’/modification of people. Nanotechnologies may make it possible in the future ‘to bring healthy people to perfection according to their own taste’. This raises both ethical and societal questions.

Doctors gain lot of their knowledge through practical experience (trial and error) and from information which they receive from the pharmaceutical industry. Such knowledge is not available for other areas of application (such as consumer products). Knowledge about the risks of nanoparticles in the medical sector could possibly be used to assess the risks of (similar) nanomaterials in other areas of application. Given the confidential nature of the data it is open to question whether information can be made available in this way.

4.2.2 Knowledge gaps

Compared with other nanotechnology application areas there is a relatively large amount of information on the area of medical applications or this information is potentially being generated. In the area of medical technologies important aspects which still need to be addressed for the risk assessment include determining:

- the biocompatibility of medical products/materials in which nanoparticles have been used;
- the toxicological aspects of nanomaterials (particularly free, non-degradable and insoluble nanoparticles);

- the applicability of the current test methods, whether they are adequate or whether new methods should be developed;
- the relevant aspects of nanoparticles which need to be taken into account in risk research (such as form and dimensions); information is still lacking on the major toxicological determinants;
- the distribution of particles which enter the body by various routes.

4.3 Coping with risks

4.3.1 The regulatory framework

The fact that nanotechnologies are converging technologies means that it is not always clear which regulatory system applies when nanotechnologies are used in medicines and medical technology. In practice, combined products are created in which it is not always easy to establish the primary effect mechanism and the primary intended use. As a result confusion may arise about the path to be followed to gain market access. This issue is given high priority in both the pharmaceutical and the medical device industries. In March 2008, for example, this theme received extensive coverage at a conference of the Drug Information Association (DIA Euromeeting, Barcelona, 3-5 March 2008, www.diahome.org).

There are clear differences between the legislation for medicinal products and the legislation for medical technology. The legislation on medicinal products is highly centralised: European and national government organisations handle the assessment and registration of medicines. Passage through these procedures ultimately leads either to registration or not. Nanomedicines are registered under the proviso that they only contain nanoparticles within a specified size range. It is difficult to determine whether a medicine only contains nanoparticles of the specified size range. Nanomedicines that have been registered meet the present requirements for medicines and will have been tested for efficacy and safety and quality (http://www.rivm.nl/rvs/075_nanotechnologie/risicos_mens/geneesmiddelen/).

Responsibility for the access of medical devices to the market is as far as possible decentralised. For medical devices involving little risk it is not necessary to follow an extensive route via various bodies: manufacturers themselves are responsible for a dossier which ensures quality and safety. Notified bodies, such as KEMA in the Netherlands, issue a CE-mark required for access to the market of products involving a greater risk. These bodies are subject to government supervision.
The following risk classes are applied:

- Class 1 (low risk): products such as adhesive bandages and plaster;
- Class 2a and 2b: for example, surgical instruments, diagnostic equipment;
- Class 3 (high risk): for example, products which are broken down in the body, contraception, products which end up in the bloodstream and have an influence on vital organs, aids with drug components such as nanosilver and implants (with the exception of materials for dental applications.

The most important factors taken into account in this risk classification system are potential invasiveness and contact with vital body structures such as the heart, central blood circulation and brain, including the central nervous system. As a result many nanotechnological applications end up in the highest risk class.

In 2007 the working group of the European Commission for New and Emerging Technologies in Medical Devices - Nanotechnology (N&ET WG- Nanotechnology) assessed the applicability and

suitability of the present regulatory framework in relation to nanotechnology in medical technologies (N&ET Working Group, 2007). The N&ET WG – Nanotechnology came to the conclusion that the legislation on medical devices can also be applied to medical devices in which nanotechnology is used. This legislation is based on risk management and this risk management approach is also suitable for controlling the risks of nanotechnology in medical technologies. This applies both to the use of free nanoparticles as well as to fixed materials with nanostructures on the surface.
The N&ET WG – Nanotechnology recommended that a new classification rule be introduced for 'free nanoparticles' which will ensure that all products with free nanoparticles end up in the highest risk class:

> *'All devices incorporating or consisting of particles, components or devices at the nanoscale are in the highest risk Class III unless they are encapsulated or bound in such a manner that they cannot be released to the patient's organs, tissues, cells or molecules.'*

The working group also noted the following:

- In the definition of the nanoscale the working definition adopted was: at least one dimension between 1 and 100 nm;
- This rule should be reviewed after three to five years.

Because of the fact that the risks of nanotechnology are partly new and not entirely known, this working group recommended that guidance in this area be developed. A start has been made on this in 2008.
This guidance should cover:

1. The nature of the risks which need to be considered;
2. Possible solutions for risk management;
3. The organisational structure for the exchange of experience by means of a Voluntary Reporting Scheme;
4. Nessecary actions which needs to be taken in the post-marketing phase;
5. Interpretation of the legislative requirements before introducing nanoproducts onto the market;
6. Which parts of the guidance apply to in vitro diagnostics (IVDs).

The N&ET WG – Nanotechnology will also try to coordinate with groups within the EMEA (European Medicines Evaluation Agency) that are studying the issue of nanotechnology for medicines. Companies can also turn to this body for advice. EMEA also includes the following three advisory groups (Purves, 2008):

- Innovation Task Force – early consultation in the context of regulatory, scientific and other matters which may arise during the development of innovative products, for example whether the product is a medicinal product (http://www.emea.europa.eu/htms/human/mes/itf.htm);
- Scientific Advice Working Party – scientific advice on preclinical and clinical research to be carried out in relation to quality, safety and effectiveness (http://www.emea.europa.eu/htms/human/sciadvice/Scientific.htm);
- Small and Medium Size Enterprises (SMEs) Office – procedural and scientific support for SMEs at reduced rates (http://www.emea.europa.eu/SME/SMEoverview.htm).

In 2006 EMEA also published a 'reflection paper' on its website (http://www.emea.europa.eu/pdfs/human/genetherapy/7976906en.pdf).

According to the N&ET WG – Nanotechnology, the present vigilance system for medical devices for reporting serious incidents to the authorities does not need to be changed. This system is sufficiently generic to also include nanotechnology matters. The working group does, however, emphasise the need for an active system of post-marketing surveillance by manufacturers. It may also be necessary to

adjust the present standards to incorporate nano aspects (e.g., EN ISO 10993: Biological evaluation of medical devices).

4.3.2 Risk assessment

Specific assessments have already been carried out for nanomedicines. In the Netherlands RIVM is one of the organisations which assess nanomedicine dossiers in relation to safety and quality on behalf of the Medicines Evaluation Board (CBG). This covers the chemical, pharmaceutical, pre-clinical and toxicological aspects.

The following applies in relation to medicines and medical devices:

- A comprehensive dossier should be created;
- Tests should be carried out in vitro, in vivo and in patients;
- Strict manufacturing standards should apply;
- Access to the market is granted under strict conditions;
- The possible behaviour of nanoparticles should be taken into account in all risk assessments. However no specific requirements have been laid down in monographs, standards or guidelines which products are required to meet. This applies for example, to the range and the average size of nanoparticles during the production of approved products;
- There is no requirement to specifically report whether or not a drug or medical device contains free nanoparticles. This makes it difficult to obtain an overview of products of this type which are already on the market. Such a list would also help to make risk assessors alert to this;
- A post-marketing surveillance system is used for both medicines and medical devices. As a result of this, products are sometimes taken off the market. The manufacturer is responsible for the post-marketing surveillance. For medicinal products, LAREB (a part of the CBG) maintains a central register of side-effects.

At present it is mainly nanomedicines used in oncology which are being registered. Contrast media for imaging techniques are also on the market. For registration a risk-benefit analysis is carried out on the basis of expert judgement.

4.3.3 Risk management

Risk management is important to all the parties in the product life cycle. This should therefore be a continuous process between manufacturers, authorities, healthcare providers, notified bodies and laboratories, et cetera (Geertsma, 2007). Under the legislation for medical devices a manufacturer is required to have a risk management strategy (see also under regulatory framework). The industry is required to assess every risk for every product and reduce it to an acceptable level. The mandatory risk management strategy, which includes a risk assessment, will essentially be sufficient provided that manufacturers, the competent authorities and institutes are aware of the need to carry out a specific toxicological or nanotoxicological risk assessment (De Jong et al., 2005).

Risk management in the field of medical technologies is carried out in accordance with the method laid down in the international standard EN ISO 14971 ‘Medical devices - Risk management - Application of risk management to medical devices’. This is a general method which describes a continuous process with iterative steps throughout the entire life cycle of a product. Important steps in this process are the identification of a risk, followed by risk assessment, risk management, evaluation of the acceptance of the remaining risk further to implementation of the risk management measures and gathering post-production information. All the steps should be repeatedly applied by a multidisciplinary team. To further evaluate risks (or sets of risks) specific standards can be used, such as the series EN ISO 10993

– ‘Biological evaluation of medical devices’. These may be adapted in certain areas to include nano aspects.

For medicines too there is a guidance document on risk management: ICH Q9 Quality Risk Management (http://www.emea.europa.eu/Inspections/docs/ICHQ9Step4QRM.pdf). The method this document describes is very similar to that for medical devices.

4.4 Observations

- A great many developments are taking place in the area of nanomedicine. These concern medicines, medical devices and combined products. By making use of the added value of nanotechnology in all sorts of new technologies, important innovations are possible in the diagnosis, treatment and prevention of disease. This could ultimately lead to changes in the organisation of our healthcare system;
- The legislation on medicines and medical devices requires careful risk assessment and risk management before products may be brought onto the market. Even though the specific risks of nanomedical products are not yet fully known, they will in any event be thoroughly evaluated in their registration dossiers and technical documentation. The availability of alternatives and the clinical benefits of the products will also be taken into account in this process. For products which are made at the borderline between medicines and medical devices, it is important to make sure that they do not fall between the two sets of legislation.

Knowledge about the risks of nanoparticles in the medical sector, particularly in the area of methodology, can be used to assess the risks of similar nanomaterials in other areas of application. The use of the underlying research data should also be evaluated but given the confidential nature of such information, this is less likely to occur.

5 Food production

In the area of food production nanotechnology is used along the entire length of the food chain, i.e.:

1) during cultivation, e.g., the use of nano crop protection products;
2) industrial processing, e.g., in the use of nano-sieves;
3) increasing food values, e.g., by introducing nutrients in nano form into the product (increased bioavailability);
4) in food packaging materials.

Nanotechnology in food products is seen as an area with many promising applications. For example, it is expected that nanotechnology can make a useful contribution to the optimisation of production processes and increase the quality and shelf-life of food. Besides this, with the aid of nanotechnology healthy food could be developed and introduced for preventive healthcare.
Bearing in mind the wider applications in society and the scientific potential present in the Netherlands, 'food and health' is one of the five main themes mentioned for the government's research agenda in the paper which sets out the government's vision on nanotechnologies (Netherlands' government, 2006).

Figure 5.1 shows in outline where nanotechnology is utilised in food production.

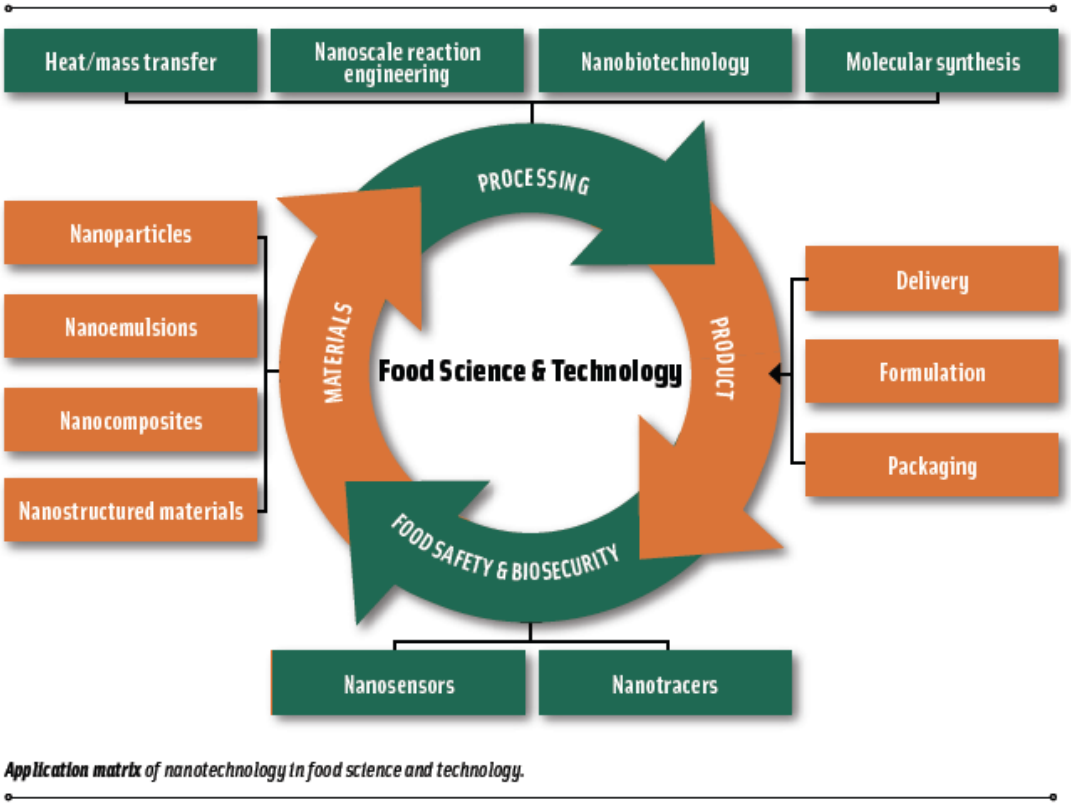

Figure 5.1. **Nanotechnology in the food production chain (from: Weiss et al. (2006)).**

5.1 Applications

5.1.1 Present applications

In 2007 at the request of the Food and Consumer Product Safety Authority (VWA), the Institute of Food Safety (RIKILT) and the National Institute for Public Health and the Environment (RIVM) undertook a survey of the use of nanotechnology in the food production process. This inventory gives a picture of applications (see Table 5.1) and products which are currently already on the market (Bouwmeester et al., 2007, 2009).
Table 5.1 provides a summary of the main uses (Bouwmeester et al., 2007):

Table 5.1: Summary of the uses of nanotechnology in the food production chain.

Phase in chain	Application	Nanotechnology	Function
Agricultural production	Nanosensors	Nanospray on food base material	Binds and colours micro-organisms
		Hand-held instruments	Tracing contaminants, et cetera
		Used in packaging materials	Detection of food spoilage
	Crop protection products	Nano-emulsions, encapsulations	Increased effectiveness, water solubility and adhesion to crop
	Water treatment/ soil decontamination	Filters with nano pores	Pathogens / removal of contaminants
		Nanoparticles	Removal of contaminants or catalyzation of oxidation of contaminants
Production and processing of food	Food production	Nano ceramic equipment	Large reactive surface
	Fridges, storage containers, equipment for food preparation	Incorporated nanoparticles, mainly silver, sometimes zinc oxide	Antibacterial coating of equipment for storage and treatment of food
Preservation	Food products	Nanosilver sprays	Antibacterial activity
	Packaging materials	Built-in sensors	Detection of food decay, monitoring of storage conditions
		Built-in nanoparticles	Extending property limits, strength of materials
		Built-in active nanoparticles	Oxygen capture, preventing growth of pathogens
Functional foodstuffs, consumption	Supplements	Colloidal metal nanoparticles	Desired better uptake claimed
		Delivery systems ‘nanoclusters’	Protection and possibly targeted delivery of contents
		Nanosized/ – clustered food and drink (nutrients)	Better uptake claimed

The inventory shows that from the point of view of potential risks to humans and the environment it is important to distinguish between:

1) nanotechnologies which are used to facilitate the production process, and
2) applications where nanoparticles are intentionally added to food or *could* unintentionally end up in food (Bouwmeester et al., 2007, 2009), e.g., through residues of nano crop protection products and through the leakage of nanoparticles out of packaging materials.

ad 1) Examples of this are the use micro and nano-sieves to filter bacteria or yeast cells out of a food product and the use of hand-held equipment for monitoring.

Ad 2) Nano particles which are intentionally added to food can be generally divided into:
Nanoparticles which are intentionally introduced into food:

- Various types of nanoparticles are added to foods as an additive or supplement (see also Table 5.2). Such particles are added in a nano form to improve bioavailability (uptake) in the body.
- 'Nanodelivery' systems which can often be considered soluble or degradable. 'Delivery' systems (with the aid of encapsulation) in food are often made of peptide or lipid monomers (i.e., small molecules of two or more amino acids or fats which through repeated linking can grow to become a very large molecule (polymer)). An important application of such substances is food additives for the targeted delivery of bio-active substances and to increase bio-availability.

Nanoparticles which *could* unintentionally end up in food:

- Non-degradable and insoluble particles such as nano forms of aluminium oxide, lanthanum and iron which are used in water treatment, or silver/zinc with an antimicrobial effect in packaging materials and storage containers.
- Encapsulated crop protection products which, for example, adhere better to crops than the non-encapsulated form of the crop protection agent.

Table 5.2 provides an overview of various types of nanoparticles that are used in food production. As is the case with many nano products, here too, it is often unknown whether the nanoparticles are also still present in the final product and if so, in what size (form) (Bouwmeester et al., 2007, 2009).

Table 5.2: Overview of the type of nanoparticles used in the food production chain.

Type of nanoparticles	Application	Function
Colloidal metal nanoparticles	Food additive	Desired better gastro-intestinal uptake claimed
Metal nanoparticles (silver, zinc oxide)	Food additive / supplement	Better uptake claimed
	Packaging materials / storage	Extending property limits
	Equipment for food preparation	Cleaning of surfaces
	Fridges, storage containers	Anti-bacterial coating of equipment for storage and handling of food
	Water treatment/ soil decontamination	Removal of contaminants or catalyzation of oxidation of contaminants
	Sprays	Anti-bacterial
Nanosized nutrients / food	Food additive / supplement	Better uptake claimed
Complex structures on nanoscale	Nanosensors in packaging	Detection of food spoilage
		Monitoring of storage conditions
	Hand-held equipment	Detection of contaminants, et cetera
Incorporated active nanoparticles	Packaging materials (possible migration from)	Oxygen capture, preventing growth of pathogens
Filters with nano pores	Water treatment	Removal of pathogens, contaminants
	Monodisperse emulsions	Product development
Delivery systems (nano encapsulations)	Food additive / supplement	Protection and targeted delivery of contents
	Crop protection product	Increased effectiveness, water solubility and adhesion to crop, initial local discharge

5.1.2 Future applications

Various analyses have shown that nanotechnology is generally expected to have a major impact on the food industry (Joseph and Morrison, 2006). The applications are aimed at sustainable production processes, better quality and safety of food, advanced packaging materials and improvements in health. The forces driving these developments are climate change, cost efficiency and population growth (Joseph and Morrison, 2006).

Many of these applications are still at the research stage. Among these, the developments in the area of new packaging materials are closest to market introduction. The first products with a longer shelf-life are coming onto the market. Sensors based on nano and microtechnology (i.e., the design, characterisation, production and application of structures, instruments and systems for regulating the form and size at the nanometre or micrometre level) create better means of ensuring quality and food safety. Applications in the food production process make the process sustainable and delivery systems for the introduction of taste and aroma enhancement or nutrients can provide health benefits. There are also many developments taking place at the point where nano, bio and info technologies meet. Examples include the integration of electronic communication, sensors, reporting systems, advanced packaging materials, localisation (GPS) and control systems leading to advanced ‘smart nanosystems’ in the food industry. This combination of different areas of technology brings new challenges for the

regulatory framework.

In the longer term future it is foreseen that nanotechnologies could bring about breakthroughs in the decoding and analysis of 'crop DNA' and help to predict, manage and improve agricultural production. Furthermore, nanotechnology will probably make it possible to manipulate food at the molecular and atomic levels, which will make it possible to increase food production with more precision, at a lower cost and with greater sustainability.

A combination of technologies will also make it possible to develop more advanced delivery systems in the human body. Applications would appear to be possible first in functional foods.
The 'Roadmap [to] Microsystems & Nanotechnology in Food & Nutrition' gives a clear overview of the opportunities and prospects which microsystems and nanotechnology have to offer the Dutch food industry and its suppliers in the coming years. A number of key development areas in this field are set out in this Roadmap for companies to apply new technologies. The following applications areas are indicated as 'potentially successful themes' (Prisma & Partners and MinacNed, 2006).

- Filtering and fractionation: the development of process technology components in the form of sieves and filters. Possible applications include the treatment and filtering of raw materials and semi-manufactures, in fractionation and cold sterilisation (e.g., with Aquamarine sieves). Other possible examples include equipment which replaces unhealthy ingredients (such as saturated fats) with healthy ingredients (unsaturated fats);
- Sensor/detection systems and processing: the development of sensors and diagnostic kits which determine the quality of food (more quickly and cheaply), monitor the production process and provide early detection of microbes and other types of contamination. This also relates to the *downscaling* of food production and preparation. This could take the form of equipment which operates locally on the farm or in the consumer's home (filtering, mixing, emulsifying, individualising food). Through the parallel linking of such units *up-scaling* is also possible, thereby creating flexible central production units;
- Emulsions, texture and delivery systems: manufacturing food with a different texture and/or composition. For example, double emulsions (water-in-oil-in-water). This makes it possible to prepare ingredients with a very low fat content. Delivery systems are applications in which useful ingredients such vitamins can be precisely dosed and released in a controlled manner, for example during the meal (aromas) or in the body (nutrients). Encapsulation can be used to enhance the dispersion of nutrients in the body. In such applications the encapsulation material remains in the gut wall. Not many applications of '*delivery containers*' in the blood circulation may be expected. This would mainly be used pharmaceutically for curative purposes. There are companies which do not consider encapsulation as nanotechnology because the particles used are often larger than 100 nm. If the wall of such a particle were to be modified at the nanoscale however, then it can be seen as nanotechnology;
- Packaging and logistics: This theme has two approaches. One is to provide better packaging for food ingredients, e.g., as protection against oxidation, bacteria or light. The second is the inclusion of sensors or RFID (Radio Frequency Identification) tags in packaging (see also above). Sensors could show the status of food in the packaging and where possible correct it. RFIDs could contain information about the ingredients, origin or current status of food, such as the vitamin content or the hardness of fruit.

5.1.3 Developments in the Netherlands

The Netherlands is one of the world leaders in the development of technological applications in the food production chain. Apart from the scientific aspects there is also a lot of focus on public perception (see also Annex 5), acceptance by consumers, and sound risk assessment. This is also one of the reasons why, based on the available expertise in this field and the scientific potential present in the Netherlands, 'Food and Health' is one of the five main themes for the research agenda referred to in the government paper setting out the government's vision on nanotechnology (Netherlands' government, 2006).

The Dutch government is therefore funding several initiatives to build on this position. For example, at the recommendation of the Innovation Platform, various projects are being funded, such as 'Nano in food & health' (until 2007) and 'Nano4Vitality'(http://www.nano4vitality.nl/) (as the follow up). This is a joint public-private programme involving a number of provincial authorities, universities and companies in the East Netherlands. This programme is focused on nanotechnology research and development in relation to food and health.
It is envisaged that a centre (CAT Agrofood) will be set up at Wageningen University and Research centre (WUR) to bring together all the facilities in the area of advanced technology. This will also include nanotechnology. This centre can be seen as a place where nanotechnology related to food and food products can develop and where universities and industry can interact to achieve the most benefit. Similar to the idea behind NanoNed, the idea behind CAT Agrofood is to bring facilities (e.g., clean rooms, measuring equipment, et cetera) together. In this way a specialist facility will be created which can more efficiently contribute to scientific, technological and economic development.

5.2 Potential risks

With regard to food production there are also many questions concerning the potential risks: methodological, on the one hand, and specifically product-related on the other. In general terms, it may be said that here too, the priority for risk research must be placed on insoluble particles. These could be found in food products as a result of direct addition to foodstuffs or because they end up in food products from packaging materials or during cultivation or processing (Bouwmeester et al., 2007).

5.2.1 Present understanding of risks

- The possible migration of particles out of the packaging into food products is an important area of concern (Bouwmeester et al., 2007). Migration tests as currently described in guidelines should be tested for validity for nano applications;
- Extra attention should be given to the use of nano crop protection products which lead to better adhesion to the plant because this could lead to increased residues in fruit and vegetables. No particular risks may be expected in relation to applications such as meat replacement products, or other consumable or non-persistent substances in food applications;
- The increased bioavailability of nutrients involves a potential risk of overdosing;
- Packaging with nanoparticles could end up in the environment. There is, however, only very limited consideration of what happens to these particles further to landfilling and incineration. Insoluble and non-degradable particles have the greatest risk potential in this respect.

In accordance with a recent recommendation by the Food and Consumer Product Safety Authority (VWA) it cannot be assumed that foods or food ingredients with manufactured nanoparticles are just as safe as foods or food ingredients not in a nano form. This can only be established by a safety

assessment which specifically addresses nano forms. For degradable, soluble nanoparticles which naturally occur in foods (emulsions, micelles and liposomes) there is, however, sufficient scientific background to be able to assert that the usual risk assessment guarantees safety (VWA, 2008).

5.2.2 Current / planned risk research

5.2.2.1 National

Growing attention is being given in the Netherlands to the safety of nanotechnology in food. On the one hand, various research projects are in progress to develop valid methods for testing safety. This is being done by government institutes, universities and by the industry. These projects generally focus on human endpoints. Besides this, more specific studies are being carried out on particles which are used in the food production process, to obtain information on the behaviour of these particles under valid test conditions.
In 2007 the Food and Consumer Product Safety Authority (VWA) set up a board of experts with stakeholders representing various government and semi-government organisations. This board aims to coordinate research efforts as far as possible and discuss developments in the field.

5.2.2.2 International

The European Food Safety Authority (http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_home.htm) has been asked by the European Commission to draw up an opinion on the safety of the use of nanotechnology in food and food production chains. On the basis of previous risk evaluations by other Scientific Committees of the EU of the Directorate-General for Health and Consumer Protection, a specific opinion has now been requested for both human food and animal feed. Besides the possible human and animal risks, this body has also been asked to assess the potential risks to the environment due to the use of nanotechnology in the food sector.
Two types of risks must be assessed for humans:

- Risks of direct exposure to 'nano' food products, and
- Risks of possible indirect exposure through foodstuffs of animal origin where food with 'nano' has been fed to the animals.

Aspects of food technology and the packaging of food also need to be considered in the opinion. In the United States an analysis was recently carried out of the most important developments in the packaging industry and the regulatory consequences (Taylor, 2008). It was concluded that for nanomaterials in this application area too, there are still a significant number of unanswered scientific and regulatory questions.

5.2.3 Remaining knowledge gaps

In the RIKILT / RIVM report *'Health Impact of nanotechnologies in food production'* (Bouwmeester et al., 2007) an overview is given and recommendations are made regarding the prioritisation of scientific research. The research topics are mostly methodological in nature and therefore not always specific to the application area of food production. The choice of particles which should be tested however, will be specific to this field of application. The following topics are considered important:

- Characterisation of nanoparticles: nanoparticles have new properties compared with chemical substances not in nano form. To be able to make a proper estimate of consumer exposure these properties must be characterised. Analytical *tools* need to be developed for this purpose to isolate and characterise nanoparticles in food and biological matrices;
- Characterisation of the form in which particles are present in the products. This information is essential because it must be determined what people and the environment will ultimately be

exposed to. Nanoparticles which are added at the start of a production process could change in form during processing and use;
- The measurement of nanoparticles in food matrices;
- Investigation of the validity of existing migration tests for nanoparticles.

5.3 Coping with risks

5.3.1 The regulatory framework

The general principle in the EU for the time being is that the present regulatory framework will be maintained and modified if necessary. Various EU directives and regulations apply for the authorisation of substances in food:

- The European General Food Regulation (EC/178/2002);
- Novel food [and novel food ingredients] Regulation (EC/258/97);
- Food additives, enzymes and flavorings (89/107/EC; 94/36/EC; 94/35/EC; 95/2/EC and their amendments);
- Food enrichments regulation (EC/1925/2006);
- Food supplements directive (2002/46/EC);
- Food contact materials (EC/1935/2004);
- Regulations and directives on pesticides and veterinary drugs (Bouwmeester et al., 2007).

This legislation however was not developed with a view to nanomaterials. Therefore there are still clear gaps in the implementation of this legislation for these nano substances. These gaps can only be filled, however, by investigating what additional information is critical for the risk assessment of nanoparticles.

It is not clear whether the European Novel Food directive applies to nanomaterials. The Food and Consumer Product Safety Authority (VWA) however advises that foodstuffs or ingredients which include manufactured nanoparticles should be considered ‘new’ so that they become subject to the Novel food [and food ingredients] Regulation (EC/258/97) (VWA, 2008).

5.3.2 Risk assessment

Too little is yet known about exposure and the toxicity of nanoparticles for a risk assessment of nanotechnologies in food products and the food chain. This is consistent with the knowledge gaps which have been identified in relation to nanoparticles in general (Bouwmeester et al., 2007).
Some of the available products in this application area are subject to pre-marketing risk assessment. A great many developments are currently taking place in the area of additives and aromas. The Food and Consumer Product Safety Authority (VWA) recommends that the safety of additives and aromas containing nanoparticles should also be assessed, even for nano formulations of products previously admitted (Prisma & Partners and MinacNed, 2006).

5.3.3 Risk management

Once a nano food product is on the market the risk management options become limited. Civil organisations are seeking ways of limiting consumer exposure through labelling and moratoria (see section below).

5.3.4 Societal aspects

The uncertainties surrounding the risks of nanotechnology in the food industry would appear to lead to more extreme standpoints being adopted than in other fields of application. This is mainly due to consumer organisations and pressure groups. Differences in risk perception would appear to be a plausible explanation for this. In Great Britain, for example, the Soil Association, the biggest labelling organisation in the area of organic products, has decided that it will no longer certify any food products where nanotechnology has been used. *Friends of the Earth* recently went a step further by calling for a moratorium on the use of nanotechnology in food, until sufficient is known about the risks to humans and the environment.

At the 'Nano food safety' workshop of the Rathenau Institute and the Food and Consumer Product Safety Authority (VWA) in 2007 it became clear that there is need for dialogue and information exchange on nanotechnology in food. Internationally too, this debate is starting to gain momentum in scientific, policy and commercial circles. As a result various studies are already being carried out internationally on the public perception and acceptance of nanotechnology in food.

5.4 Observations

- Based on previous experience with the introduction of biotechnology, it seems that the food industry operates with great caution;
- Both nationally and internationally the lack of information is leading to more public disquiet;
- The regulatory framework appears to provide a good basis to guarantee the safety of nano foods, but in the area of enforcement there still appears to be some gaps;
- Scientific knowledge is mainly what is needed to fill these gaps;
- More information is needed on the validity of migration tests from packaging materials;
- There are still no sufficiently validated measuring methods available to determine the quantity and form of nanoparticles in foods;
- More research is necessary on exposure, as well as the absorption, distribution, metabolism and excretion (ADME) of nanoparticles for food products containing non-degradable and insoluble particles.

6 Consumer products

Nanotechnology is now already being used in a wide range of consumer products, such as cosmetics, household equipment, electronics, toothpaste, cleaning products and clothing. For various applications human exposure to nanoparticles would not seem to be very likely. With other applications, such as cosmetics, toothpaste and also textiles, dermal or oral exposure to nanoparticles can occur.

6.1 Applications

6.1.1 Current applications

It is not possible to provide a complete overview of all current applications of nanotechnology in consumer products. There are various information sources which can be drawn upon, but these do not give a complete and reliable picture. The following factors play a part in this:

- There are products on the market with a 'nano' claim while they contain no nano materials and were also not made with the aid of nanotechnology;
- Not all manufacturers list their nano products as such, and consumer information or mandatory labelling are not statutorily laid down;
- A large and growing number of products with nanomaterials is available;
- It is difficult to determine in which countries or parts of the world such products are available (Dekkers et al., 2007b).

There are various databases with an overview of nano applications in consumer products. A well-known public database is that of the Woodrow Wilson International Center for Scholars (Project on Emerging Nanotechnologies) (http://www.nanotechproject.org/inventories/consumer/). This database is not complete but claims to be: *'the best available look at the 500+ manufacturer-identified nanotechnology-based consumer products currently on the market*' (US market). Such databases however are compiled on the basis of information from manufacturers and the quality cannot be guaranteed.
Another source of information on present and future applications are reports by consultancy and research bureaus. Such reports however are not publicly accessible and relatively costly to obtain. In a government context the Danish EPA on behalf of the European Parliament and the Dutch Food and Consumer Product Safety Authority (VWA) recently carried out a survey of consumer products which contain nanomaterial.
The Danish report '*Survey of nanotechnological consumer products'* (Danish EPA, 2007) attempts to estimate the potential human exposure to such products. This study identifies 243 products, with the main nano application being a dirt-resistant effect.
In the report '*Nanomaterials in consumer products*' (2007a) written by RIVM and WUR on behalf of the European Parliament, an overview is given of currently available and future applications of nanomaterials in consumer products in the EU (Dekkers et al., 2007a). In 2007 RIVM also carried out a survey on behalf of the Food and Consumer Product Safety Authority (VWA) of nano consumer products which may be on the Dutch market. In the EU a total of 143 products have been identified which actually or probably contain nanomaterials, approximately 120 of which are available on the Dutch market (Dekkers et al., 2007b).

In the above reports a dinstiction is made into the following product categories (Dekkers et al., 2007a):

- Electronics and computers;
- Household and do-it-yourself (DIY) products;
- Personal grooming and cosmetics;
- Motor vehicles;
- Sports articles;
- Textiles and shoes;
- Filtering, treatment, neutralisation, et cetera;
- Other.

The most important product categories (in terms of worldwide market share) are motor vehicles and electronics/computers, followed by personal grooming products/cosmetics and household and DIY products (see Table 6.1) (Dekkers et al., 2007a):

Table 6.1: Global value of nano applications by type of consumer product (excluding food and drink products).

Product segment/year	2004		2005		2010	
	$ Million	%	$ Million	%	$ Million	%
Private cars	4284	73.0	4381	72.5	5026	52.7
Electrical and electronic goods	495	8.4	490	8.1	2859	30.0
Household chemicals	635	10.8	683	11.3	982	10.3
Other*	452	7.7	490	8.1	678	7.1
Total for all products	5866	100.0	6044	100.0	9545	100.0

*Including photographic equipment and film, textiles and clothing, personal grooming products, sports equipment and optical consumer products. (Adapted from: BCC, 2005 cited in Electronics.ca Research Network (2005)).

Table 6.2 provides an overview of the various applications and some examples of products (Dekkers et al., 2007a).

Table 6.2: Product categories with examples of products*

Category	Subcategory	Examples of products
Electronics and computers	Mobile (audio) equipment	*MP3 players, mobile phones*
	Large household equipment (white goods)	*Fridges, washing machines, irons, vacuum cleaners*
	Computer hardware	*Processors and chips (e.g., game computers), memory and hard disks,* fans*, mouse*
	Screens	*LEDs in pocket torches, OLEDS in screens*
	Energy related	Solar cells, batteries
	Ink and paper	*Ink for electronic equipment, photographic paper*
Household and DIY products	Cleaning products	Dishwasher, washing-up and hand washing soaps, rubber gloves, *disinfectant soap or liquids, fabric softener, cleaning products for lenses, screens and glasses,* odour-eaters

Category	Subcategory	Examples of products
	Cooking utensils and kitchen equipment	*Chopping boards, tableware, cooking utensils and kitchenware,* teapots, porcelain, baby mugs, baby milk bottles, bottle brushes, dishes (also for pets), food storage containers (antibacterial), food storage bags, *plastic and aluminium foil*
	Construction materials	Locks, door knobs, handles, water taps (antibacterial), *glass (self-cleaning)* wooden floors, *cement and concrete products,* toilets, tiles
	Paint	*Paint (kitchen, bathroom, insulation and radio frequency blocking)*
Personal grooming products and cosmetics	Sunscreen/tanning products	*Sunscreen (sun block or tanning) lotion, cream, oil*, sunscreen powder, hair protection spray.
	Baby care products	Baby sunscreen cream, pacifiers
	Hair products	Shampoo, conditioner, gel and styling products, hair regrowth products
	Skincare	*Razors, facial masks, facial steamers, skin creams/lotions/oils/sprays/powders,* deodorant, skin whitening lotions, *fragrances,* wet wipes, soap, body gel, shower gel, et cetera
	Oral hygiene	*Toothpaste,* teeth cleaner, toothbrush
	Make-up and nail care	Make-up instruments and brushes, make-up remover and cleansing products, lipstick, mascara, foundation, blusher
	Freely available healthcare products	*(Sticking)plasters, home pregnancy tests,* thermal patches, joint and muscle pain cream, *condoms,* insect repellent products
Motor vehicles	Exterior	*Glass and windshields, painted or coated exteriors,* tyres
	Other	Engine oils, fuels and *catalytic converters*
Sports articles	Rackets and sticks	*Rackets*, bats, golf clubs, *hockey sticks, skis,* snowboards, *bicycle frames and other bicycle components*
	Balls	Bowling balls, tennis balls, *golf balls*
	Other	Wetsuit, fishing lure, horse shoes
Textiles and shoes	Clothing	*Socks, pants*, *shirts,* pullovers, cardigans, shorts (including swimming trunks), *jackets,* elbow and knee protectors, underwear, gloves, cap, headband, ear warmers, scarves, ties, *underwear*
	Other textiles	Sheets, *bed and mattress,* pillows and cushions, umbrellas, bags and suitcases, soft toys, other materials
	Shoes	Insoles, shoes
Filtration, treatment, neutralisation and cleaning	Air or water filtration and treatment	Air filtering and treatment equipment, masks and gas/dust masks, water filtering or treatment equipment
	Air conditioning	*Air conditioning and heating systems*
	Cleaners and neutralizers	Air cleaners and treatment equipment, chemical (gas/liquid) neutralizers
Other	Coatings	*Anti-fogging coatings, self-cleaning coatings, water and dirt-resistant coatings, antibacterial coatings, wax, lubricants, protective layers for screens (scratch-resistant)*
	Other	Diamonds, (antibacterial) watch-straps, sunglasses

[*] Products shown in italics are known to be, or are expected to become, available on the European market.

In many of these applications metals in nano form are extensively used, such as nanosilver (antimicrobial effect), nano titanium dioxide and nano zinc oxide. These are forms which may be

considered non-degradable and insoluble. The SCCP has determined which type of particles are expected be found in cosmetics. Manufacturers claim, for example, that fullerenes and nanovitamins could be present in cosmetics (SCCP, 2007).

6.1.2 Future applications

In all these product categories the concept of less dirt adhesion through more hardened materials, is applied. In this field of application we also see 'converging technologies'. The developments in textile applications would appear to be the most innovative. In these applications not only have odour and dirt repellent textiles been developed but also textiles incorporating graphics that can change colour. Although they do not fall within the scope of consumer products, innovative developments in the area of military attire are also worth mentioning: bullet-proof vests which absorb the impact of a bullet better thereby helping to prevent injuries. *Converging technologies* are mainly seen in healthcare where textiles are being developed which incorporate minute forms of electronic equipment for monitoring. In addition to this, '*smart and interactive*' textiles are also being developed. All in all, in contrast with food applications, what we see here is more product innovation than process innovation.

6.2 Potential risks

6.2.1 Present understanding of risks

The potential risks of nanoparticles in consumer products depend on the toxicity of these particles and the potential exposure to them. There is little information available about the toxicity of nanoparticles once they have been included in the products. Furthermore it is difficult to determine the actual exposure as shown by various surveys. In overviews by various organisations it has been attempted to gain some sort of structured overview of the potential exposure and toxicity. But the issue does not lend itself to general statements about the risks of nanoparticles in consumer products.
Most studies still focus on the risks to the consumer, although more recently a few cautious steps have been taken in the direction of analysing the risks to the environment.

6.2.1.1 Exposure

Exposure to nanoparticles from consumer products can take place via various exposure routes and during various phases of the product life cycle (see Chapter 3 for an overview). For products like sprays, such as window cleaners and cleaning products for sanitary fittings, inhalation is probably the main route of exposure for consumers. For products applied to the skin, such as cosmetics, dermal exposure will be the main route for consumers. The oral route will generally be less prevalent, with the exception of products such as toothpaste and lipstick. As soon as nanoparticles from consumer products end up in the environment any exposure will mainly take place via air, drinking water or food products. This indirect exposure through the environment may be expected to be much lower, but it will be more continuous than the direct exposure via products.

Table 6.3 provides an overview of the characteristics of human and/or environmental exposure to nanomaterials from consumer products.

Table 6.3: Main characteristics of human and environmental exposure to nanomaterials from consumer products.

Characteristic	Remarks
Type of nanomaterial	Free nanoparticles or nanostructures integrated into larger structures
Exposure route	Inhalatory, dermal or oral exposure
Physical form of consumer product	Spray, powder, liquid, emulsion or solid substance
Application of the consumer product	Applications with direct human exposure (e.g., sunscreen products) or indirect human exposure (e.g., food storage bags, computers) Applications with direct emission to an environmental compartment (e.g., toothpaste) or with indirect emission to the environment (e.g., computers)
Type, use of the consumer product	Widely used or rarely use product
	Frequency and amount of product used
Concentration of nanomaterial in the product	
The main characteristics influencing the fate and behaviour of nanomaterials in living systems and the environment	Size Surface area Surface chemistry Water and fat solubility (K_{ow}*) Organic carbon-normalised solids-water partition coefficient (K_{oc}) Vapour pressure (mainly important for liquids) Coagulation or aggregation state Chemical composition (including coatings and purity)

* K_{ow}, octanol-water partition coefficient

6.2.1.2 Toxicity and potential risks

There is still insufficient known about toxicity measuring and test methods for humans and the environment to be able to assess the ultimate validity of toxicological and ecotoxicological studies. This makes it difficult to examine statements about the potential risks of nanomaterials in consumer products. On the basis of the main properties of products it is possible to make an estimate of what product categories could ultimately lead to a potentially high or low level of exposure. In this way an initial outline of the potential risks of nanoparticles in consumer products can also be made.

Potentially high levels of exposure may be expected from consumer products which include free nanoparticles, leading to direct human exposure. Examples of such products include cleaning products, personal grooming products and cosmetics. A low level of exposure may be expected from nanomaterials in an ‘embedded’ form, such as in electronics and computers, cooking utensils, sports articles and coatings. The question remains however, whether nanoparticles can actually enter the body (be bioavailable) if they are on the skin, or enter the lungs or gastro-intestinal tract (see Chapter 3).

6.2.2 Current / planned risk research

Various studies are being conducted nationally and internationally on exposure and toxicity of particles used in consumer products. Manufacturers are also looking at additional tests to obtain relevant information, particularly on toxicity. As in the domain of food, here too, not a lot of attention has thus far been devoted to the potential migration of free nanoparticles out of the products into humans or the environment.
In the EU, the Scientific Committee on Consumer Protection (SCCP) is currently assessing a number of existing products in terms of their risks to humans and the environment. Based on the opinions of this Committee it appears that there are still uncertainties about the toxicity of the particles used and the method by which the toxicity can best be determined.

Recently, in its recommendation to the Ministers of Health, Welfare and Sport (VWS) and Agriculture, Nature and Food Quality (LNV) on nanoparticles in consumer products, the Food and Consumer Product Safety Authority (VWA) stated (2008) that research is taking place 'but that the research required is very extensive, and at the moment there appears to be no official body to oversee whether all of this research is done. There is some exchange of information but no strong coordination'. Investment in research is required, in which priority should be placed on non-degradable, insoluble nanoparticles which already seem to be often used. Coordinated research efforts must be aimed for 'in the Netherlands at least, but preferably at a European or global level'. Investment is also needed in measuring methods and measuring equipment, by which nanoparticles in consumer products can be demonstrated and characterised (VWA, 2008).

6.2.3 Remaining knowledge gaps

In general, the following gaps can be identified which are relevant for human and environmental risk assessment:

- What products are on the market and what are the characteristics of the particles in these products?
- Migration/emission of nanoparticles from products; are the tests valid and to what degree does testing take place?
- Toxicity/ecotoxicity of particles in these products.

6.3 Coping with risks

6.3.1 The regulatory framework

Various directives and regulations apply to consumer products:

- 'Existing Substances Regulation'; Regulation (EEC) No 793;
- 'Dangerous Substances Directive'; Directive 67/548/EEC ;
- 'Marketing and Use Directive'; Directive 76/769/EEC;
- 'REACH'; Regulation (EC) No 1907/2006;
- 'Biocides Directive'; Directive 98/8/EC;
- 'Toys Directive'; Directive 88/378/EEC;
- 'General Product Safety Directive'; Directive 2001/95/EC;
- 'Cosmetics Directive'; Directive 76/768/EEC;
- 'Electrical and Electronic Equipment Directive' (WEEE); Directive 2002/95/EC;
- 'Preparations Directive'; Directive 1999/45/EC;
- 'Waste Directive'; Directive 2006/12/EC.

The present regulatory framework sets no specific standards for nanomaterials, but appears to cover safety aspects properly. This general legislation should, in principle, enable the authorities to take action if nanoproducts pose risks to health, safety or the environment (Dekkers et al., 2007a).

The question is whether new risks of nanomaterials in consumer products will be recognized under the present legislation. More needs to be known about the extent to which the present legislation actually addresses the potential risks. For this more exposure research needs to be conducted and new research methods and possibly directives will have to be drawn up.

6.3.2 Risk assessment

Under the Cosmetics Directive ingredients in consumer products for certain applications, such as UV filtering, hair colouring and food preservation, should be assessed (by the SCCP). Logically this should also apply to the nano forms but the Directive gives no specific description of how this should be handled. It is also not set out in the SCCP's '*Notes of Guidance for Testing of Cosmetic Ingredients and their Safety Evaluation*'.

In its recommendations the Food and Consumer Product Safety Authority (VWA) states that there are as yet no routine methods for measuring and characterising nanoparticles in 'complex mixtures' such as consumer products. According to the Food and Consumer Product Safety Authority (VWA) *'Essential information is lacking for every step in the scientific risk assessment of products with nanoparticles'* (VWA, 2008).

Companies make their own characterisations of the nanoparticles they produce. It is still unclear whether existing protocols can also be applied to nanoparticles. It is unknown which particles (of what size) lead to what risks. Experience must be built up on a case-by-case basis in this area.

Because of the lack of methodological data on nanoparticles it is also not yet clear what dossier requirements should be made of companies and thus what information the dossiers supplied should contain. Nevertheless, there are already products on the market.

To generate more information for dossiers, similarities with other application areas can be looked for. It is quite possible, for example, that the pharmaceutical industry holds knowledge about substances which are also used in consumer products. Between the application areas however it differs to what extent the research can be extracted.

6.3.3 Risk management

The risk management options for consumer products become limited once they have been brought onto the market. Measures to reduce consumer exposure are relatively drastic in nature (e.g., moratoria, labelling, et cetera). This makes it all the more imperative to determine the toxic properties of nanoparticles which have been incorporated in such products. National and international policy frameworks also appear to be focusing on this.

From the point of view of supervision, the Food and Consumer Product Safety Authority (VWA) recently recommended to the Ministers of Health, Welfare and Sport (VWS) and Agriculture, Nature and Food Quality (LNV) that 'manufacturers be required to provide information about the presence of nanoparticles in consumer products. REACH and the legislation on cosmetics may provide a framework for this.' (VWA, 2008).

6.4 Observations

- There are still insufficient validated measuring methods to be able to determine the form and quantity of free, non-degradable and insoluble nanoparticles in consumer products;
- A multitude and variety of products is already on the market. There is no complete overview or sound basis for safety;
- Toxicity studies are usually based on the characteristics of the nanoparticles as they are added to the products and not on the characteristics of the nanoparticles once they are present *in* the products. It is these characteristics which are actually most relevant for determining the toxicity;
- Research on exposure, ADME and the effects of non-degradable and insoluble particles, and products with such particles, is at present mainly aimed at exposure via the dermal and inhalatory routes. The oral route however, is also important for consumer products and therefore needs more attention;
- The wide range of products in which nanoparticles are already used underlines the need for life cycle analyses (LCAs) to be made.

7 Health and safety in production and use

This chapter will look at the health and safety aspects for workers who could come into contact with nanomaterials in the workplace. This specifically concerns the safety of those who are involved in the production and application of nanomaterials or research work (in labs / research and development departments) related to nanomaterials.

Nanotechnology and nanomaterials are currently still largely in development. They are, in general, not yet applied on a large scale, with the exception of bulk substances such as carbon black, titanium dioxide and fumed silica (silicon dioxide). Compared to the general population the workers involved in research on and the production and application of nanomaterials are potentially at a relatively higher risk (Borm et al., 2006a). Workers will generally be exposed to higher levels of chemicals for longer periods. This probably also applies during the production and application of nanomaterials (SCENIHR, 2006). For these reasons the health and safety of people working with nanomaterials is currently an important area of concern (ISO/TC 229 WG3 PG1).

The main industries working with nanomaterials in the Netherlands and where workers could be exposed to nanomaterials are:

- The chemical and materials manufacturing industries (largest sector);
- Food industry;
- Electrical engineering industry.

However there is no complete picture available of precisely how many and which companies in the Netherlands are working with nanomaterials (Borm et al., 2008). What is clear is that both large multinationals and smaller companies are engaged in research, development and the production of nanotechnology. From the EU NANOSH project it appears that neighbouring countries, such as Germany and Belgium, have production facilities where tonnes of nanoparticles per year are being produced, in almost bulk quantities: carbon nanotubes, nano titanium dioxide and nano zinc oxide. In the Netherlands the large scale production of nanomaterials based on this research seems to be limited to the suspension form (particles in fluid). Besides industry, research centres where research is done on and with nanomaterials are also relevant from the occupational health and safety point of view. The report from Zuyd University (Borm et al., 2008) which is published last october, provides more insight into the number of people in industry and research institutes who regularly work with nanoparticles and the type of nanoparticles that are being used.

7.1 Production processes

There are various ways of optimising the properties of nanoparticles. These are properties such as dimensions, distribution of dimensions, surface properties, symmetry, purity and the ability to manipulate them (HSE, 2004). Nanoparticles are therefore produced in various ways. The methods for manufacturing nanoparticles can be divided into a number of groups (see also Table 7.1):

- Processes in the gas phase, including pyrolysis, evaporation at high temperatures, and synthesis in plasma;
- *'*Vapour deposition synthesis*'*.

The advantage of both these bottom-up processes is that fairly pure particles are produced with a narrow distribution of particle size. One drawback is that the surface properties are more difficult to

manage and therefore in the phase following production, the product has to be modified to disperse the particles.

- Colloidal methods or methods in the liquid phase in which chemical reactions in solution lead to the formation of colloids (bottom-up). The advantage of this method is that it enables optimum control of the surface properties but the drawbacks are the cost and the more limited possibilities for up-scaling;
- Mechanical friction and attrition processes (top-down) (IRSST, 2006). The low cost is the main advantage of this production method. The main drawback is that agglomerates and often aggregates of particles are produced rather than separate particles which can cause problems in the dispersion.

The production method is critical to the quality of the product (number of individual particles, spread of particle size distribution, surface properties) and therefore also to the post-synthesis modifications required to be able to disperse the material produced.

7.2 Potential risks

7.2.1 Possible exposure of workers to nanomaterials

Nanomaterials in the form of individual particles, agglomerates of nanoparticles, or particles of nanostructured materials in the air or on the skin constitute the greatest risk to workers (NIOSH, 2006).

There are three main exposure routes for workers:

- Inhalation (this is perceived to be the main route for workers). Research among workers has revealed that exposure to aerosols of fine and ultrafine manufactured particles has an adverse effect on lung function and the airways. The role of ultrafine particles in relation to other contaminating substances in these work environments, however, is uncertain in this (NIOSH, 2006);
- Oral exposure. This route receives less attention in the context of occupational health and safety. Some of the inhaled particles however could ultimately be orally ingested. These are particles which end up in the upper respiratory tract and further to transport in the mucus layer are ultimately swallowed. It is unknown whether this is a relevant route for nanoparticles;
- Dermal exposure. Little is also currently known about this. Given that this route is relevant in the work situation, more research in this area is needed.

Workers may be exposed to nanomaterials during the production or synthesis of materials. Table 7.1 shows the possible exposure by production method (see also Section 7.1).

Table 7.1: Potential sources of occupational exposure for various synthesis methods (HSE, 2004).

Synthesis process	Formulation of particles	Exposure source or work activity	Primary exposure route
Gas phase	In air	Direct leakage from reactor, especially if the reactor is operated at positive pressure	Inhalation
		Product recovery from bag filters in reactors	Inhalation/dermal
		Processing and packaging of dry powder	Inhalation/dermal
		Equipment cleaning/maintenance (including reactor evacuation and spent filters)	Dermal (and inhalation during reactor evacuation)
Vapour deposition	On substrate	Product recovery from reactor/dry contamination of workplace	Inhalation
		Processing and packaging of dry powder	Inhalation/dermal
		Equipment cleaning/maintenance (including reactor evacuation)	Dermal (and inhalation during reactor evacuation)
Colloidal/attrition	Liquid suspension	If liquid suspension is processed into a powder, potential exposure during spray drying to create a powder, and the processing and packaging of the dry powder	Inhalation/dermal
		Equipment cleaning/maintenance	Dermal

Note: Ingestion would be a secondary route of exposure from all sources/activities from deposition of nanomaterials on food or mucous that is subsequently swallowed (primary exposure route inhalation) and from hand-to-mouth contact (primary exposure route dermal). Ocular exposure would be an additional route of exposure from some sources/activities from deposition of airborne powders or mists in the eyes or from splashing of liquids.

As the above table shows, there are various possible sources and routes of exposure with each production process. Work activities for the purpose of packing, transferring or cleaning offer possibly the greatest source of exposure. The production itself may be expected to result in relatively less exposure because this often takes place in closed systems.

In gas phase processes there is the possibility of inhalation exposure when leakage occurs, certainly when this involves a process under pressure. The type of aerosol that could be released will depend on the phase in the production process in which the leak occurs (HSE, 2004).

Inhalation exposure can also take place during the recovery of the product. For example, particles produced in certain processes are captured in a filter. Poorly functioning filters could lead to the release of particles in the work environment, for example. The potential exposure will depend on the properties of the process and of the product (HSE, 2004). About this the NIOSH (National Institute for Occupational Safety and Health) has the following to say:

'In general, it is likely that processes generating nanomaterials in the gas phase (after removal of the nanomaterial from an enclosed generation system), or using or producing nanomaterials as powders or slurries/suspensions/solutions (i.e., in liquid media), pose the greatest risk for releasing nanoparticles.'

The maintenance of production systems (including cleaning and the removal of materials from the extractor) could possibly also lead to exposure (NIOSH, 2006).
Furthermore, occupational exposure can occur during the transport, formulation, end use and waste processing or recycling of products. The diagram in Figure 7.1 shows in which parts of the production/use chain for manufactured nanoparticles moments of exposure can occur.

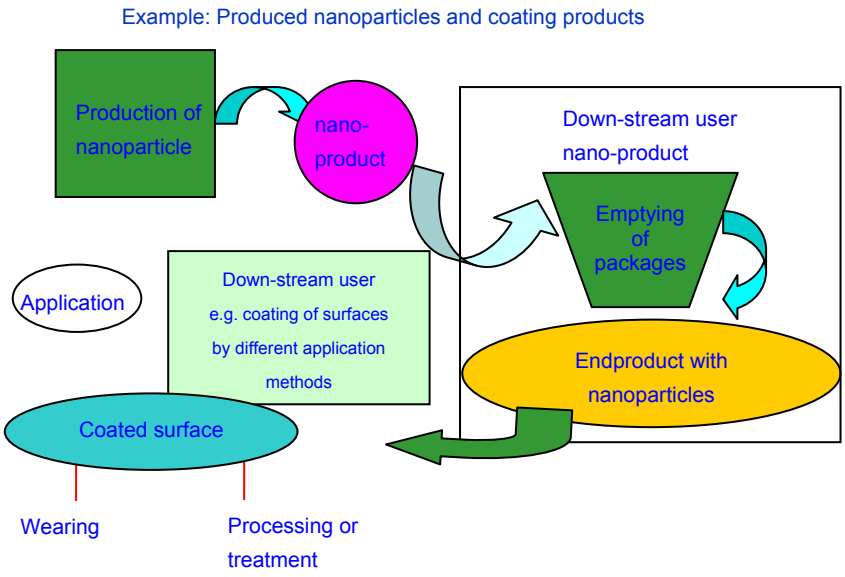

Figure 7.1: Diagram of the production and use chain for a coating containing nanoparticles.

The nanoparticles are produced in the first part, the nanoproduct is incorporated in the coating in the second part, and finally the coating is applied once more. In all parts there may be potential exposure to nanoparticles, although the form, nature and degree of exposure will differ per link in the chain.

The following work activities involve a possibility of exposure to nanoparticles:

- The transfer of nanoparticles (e.g., powders) from the packaging to a mixing vessel or reactor (inhalatory exposure);
- Filling (liquid) product which contains nanoparticles (dermal);
- The processing/use of a product that contains nanoparticles (depending on method of use, dermal and/or inhalatory);
- Mechanical treatment of surfaces (e.g., sanding) to which a product containing nanoparticles has been applied (inhalatory);

- Maintenance and cleaning of equipment and processes in which nanomaterials are manufactured or the cleaning of extraction systems and waste material or 'spilled' material (dermal and/or inhalatory).

7.2.2 Possible toxicological effects of nanomaterials

See Section 3.4 for a description of the toxic effects of nanomaterials.

7.2.3 Other risks

It is conceivable that when working with nanoparticles other risks than just the toxicological risks play a role. There are theoretical indications that certain nanomaterials carry a relatively high ignition or combustion risk:

> *'Decreasing the particle size of combustible materials can increase combustion potential and combustion rate, leading to the possibility of relatively inert materials becoming highly reactive in the nanometer size range'* (NIOSH, 2006).

Research material from the NANOSAFE2 project has recently been released in which the combustion and ignition risks of nano powders (powder of nanoparticles, e.g., carbon nanotubes, carbon black and aluminium) was compared with micro powders (powder made up of microparticles, separate entities which have three dimensions in the order of micrometres) (NANOSAFE, 2008). With regard to the risk of explosion, the explosion sensitivity (expressed as Minimum Ignition Energy (MIE)) and seriousness (Explosion Severity) lies in the same order of magnitude as that of coal dust and flour. The ignition temperature depends on the specific surface of the particles. Aluminium nanoparticles behave differently than aluminium microparticles and oxidize even at low temperatures. For some metals the risk of explosion can increase significantly with declining particle size (NIOSH, 2006).

Companies wanting to set up production facilities have questions about the external safety (i.e., managing the risks which people run due to the storage, production, use and transport of hazardous substances in their environment), the siting of such facilities and the measures to be taken to manage the external safety risks. At present there is very little information available on possible explosion risks. The safety of transport is also a relevant topic in this context.

Besides the possible risks of combustion or explosion some nanomaterials could potentially also set off (unexpected) catalytic reactions. Particles on a nanoscale and nanostructured porous materials have for some time been used as catalysts for speeding up reactions or lowering the temperature required for reactions to take place.

7.2.4 Risk research

The Ministry of Social Affairs and Employment (SZW) has commissioned a study to obtain an overview of the potential risks in the workplace. Zuyd University (Professor P. Borm) conducted this study in association with the ArboUnie (Health and Safety Association) (Borm et al., 2008). In this study an inventory was made of the present management measures in the workplace and 'good practices' collected. The study has been completed in October 2008, followed by a symposium with workshops, organised for those taking part in the study (see for more information: www.nano4all.nl). In the context of the 6th Framework Programme (NANOSH) (www.ttl.fl/internet/partner/ NANOSH) and the 7th Framework Programme (NANODEVICE) TNO is doing research on inhalatory and dermal

exposure through measurements at workplaces. This is taking place in the Netherlands and in other countries.
Under the 6th Framework Programme the Research and Consultancy on Sustainability organisation (IVAM) of the University of Amsterdam is also involved in providing information to stakeholders on health and safety aspects (NANOCAP) (www.nanocap.eu).

There is an overview of studies sponsored by the EU and national governments concerned with the impact of nanotechnology on health and the environment (Aguar and Nicolas, 2008). This covers three projects in the 5th Framework Programme and 11 in the 6th programme Activities are focused on generating data but also harmonisation and standardisation by organisations such as ISO, CEN, ASTM, BSI and OECD, in relation to carrying out measurements as well as directives for the safe production and use of nanoparticles. A overview of these is included in a TNO report (TNO, 2008).

Other relevant research is taking place in the United States and the United Kingdom (see also NIOSH (2007), *Progress toward safe nanotechnology in the workplace* and DEFRA (2007), *Characterising the potential risks posed by engineered Nanoparticles*).

7.2.5 Remaining knowledge gaps

- Size of the potential population exposed:
  - The survey conducted by Zuyd University (Borm et al., 2008) provides some insight but a total overview of how many and which companies are working with nanomaterials is difficult to make due to the dynamic nature of the developments;
- Exposure moments:
  - Potential exposure moments, particularly for workers, are still difficult to ascertain because:
    - flows of nanomaterials between products, downstream users (defined under REACH as any natural or legal person established in the Community who is not a manufacturer or importer, who uses a substance as such or in a preparation in industrial or professional activities) and consumers for the various application areas has not yet been systematically identified;
    - it is not yet always clear whether certain products or semi-manufactures contain or could contain nanoparticles;
- Nature and extent of exposure:
  - Lack of insight into potential exposure moments;
  - Lack of quantitative data for almost all exposure scenarios;
  - It is unknown to what extent nanoparticles, rather than agglomerates, for example, are involved in exposure scenarios;
  - The 'fate' of single nanoparticles in the air is very limited (Dissemination Workshop NANOTRANSPORT, Brussels 16 April, 2008. http://research.dnv.com/nanotransport/). It should be noted that this concerns particles which have already been manufactured. New types and modifications could possibly exhibit different agglomeration behaviour;
  - Any dermal exposure to powders and suspensions containing nanoparticles has not yet been systematically determined;
- Extrapolation to exposure:
  - The extrapolation of measured data to relevant exposure in terms of health risks is essentially not yet possible. This will be considered in more depth in the next section.

7.3 Evaluation and management of occupational toxicological risks

7.3.1 The regulatory framework

Nanoparticles are not specifically mentioned in occupational health and safety legislation. The health and safety legislation functions as 'umbrella' legislation under which employers must ensure the safety of their workforce in the widest sense. The employer must prevent or limit hazards as far as possible at the source or, if necessary, introduce protective measures. If it becomes known that nanomaterials are carcinogenic or mutagenic, the additional requirements in the Health and Safety Act will apply. Employers and employees can further make agreements about the way in which nanomaterials will be handled in the workplace. This could, for example, be laid down in a health and safety catalogue.

Like other chemical substances, substances in nano form are covered by the European chemicals legislation REACH. This legislation appears to offer a sufficient framework to be able to address the risks posed by nanomaterials to workers. General information on the regulatory framework and in particular on REACH, the European legislation on chemicals, can be found in Annex 4 (The regulatory framework).

7.3.2 Risk assessment

Quantitative and qualitative assessment methods can be used to asses the risks of potentially adverse health and safety effects of hazardous substances in the workplace. Quantitative risk assessment for nanoparticles is not possible at the moment because due to the lack of adequate data on dose-effect relationships, and thus no exposure levels can be derived or estimated at which an effect can occur. Qualitative or relative methods, however, can be used, such as comparative or 'hazard ranking' methods (i.e., methods in which substances are ranked in order of their intrinsic hazard) or exposure benchmarking (benchmarking is the assessment of substances on the basis of a reference point). Laboratory experiments are currently being designed which will generate data to be able to estimate risks and uncertainties (NIOSH, 2007).
In the sections which follow we will further consider those aspects which are important in determining potential exposure and how this is now done.

7.3.2.1 Measuring in the workplace

The inhalatory exposure of workers to nanoparticles is still difficult to measure but more and more measuring equipment is becoming available to be able to quantify certain parameters. A lot of this equipment however can only be deployed at fixed points (stationary), which makes it difficult to determine exposure for the ambulant worker. The measuring equipment can select by particle size for online detection but cannot make a distinction between different sorts of nanoparticles. These could be from nanomaterials or background contamination due to traffic, for example, as well as other sources such as cigarette smoke, internal transport or welding. This means that the measurements must form part of an adequate measuring strategy which includes source identification, ventilation patterns, background measurements and sampling for offline characterisation of particles. Recommendations and approaches for such a measuring strategy are described in the literature (Brouwer et al., 2004; NIOSH, 2006, ISO/TR 27628, 2007) and are being constantly refined in ongoing projects.

Until more information is available about the toxicology of nanoparticles it remains uncertain which exposure parameters (exposure metrics) are relevant to be able to make a risk estimate for workers. Current research, as described above in this report, shows that in the case of nanoparticles mass may well be less important than parameters such as particle size, number of particles, form, surface and surface activity.

When nanoparticles are measured in the workplace the parameters currently looked at are:

- (Particle size selective) mass concentration;
- (Particle size selective) number concentration;
- Specific particle surface concentration.

The identification of other possibly relevant parameters when carrying out measurement is still the subject of discussion (see also Section 3.2.1). Borm et al. (2006a) recommend that international agreement be reached about the relevant particle parameters for the exposure of workers.
Besides the matters discussed above concerning 'exposure metrics', there are also additional questions surrounding the relevant measure of exposure. What is the most relevant measure for health risk? Is it the average 'exposure' over a day, the cumulative exposure, the peak exposure or the increase in the exposure parameter when undertaking an activity relative to the background concentration ('increment of exposure')?

7.3.2.2 Measuring methods

Equipment to quantify parameters for inhalatory exposure is thus available. A distinction can be made between (near) 'real-time' measuring of certain exposure parameters ('on-line detection') and sampling of the workplace air or breathing zone for further analysis of the sample ('off-line analysis'). The first group of equipment is usually large and not battery powered, so that measurements can only be made at a fixed location (stationary measurements). Smaller and more portable equipment is in development. Sampling, often with the aid of a pump-filter combination, can be carried out either at one place ('area sampling') or at the individual ('personal sampling'). There is also equipment which can be used to collect nano aerosols directly on a TEM grid so that sample preparation is no longer necessary for this form of electron microscopy. Recently specially adapted filters have been developed which can be used for direct sampling on TEM grids as a personal (breathing zone) measuring method.

To obtain an accurate picture of the exposure of workers NIOSH recommends personal measurements. According to NIOSH, area sampling and stationary real-time methods are more suitable for assessing whether engineering controls and work processes should be improved (NIOSH, 2006). An overview of the currently available equipment to be able to determine direct or indirect exposure parameters is given in Table 7.2.

In the area of dermal exposure no specific quantitative methods have yet been developed. In principle, it should also be possible to use the removal methods and the interception methods to sample the accumulated loading of the skin with nanoparticles (ISO/TC 229 WG3 PG1).
A qualitative assessment method has been made suitable and applied for the assessment of dermal exposure to nanoparticles. This is called the DREAM method and is intended to establish the likelihood of skin exposure and the potential routes. Examples include through deposition or contact with contaminated surfaces (Brouwer et al., 2007).

Table 7.2: Instruments and techniques for measuring nano-aerosol exposure (ISO/TR, 2007).

Metric	Devices	Remarks
Mass directly	Size selective static sampler	The only devices offering a cut point around 100 nm are cascade impactors (Berner-type low pressure impactors, or Microorifice impactors). Allows gravimetric and chemical analysis of samples on stages below 100 nm.
	TEOM® Tapered Element Oscillating Microbalance	Sensitive real-time monitors such as the Tapered Element Oscillating Microbalance (TEOM) may be useable to measure nano-aerosol mass concentration on-line, with a suitable size selective inlet.
Mass by calculation	ELPI Electrical Low Pressure Impactor	Real-time size-selective (aerodynamic diameter) detection of active surface concentration giving aerosol size distribution. Mass concentration of aerosols can be calculated, only if particle charge and density are assumed or known. Size-selected samples may be further analysed off-line (as above).
	SMPS Scanning Mobility Particle Sizer	Real-time size-selective (mobility diameter) detection of number concentration, giving aerosol size distribution. Mass concentration of aerosols can be calculated, only if the particle shape and density are known or assumed.
Number directly	CPC Condensation Particle Counter	CPCs provide real-time number concentration measurements between their particle diameter detection limits. Without a nanoparticle pre-separator, they are not specific to the nanometre size range. P-Trak has diffusion screen to limit top size to 1 µm.
	SMPS	Real-time size-selective (mobility diameter) detection of number concentration, giving number-based size distribution.
	Electron Microscopy	Off-line analysis of electron microscope samples can provide information on size-specific aerosol number concentration.
Number by calculation	ELPI	Real-time size-selective (aerodynamic diameter) detection of active surface-area concentration, giving aerosol size distribution. Data may be interpreted in terms of number concentration. Size-selected samples may be further analyzed off-line.
Surface-area directly	Diffusion Charger	Real-time measurement of aerosol active surface-area. Active surface-area does not scale directly with geometric surface-area above 100 nm. Note that not all commercially available diffusion chargers have a response that scales with particle active surface-area below 100 nm. Diffusion chargers are only specific to nanoparticles if used with an appropriate inlet pre-separator.
	ELPI	Real-time size-selective (aerodynamic diameter) detection of active surface-area concentration. Active surface-area does not scale directly with geometric surface-area above 100 nm.
	Electron microscopy	Off-line analysis of electron microscope samples can provide information on particle surface-area with respect to size. TEM analysis provides direct information on the projected area of collected particles, which may be related to geometric area for some particle shapes.
Surface area by calculation	SMPS	Real-time size-selective (mobility diameter) detection of number concentration. Data may be interpreted in terms of aerosol surface-area under certain circumstances. For instance, the mobility diameter of open agglomerates has been shown to correlate well with projected surface area.
	SMPS and ELPI used in parallel	Differences in measured aerodynamic and mobility can be used to infer particle fractal dimension, which can be further used to estimate surface-area.

7.3.2.3 Measuring strategy

There is as yet no single method by which all the various characteristics of exposure to nano-aerosols (nanoparticles) can be determined. To be able to characterise exposure to nanoparticles in the workplace a 'multifaceted approach' will therefore have to be adopted in which various of the above techniques must be combined. Further to Brouwer et al. (2004), NIOSH recommends the summarised strategy to follow as:

1. Identify the source of the nanoparticle emission with the aid of a CPC. First carry out measurements of background concentrations;
2. Carry out nanoparticle surface measurements and establish the distribution of particle size (static/environment monitoring);
3. Carry out personal sampling with the aid of filters or screens which are suitable for analysis with electron microscopy or chemical identification.

By combining these techniques the exposure of workers to nanoparticles can be determined. With this approach it is possible to determine both the presence and the characteristics of nanoparticles. Because this approach is largely based on statistical or environmental sampling some uncertainty will always remain in the assessment of exposure for individual workers (NIOSH, 2006).
In projects such as NANOSH the measuring strategy is becoming increasingly refined thereby enabling better interpretation of the measurement results in terms of exposure to nanoparticles. Thus continual recording of the particle concentration at a 'background site', mapping the air flow patterns and the collection of particles before and during activities with nanoparticles, together with a record of activities, constitute important aspects of the measuring strategy.

7.3.3 Risk management

Because neither the hazard aspect (toxicity) nor the exposure aspect have yet been sufficiently determined and thus risk assessment is essentially not possible, from a precautionary point of view the risk can be minimized by avoiding exposure as far as possible or keeping it as low as possible. National and international standardisation organisations such as ISO, ASTM and BSI have published documents which provide guidelines for the safe manufacture and use of nanomaterials. Other bodies are also engaged in the development of policy, codes of practice, recommendations relating to aspects of 'responsible care' or the safe manufacture and use of nanomaterials (EC, 2007).

It is important that measures for controlling exposure are incorporated in a framework for risk management. This could be a framework for nanomaterials, like the Nanorisk framework (http://www.nanoriskframework.com), the approach proposed by NIOSH (2006, 2007) or a more general framework for hazardous substances in the workplace, such as COSSH (HSE, 2002).
The principle behind the control measures to be taken is the occupational health strategy or the hierarchy of control measures; measures aimed at tackling the source are to be preferred over technical modifications, et cetera. Personal protective equipment is the type of measure placed at the bottom of the hierarchy.
This hierarchy has been adopted in all the documents with recommendations for safe working with nanoparticles (TNO, 2008). The most detailed information can be found in the documentation of the ISO (ISO/TC 229 WG3 PG1) and the BSI (BSI, 2007), while the *International Council on Nanotechnology* (ICON) provides an overview of the control measures actually applied in production and R&D facilities (ICON, 2006). This last source includes more general measures for preventing the creation and dispersion of particulates. Examples include modifications to the process (e.g., 'wet working'), a fume cupboard, clean room and extraction/ventilation. In recently conducted research for the NANOSAFE2 project, specific process modifications have also been developed for safer production. Examples include the design of a type of reactor for the synthesis of nano powders which prevents emissions, and the development of a 'wet' system for recovering nanoparticles in the laser pyrolysis process (Newsletter 2; www.nanosafe.org).

The effectiveness of the entirety of measures for reducing exposure to nanoparticles is still uncertain, because there is often no data or measured data available. Data on effectivity tests of filters and filter materials, clothing and glove materials has recently been published (NANOSAFE, 2008). From this it appears that filters are also very effective for nanoparticles, even low-efficiency filters for recirculation

systems (Pui et al., 2008). This also applies to non-permeable clothing materials. Cotton materials however show substantial penetration of nanoparticles, as do some glove materials. This means that in the selection of personal protective equipment, for example, the choice of material is critical to its effectiveness.

Besides the often missing data on the performance of control measures, the lack of criteria for a 'safe' level of exposure or threshold values, also play a part in the assessment of effectiveness. This means that only a relative assessment can be made. The formulation of 'good working practices' as a benchmark for general activities with nanomaterials could constitute a first step towards the development of performance criteria for control measures.

Companies and research institutes often do as much as possible to prevent the exposure of workers. The basic measures include 'wet working', the use of nanomaterials in a matrix, protection and the use of extraction and personal protective equipment (breathing equipment and protective clothing). In some cases work is carried out in clean rooms. As indicated above, the current situation with regard to 'good working practices' in the Netherlands is presented in the report by Borm et al. (2008).

7.3.4 Medical surveillance

There are no specific effect parameters for nanoparticles. Therefore a nano-specific medical screening study was not considered appropriate (NIOSH, 2007). What has been recommended however is to link the results of medical screening to exposure records in order to facilitate epidemiological studies in the future (Nasterlack et al., 2008).

7.4 Observations

- The occurrence/presence of nanomaterials and potential exposure scenarios have not yet been fully determined;
- The extrapolation of measured data to obtain personal inhalatory exposure is not yet straightforward and quantitative data on the aggregation of particles is lacking;
- The measurement and interpretation of dermal exposure is not yet possible. Furthermore, the effect of nanoparticle modification (a process in which the surface-active substances are linked to particles to promote dispersion) on exposure and uptake is still unknown;
- The development of a sound measuring strategy is vital to be able to interpret the measured results (often obtained with stationary equipment). It is important here to make a distinction between background concentrations and task-related exposure and between manufactured nanoparticles and other types of nanoparticles. In various EU projects work is being done on a blueprint for a measuring strategy;
- On the basis of present understanding there are notable 'good practices'. However, there is still no clear insight into the effectiveness of control measures for nanomaterials;
- The lack of relevant exposure data and insight into the relationship between exposure and effects means that a quantitative risk assessment is not yet feasible. A relative risk assessment based on a comparison of exposure scenarios with exposure data from 'good practices' could provide a first step. Quantitative exposure data and categorization of the toxicity of nanoparticles based on general particle characteristics would be required for this;
- The present legislation (Health and Safety Act and REACH) for the time being appear to offer an adequate framework to address the risks of nanoparticles. It would be desirable, however, to devote particular attention to nanoparticles in the implementation of the legislation, such as when health and safety catalogues are drawn up.

8 The environment: risks and sustainable applications

Nanoparticles have occurred in the environment for a long time: as a result of natural processes, but also due to human activities (e.g., combustion engines). In addition, nanoparticles are increasingly produced for a specific purpose. Depending on the technique used, nanoparticles can end up in water, air, soil or sediment. This can take place during production, use or in the waste phase. Because of the specific properties of manufactured nanoparticles it is important to gain more insight into nanoparticles, including their fate and behaviour, and persistence, in the environment (Borm et al., 2006b).

8.1 Current and future applications of nanotechnology

8.1.1 Nanotechnology applications: potential emissions to the environment

A wide range of nanotechnology applications is already available, the number of which will only increase in the short term. From these applications various emissions of nanoparticles into the environment may be expected. In general, it may be expected that applications of free nanoparticles will lead to relatively high emissions and that in the waste phase of products relatively high emissions will occur as well. The overview given below per application area indicates what the potential emissions to the environment are. This overview is largely based on the RIVM report 'Nanodeeltjes in water' [Nanoparticles in water] (Struijs et al., 2007).

Medical and antibacterial applications

- Medical applications. These relate to fullerenes or 'buckyballs' which have so far only been used to a limited extent in drug delivery systems. In the future however these could be used to reduce the dosage of medications. These applications, however, are not expected in the next ten years. Given that this is a very small field of application, this route is not considered to be highly relevant;
- Antibacterial applications. Here nanosilver is most commonly referred to. Applications are mainly in medical dressings, as well as clothing and washing machines. Depending on the way in which the waste is processed, limited emissions to water could occur in the waste phase for medical dressings. In the case of clothing and washing machines it cannot be ruled out that a significant part of the nanoparticles present will end up in the environment. See the following website for a recent example: http://technology.newscientist.com/channel/tech/dn13602-smelly-sock-treatment-leaks-silver-nanoparticles.html?feedId=online-news_rss20 (accessed on 15 April 2008). This website shows that after a few washes, silver particles applied to socks have disappeared completely from the socks. Some of the silver particles washed out will be removed in a sewage treatment plant, and some will end up in the environment.

Food production

- Packaging material. Here nanoparticles are used to limit or inhibit the permeability of gases, and thus increase the shelf-life of all kinds of products. These are mainly nanoclays, a composite of mineral clay particles of nanometre dimensions and polymers (http://www.research.bayer.com/ausgabe_15/15_polyamid.pdfx). Emissions to the water

compartment may be expected only to a limited extent in the waste phase, because there are no applications which come into direct contact with water;
- Crop protection products (pesticides and herbicides). Experiments are being conducted with nanosized crop protection products and with crop protection agents which are encapsulated in nanoparticles (ETC Group, 2004). At the moment these applications are still in a highly experimental phase and this route is therefore not considered to be relevant in the near future.

Consumer products (see also Chapter 6)

- Sunscreen products. This concerns the use of titanium oxide (TiO_2), and to a lesser extent, zinc oxide as UV protection in sunscreen products and cosmetics. This application is becoming more widely used and therefore emissions directly to surface water (during recreation) or indirectly (via the sewerage system) may be expected here (Owen and Depledge, 2005);
- Self-cleaning glass. The photocatalytic ability of titanium dioxide, in particular, is being used in glass in buildings and cars. There are also products on the market which mimic the 'Lotus effect' on car windows. This is the self-cleaning property of the lotus plant which is due to very tiny (nano scale) papillae on the surface of the leaf. Other plants such as Nasturtium and cabbage also exhibit the same effect. Material scientists are attempting to reproduce this self-cleaning effect through the development of advanced materials. When nanoparticles are incorporated in glass emissions will only take place in the waste phase. The material in car windows will gradually wear off and end up in the environment. To what extent this involves the emission of free nanoparticles however is unclear, because in this application the particles are aggregated into larger clusters. It is unclear whether weathering causes these aggregations to breakdown into free nanoparticles in the environment;
- Textiles. Nanoparticles are used to make textiles water and dirt repellent. See for example www.nano-tex.com. When this textile is used (worn, washed) there is a chance that particles will end up in the environment. Also in this case it is unclear whether these will be free nanoparticles or not;
- Cleaning products. Cleaning products are expected to lead to relatively high emissions (Dekkers et al., 2007a);
- Personal grooming products. Again relatively high emissions are expected to take place given the typical application patterns for personal grooming products.

Environmental and energy technology

- Catalytic agents. Nanoparticles are ideal as a catalyst in numerous processes. This is because of their high reactive capabilities, due to their favourable surface to volume ratio. Examples include water treatment or the in situ remediation of soil contamination. This application often involves relatively unstable nanoparticles, such as nano-iron, a metal which is naturally already present in the environment in large quantities and which dissolves during the degradation of the contamination and then forms dissolved iron. Because this use of the nanoparticles are deliberately introduced into the environment,and emissions to water and soil may be expected;
- Diesel fuel. The use of cerium oxide as a catalyst in diesel increases the efficiency of the diesel combustion, keeps the engine clean and reduces the emission of greenhouse gases (http://www.oxonica.com/energy/energy_envirox_intro.php). As a result, an increase in emissions to the environment, and ultimately to water, from exhaust fumes is therefore to be expected in the near future;

- Carbon nanotubes. These are mainly used for more effective storage of electrical energy and hydrogen. In the UK they are regarded as technologies offering great environmental benefit (Oakdene Hollins, 2007). Their use in electrical conductivity is also being further investigated which could open up a wide field of all sorts of applications. These sorts of application are currently still in the R&D phase. Emissions to surface water are only to be expected to a limited extent in the waste phase.

Other applications

- Use in rubber: e.g., 'carbon black' and carbon nanotubes in car tyres to make them stronger and more durable. Apart from being deliberately produced (manufactured), carbon black is also formed as a by-product in the incomplete combustion of petroleum products and is thus one of the first nanoparticles to be applied on a large scale. Not all carbon black particles are covered by the definition of nanoparticles because of their wide variety of sizes (Royal Society of Japan, 2004). At present experiments are being carried out with the addition of various new nanoparticles to rubber to further increase durability. The nanoparticles are incorporated in a matrix, but due to wear there is still the possibility that nanoparticles end up in the environment as a result of this application. In Germany a study is planned in the near future on the emission of carbon nanotubes from car tyres;
- Chemical Mechanical Planarization (CMP) process. Nanoparticles are used to make the surface of semi-conductors smooth and flat. The nanoparticles used for this are aluminium, silicon and carbon nanotubes. According to Borm et al. (2006a) this application was responsible for the largest production of nanoparticles in 2004. Nevertheless, due to their type of application, emissions to surface waters are unlikely to occur, except in the waste phase.

8.1.2 Future applications

Developments in nanotechnology are currently speeding up and many new applications are in the pipeline. If known products are more widely used in the future it is unknown what the possible future environmental risks will be. More unclear is what the potential environmental risks are of the following generations of nanotechnology (see also Chapter 1). Such new applications could also bring new environmental risks.

8.2 Present understanding of risks posed by nanoparticles in the environment

8.2.1 General

The risks posed by nanoparticles in the environment refers to the risks of nanoparticles in the following environmental compartments:

- Water;
- Air (direct and indirect);
- Sediment;
- Soil.

At present it is unknown in which environmental compartment the effective exposure of the ecosystem (and indirectly human exposure) to nanoparticles will be the highest. Attention also needs to be devoted to the persistence of exposure along the food chain, for example, through particles in soil entering

worms and birds, or particles in water passing from fish into birds of prey or ending up in sea mammals.

Possible effects and risks of nanoparticles in the environment are:

- Ecotoxicological effects. Ecotoxicology covers many different plant and animal species. A great deal of research is necessary before observed effects can be extrapolated to higher organisms such as mammals. There are indications that nanoparticles in the environment may have undesirable antimicrobial effects. However, it is impossible to say at this time what risks posed by nanoparticles are relevant and possibly of concern for organisms in the ecosystem. Besides the standard endpoints such as mortality, reproduction and growth, this also concerns oxidative stress, inflammations and possible genetic abnormalities. Again the degree of risk to organisms and ecosystems cannot be estimated;
- Indirect exposure of humans: nanoparticles in the environment can lead to human exposure. For human exposure the reader is referred to Chapter 5. Certain routes, barriers and endpoints from human toxicology could possibly also be used to investigate the fate of nanoparticles in the environment and for research on secondary poisoning. Examples of potential routes for indirect human exposure to nanoparticles in the environment are via agricultural livestock, agricultural produce, fish and drinking water.

8.2.2 Present understanding of risks posed by nanoparticles in water

The report 'Nanoparticles in water' examined emissions as well as the fate and behaviour of nanoparticles in water, including the potential impact on the aquatic ecosystem (Struijs et al., 2007):

Emissions of nanoparticles to water:

- There are no known analyses which can be used to make good estimates of emissions of nanoparticles to water;
- It may be expected that the greatest emissions of nanoparticles will occur during the use and waste phases. These will generally be diffuse emissions. Whether free, single nanoparticles will end up in the environment as a result is debatable. Emissions in the production phase may be assumed to be small. However, the chance that these emissions consist of free nanoparticles is greater than for emissions during use and waste processing;
- Examples of applications which could lead to relatively large emissions to water are: nanoparticles as UV block in sunscreen products, applications in water treatment and soil remediation, cleaning products, additives for diesel fuel and car tyres and possibly new applications such as crop protection products in agriculture (see also above under 'applications').

Behaviour of nanoparticles in water:

- Nanoparticles generally exhibit poor solubility in water and as such may be considered as a persistent contaminant. They can only be removed from water through interaction with each other or with other particles present in the water;
- Small nanoparticles will hardly precipitate out of water. Only large particles or clusters of particles with typical diameters > 1 micrometer will precipitate as sediment;
- Nanoparticles in water should behave in accordance with the rules of colloidal chemistry (DLVO theory). The DLVO theory states that by definition 'small' particles will coagulate to form relatively small aggregates in order to achieve the most favourable energy state. The few experiments that have been conducted give reason to suspect that the known laws may not simply apply in the same way at nanoscale. For the time being the applicability of colloid-

chemistry laws to describe/predict the flocculation/behaviour of nanoparticles in water has not yet been fully demonstrated.

Possible effects on the aquatic ecosystem:

- The available laboratory observations indicate that effects on aquatic organisms should not for the time being be ruled out. Gradually the results of studies with nanoparticles are becoming available in which such effects are shown. Handy et al. (2008) and Baun et al. (2008) for example, have recently provided overviews of the current situation concerning the ecotoxicology of nanoparticles.

8.2.3 Present understanding of risks posed by nanoparticles in air

- Emissions: Many of the nanoparticles found in the environment are the result of natural processes (e.g., volcanic eruptions) or they are emitted to the air from combustion engines. Air is also the medium which disperses nanoparticles, whether manufactured or not, to the various biotopes both close by and further away. The extent to which manufactured nanoparticles are already found in natural ecosystems is unknown;
- Behaviour: Little is known about the fate and behaviour of nanoparticles in the air. Nanoparticles are generally larger than molecules. From this it could be concluded that nanoparticles will be removed from the air fairly quickly by gravity, unless aerosol formation occurs and as a result substances are transported over long distances. It is expected that nanoparticles will hardly be broken down while present in the air;
- Effects: Little or nothing is also known about the effects of nanoparticles in the air.

8.2.4 Present understanding of risks posed by nanoparticles in soil

- Emissions: It is expected that many nanoparticles will ultimately end up in the soil. Direct emissions to the soil can occur due to the landfilling of waste, the use of nano crop protection products, spilling fuel with added nanoparticles, et cetera. It is difficult to estimate the extent to which this is already a problem;
- Behaviour: Once in the soil nanoparticles become subject to all the soil processes of which degradation and adsorption are the most important. In addition, nanoparticles themselves can also adsorb substances to the active areas on their surface;
- Effects: Apart from the direct effects of nanoparticles on soil organisms, the degradation products of nanoparticles and dissolved nanoparticles (e.g., silver ions released from silver nanoparticles) could also have effects on the soil. Here the single molecules that comprise some nanoparticles are considered. Specific examples include metals in a nano formulation, such as nanosilver, nanozinc and nanoiron, where the risks for the non-nano form have already been properly identified.

8.2.5 Present understanding of risks posed by nanoparticles in sediment

- Emissions: Generally direct emission to sediment or watercourse beds will not occur, given that the primary route is via the water phase;
- Behaviour: In the sediment the nanoparticles will be subject to the normal processes which take place in water/sediment systems. Here adsorption and breakdown will also be the most important, although further dispersion due to advection will also certainly take place;

- Effects: Effects on bottom-dwelling and sediment organisms cannot be ruled out. The extent to which this will lead to unacceptable effects will have to be derived from a more detailed risk evaluation.

8.2.6 Indirect effects of nanoparticles on the environment

Indirect environmental contamination may also occur due to the use of nanotechnologies. One example of this is the ability of nanoparticles to adsorb dissolved contaminants. This relates to the large specific surface of nanoparticles. By then taking these nanoparticles out the water together with the contaminants adsorbed onto them, significant amounts of pollutants could be removed from the environment. Conversely, nutrients could also be removed and high concentrations of environmental contaminants could turn up locally (e.g., in the sediment). This adsorption behaviour could also lead to changes in the rate at which substances are transported and converted by the environment.

8.3 Risk assessment

Crane and Handy (2007) have assessed the research strategies and methods for the characterisation of the ecotoxicological hazards of nanomaterials. Some of their conclusions are:

- Standard methods for the investigation of ecotoxicology are generally to be preferred because these work with types of organisms whose strengths and limitations for toxicological research are already known. One major uncertainty is how nanoparticles should be administered, maintained and measured in the research medium;
- Rapid testing systems (in vitro or 'genomics' which is the study of the genome (all the genes) of an organism) could provide a useful addition to existing study methods, certainly for investigating the similarities and differences between macro and nano forms of substances;
- A step-by-step (or tiered) approach to environmental risk assessment, as used for chemicals not in nano form, is probably quite suitable for assessing the risks of nanoparticles;
- Organisms in ecotoxicity studies should be exposed to nanoparticles in a way which is relevant from an environmental perspective. The form taken by nanoparticles throughout the life cycle can differ (e.g., agglomerated or free), and this should be taken into account;
- The concentration of nanoparticles should not be referred to in terms of mass to volume but perhaps as surface to volume or number to volume, for example (see also Chapter 3 where dosimetry is discussed).

Crane and Handy arrived at the following recommendations:

- The research to determine methods and strategies for ecotoxicology should primarily be aimed at realistic 'worst case' exposure scenarios for nanoparticles in the environment. The toxicity of nanoparticles in these scenarios should then be investigated;
- Governments, industry and stakeholders need to make agreements on a set of rapid and cost-effective tests which can be used to show whether nanoparticles have similar hazard properties as other forms of the same substance (not in nano form).

There are still no routinely applicable methods for determining the nanoparticle content in water samples. A large number of specific and non-specific analysis methods are potentially available, but these methods are currently at best suitable for a qualitative determination of whether nanoparticles (aggregated or otherwise) are present or not in water samples (Struijs et al., 2007).

Environmental research takes a fairly classic approach in some areas. For example, ‘classic’ organisms such as water fleas and fish are looked at in the environment. It is being investigated how existing tests can be modified for nanoparticles, but data provided by such modified classic tests cannot be extrapolated at this time, because the determinants are unknown. At the moment however it appears rational that the size of the particle, the surface/diameter ratio, as well as the surface of the particles are likely determinants for describing the behaviour and effects of nanoparticles and the extrapolation of laboratory studies to the situation in the field. Nanotechnology requires new ways of doing environmental research.

For ecotoxicology it is important to know how the particles behave and how organisms are exposed to the particles. This is a different focus than in life cycle analyses (LCAs) which stop at emissions. When LCAs also include impact analyses, they are referred to by the abbreviation LCIA. In ecotoxicology it is important that fate and behaviour in the various environmental compartments can be described. ‘Fate’ can be predicted on the basis of the physico-chemical properties of substances. In the case of the currently most common ‘hydrophobic organic substances’ on which most international risk assessment systems are based, there are clear indications that, in essence, the fate and behaviour of these substances in the environment can be predicted or modelled on the basis of the hydrophobicity of the substances. For nanoparticles however we do not yet really know which key parameter or parameters we can use to predict or model their behaviour and effects. The presence of these substances in the environment is, in any event, different and possibly more complex and extensive than that of the ‘traditional’ hydrophobic organic environmental contaminants. There are indications that the key to understanding the fate, behaviour and effects of nanoparticles should be sought in areas such as the specific surface of the particles per volume or unit weight, the particle size ratio, et cetera. Partly due to the systematic lack of data there is as yet no clarity about this.

The assessment of environmental exposure is carried out in exactly the same way as for human exposure: the behaviour of the nanoparticles in vivo may well be different from that of the non-nano chemical substances, but this is by no means certain. In the traditional risk assessment of (non-nano) chemical substances in the environment, it will be considered whether the ratio between the expected concentration in the environment (PEC, Predicted Environmental Concentration) and the concentration of a substance in the environment where it has been predicted that no undesirable effects will be observable (PNEC, Predicted No Effect Concentration) is acceptable (i.e. < 1).
Given the fact that nanomaterials can be considered as chemical substances, there is no reason to doubt the validity of this paradigm for nanoparticles. The calculation of the ratio between PEC and PNEC can, in principle, be done for all environmental compartments (water, sediment, soil and air). At present however such risk assessments cannot be carried out for nanomaterials while there is not enough data available to estimate either the PEC or the PNEC.

8.4 Current / planned risk research

RIVM:

- LER (RIVM – Laboratory for Ecological Risk Assessment) together with other RIVM centres, has compiled a report on nanoparticles in the environment;
- In addition within RIVM a study is being carried out on the possible effects of nanosilver, on which a paper (Wijnhoven et al., 2009) has been published. Plans for a follow up study are still under discussion;
- RIVM takes part in the NanoInteract FP6 project, for example (see also below). In this project RIVM researchers together with researchers from the universities of Maastricht, Nijmegen,

Dublin and Ghent, are looking at how nanoparticles behave in the environment under natural conditions and to what extent harmful effects to humans, plants and animals can occur under these conditions.

Current EU-FP6 studies in the area of HSE, dedicated to the environment, include NanoInteract, Dipna, Impart Particle Risk. Among the new calls of EU FP7 there are also a number which feature the environment as a focus area (Aguar and Nicolás, 2008), see also Section 3.5.
In addition to the above research which is being carried out in the context of EU Framework Programmes and the above FP7 calls, independent research on the environmental risks of nanotechnology is being carried out in various EU countries. Aguar and Nicolás (2008) also provide an overview of this research.

8.5 Knowledge gaps

The following knowledge gaps have been identified by Crane and Handy (2007) and Struijs et al. (2007):

- There is still no clear overview of the presence of nanoparticles in the environment, because there are still no widely applicable analysis techniques available. There is still no clear characterisation of nanoparticles. Nanoparticles are not routinely monitored and it is therefore unknown in what form or forms (e.g., as free particles or aggregates) they occur in the environment. Almost nothing is reported in the literature about the extent to which nanoparticles coagulate/flocculate or disintegrate into the basic molecules and/or precipitate in natural water. For a small number of metals it would appear that the degree of toxicity is actually linked to the solubility of the metal ions from the metal particles. It is therefore unknown what impact emissions to water could have on the presence of single free nanoparticles in water;
- From an environmental point of view it is important to know whether particles are persistent, e.g., like the heavy metals nano-TiO_2 and nano-SiO_2 or not, such as nano-silver and nano-iron. Little is yet known about the persistence of nanomaterials in relation to the nature of the medium (in terms of pH, redox, ion composition, et cetera). This also applies to the properties of the particle, such as the degree of aggregation and rate of solubility as a function of particle size. There is a difference between persistence as a substance or as a nanoparticle: a nanoparticle may be persistent as a nanoparticle (and therefore not disintegrate) and also persistent as the substance (e.g., as the fraction dissolved in water). Moreover, it is possible that the nano properties increase the persistence of the substance, e.g., in terms of the half-life for degradation of a compound, as a result of which ecosystems could be exposed to a substance for longer than would be expected on the basis of the hydrophobicity of the substance. This increase is due to the fact that a large proportion of the molecules in a nanoparticle are not accessible to the micro-organisms which are responsible for the degradation of substances, for example. Nanosilver, for example, can release small particles in the same way as a ‘slow release drug’. The working hypothesis is that the smaller the particles, the greater the toxicity. In the life cycle for nanosilver, therefore, reactivity could steadily increase;
- It seems reasonable to assume that model-based estimates of the PEC of free nanoparticles in the environment cannot be simply based on the assumption that there will be a balanced distribution between a dissolved and an adsorbed state for nanoparticles. Therefore,

measurements and predictions of partition or distribution coefficients, as are carried out for chemical substances not in nano form, would not appear to be adequate;
- There is little empirical information available on the ecotoxicity or potential bioaccumulation of nanoparticles. Research on the ecotoxicity of nanoparticles is still in its infancy. Study results are scarce and apparently contradictory results are being reported in studies subject to a great deal of substantive criticism. Depending on the exposure routes ecotoxicity data must be generated for aquatic and terrestrial microbes, plants and animals to reduce the uncertainties concerning the potential hazards of nanoparticles (Crane et al., 2007);
- Experimentally observed ecotoxicity of nanoparticles appears to depend on the way in which the specimens are handled. Apparently the actual exposure concentrations in the media investigated by the researchers could not be properly estimated. This is, among other things, because the methods used to disperse particles in ecotoxicity tests lead to solutions in which the behaviour of the particles is different from the behaviour of the same particles in the environment. This will make it difficult to extrapolate the effects observed in ecotoxicity tests to the environment. Based on the information available in the literature it also cannot be said whether and, if so, to what extent nanoparticles will actually have an impact on ecosystems (or parts of ecosystems) under natural conditions;
- There is insufficient empirical data available to enable predictions on chronic effects of nanoparticles based on acute toxicity. The lack of information on the critical properties also plays a major part in this;
- Due to their highly specific surface nanoparticles have great potential as an adsorbent for substances dissolved in water and to act as a catalyst for reactions occurring in water. These properties are utilized in water treatment. Whether the same properties of nanoparticles can influence the behaviour of dissolved substances in natural water systems is still entirely unclear;
- Nanoparticles may have indirect effects on the environment. They could, for example, act as carriers of other (possibly harmful) substances, play a role in effect routes, e.g., to fish. Due to the fact that nanoparticles have a large reactive surface, all sorts of substances can attach themselves to nanoparticles. This topic is not covered in the present technical guidance documents, but is known from research with atmospheric soot particles (fine dust). Furthermore, nanoparticles can form a film on water and in this way have an impact on the ecosystem, causing an oxygen deficit by impeding the gas exchange and overshadowing water plants.

8.6 Coping with risks

8.6.1 The regulatory framework

The present legislation for chemical substances is intended for singular substances: a metal, a herbicide, a drug, et cetera. All these substances are tested for environmental and other effects in the context of admittance to the market for these substances. For this purpose the manufacturer submits a dossier to the authorities. These data are used to undertake a risk assessment on the basis of which a policy decision is made. The reader is referred to Annex 4 for REACH and other legislation.

8.6.2 Risk management

It is still too early to speak of specific risk management measures for nanoparticles. Largely because it has not been possible to establish any actual risks so far. As the first priority a number of matters need

to be addressed: specific analysis methods, specific physico-chemical properties, specific toxicity tests, specific methods for deriving relevant PEC and PNEC values, et cetera. Once the environmental risks have been established in a number of areas, risk management can be considered. Obviously, further fate and behaviour, and effect research as well as normal risk limiting measures, such as limiting emissions, controlled emission and limiting dispersion, will always be relevant.

8.7 Observations

- Nanoparticles are being used in ever higher quantities, in ever more applications. It may be expected that, parallel to these developments, emissions to the environment will increase and thus also their effects on ecosystems;
- It is still not yet possible to properly characterise nanoparticles released into the environment.
- Little is also still known about the behaviour of nanoparticles once they end up in the environment. Knowledge about the behaviour of aerosols can be utilised for air while colloidal chemistry may offer possible starting points for water. In both cases, however, there is still an insufficient set of tools available to be able to properly describe the fate and behaviour of nanoparticles;
- This makes it difficult to identify suitable testing systems to investigate the effects of nanoparticles on ecosystems and hinders the extrapolation of the results obtained from the test systems to the environment itself;
- As a result there are at present no valid theories or accepted estimation methods which can be used to determine the risks of nanoparticles in the environment.

9 Observations and conclusions: risks of nanotechnology in perspective

The previous chapters outlined the current state-of-affairs and developments related to the risks of nanotechnology with regard to medical applications, applications in food production and consumer products in which the focus was mainly on manufactured, free, non-degradable and insoluble nanoparticles. It was determined for each area which applications of first generation nanomaterials are currently on the market or are expected to become available in the near future. Furthermore, an overview was provided of the current understanding of the risks of these applications. The risks in the area of industrial processes and occupational health and safety and the risks of nanotechnologies in relation to the environment were also considered in more depth.
This chapter puts the findings from the previous chapters in perspective.
The underlying principle for this is the general system for the assessment of the risks of chemical substances, in which the risk of a substance is determined by the hazard of the substance itself multiplied by the degree to which a person is exposed to that substance. This results in the following formula:

RISK = EXPOSURE x TOXICITY

A certain dose of a substance will lead to harmful effects (toxicity). To be able to establish these effects, an organism must thus first actually be exposed to such a dose.
Actual exposure of humans and the environment will depend on the presence of free nanomaterials (i.e., particularly nanoparticles). When nanoparticles are bonded in a hard coating, for example, the chance that a person will be exposed to them is fairly small. However, when such products are subject to wear or during waste processing nanoparticles can still be released, thereby leading to exposure of humans and the environment. When the particles are further insoluble and non-degradable, they can also accumulate in organisms or humans and be harmful.

9.1 Integrated analysis and directions for improvements

It is clear that there is still a lot of information missing to be able to estimate the risks of nanomaterials to humans and the environment. However, there are already many hundreds of products on the market, the number of which will increase considerably in the coming years. In the meantime it will be necessary to find a way of dealing as sensibly as possible with the lack of knowledge. Various analyses have already shown that it will certainly be five to ten years before sufficient information is generated to be able to estimate the risks of nanomaterials to the same extent as those of chemical substances not in nano form (Maynard et al., 2006).

An integrated analysis of the available information across the individual subpopulations shows a number of directions for improvements may be found for dealing as responsibly and as effectively as possible with the unknowns in terms of the risks to humans and the environment. Table 9.1 provides an overview of starting points for management measures within the target populations of workers, patients, consumers and the environment. For this purpose an analysis was made of the available information (in outline) for these populations. The information on possible starting points with regard to the admittance and use of nanomaterials from the table below should be combined with toxicity data.

The basic principle applied for toxicity is that toxic effects cannot be ruled out. There are, for example, indications that carbon nanotubes of certain dimensions could cause toxic effects which are comparable to the early stages of asbestos-related cancer (Poland et al., 2008). Effects however, cannot be generalised, either. Just as we cannot speak of *the* toxicity of chemical substances, so we cannot speak of *the* toxicity of nanoparticles.

Based on the foregoing and Table 9.1 the following pointers can be defined.
For *researchers and workers* involved in the production, processing and application of nanoparticles or products containing nanoparticles it has been established that they are working with nanoparticles which may to a greater or lesser extent be toxic. In the same way as working with chemical substances not in a nano form, for this group attention should be focused on minimizing *exposure* to free nanoparticles. For this it is important that 'good practices' are developed in the short term to limit exposure to nanomaterials. Various steps have already been taken in this direction.
For *patients* however, exposure is intended, but the right balance has to be found between the positive effects (action) of the drug and possible toxicity. For other medical applications a balance will also have to be found between the intended effect and possible adverse effects. These products are already subject to strict admittance requirements and continual evaluation will therefore be necessary to determine whether the admittance requirements sufficiently provide for a proper estimate of the risks of nanomaterials in this application.
For *consumers* it is difficult to identify good places to start to reduce the potential risks. It is insufficiently clear in which products nanomaterials are present. Assessments of exposure are furthermore surrounded by more uncertainties because for many products there is no information on the form in which the substance is present in a product as there is for chemical substances not in nano form. Besides this, exposure is determined by use of the products and that use in itself it difficult to determine. In addition, less toxicological data has to be provided than for pharmaceuticals, for example. A distinction can be made, however, between food and non-food products. Some substances used in food products (such as food additives) are subject to stricter requirements than the substances used in non-food products. Substances in nano form are essentially also covered by REACH. REACH offers opportunities for gathering more information on the nano form of chemical substances. Tightening up the regulatory framework or the requirement to provide information to the consumer provide further options. In France, for example, legislation is in preparation on the labelling of products which contain nanomaterials.
For *the environment* the most important opportunities lie at the source, such as limiting emissions.

Tables B6.1 and B6.2 in Annex 6 provide a more detailed overview of aspects which could or should be taken into account in exposure to nanomaterials.

Table 9.1 **Possible options for control measures relating to the admittance and use of nanomaterials in relation to the exposure of workers, the general population and the environment.**

Risk situation	Admittance	Use	Conclusion
1 (workers: researchers, production and processing workers and those involved in professional applications	Researchers, production and processing workers • Various H&S measures to prevent/limit concentration of a substance in a medium (or working environment)	Various H&S measures to limit duration and frequency of contact with nanomaterials	Various H&S measures possible to limit actual dose / external exposure (governing regulations)
	Professionally applied products • Limited influence over presence of substances • Control possible through legislation? • Risk research for specific applications?		
2 (general population)	Medical applications: • strict admittance procedures and mandatory risk management (for medical technology). Availability is often controlled (drugs not freely available). • Considered use based on thorough research of risks.	• Safe use of product based on knowledge and expertise of doctor/specialist.	• Dose in drug itself is controlled • Controlled dosage under supervision of doctor/ specialist • Dose based on risk research
	Food industry: • Use based on estimate of risks (more than for consumer products). • Novel Food Directive may be applicable: admittance requirements • Some, but not all, products with nanoparticles are monitored.	• Limited influence over use in food products is possible. • Labelling • Providing consumer information	• Limited options to influence dose in foods • Providing consumer information • Tightening-up legislation
	Consumer products: • Limited influence over presence of substances • Control possible through legislation? • Risk research for specific applications?	• Limited options • Providing consumer information	• Limited options • Providing consumer information • Tightening-up legislation
3 (via the environment)	• Emissions to the environment can be tackled at source, particularly at production stage • Possibly through legislation?	Limited options for influencing behaviour and dose.	

9.2 Observations: what do we already know?

- **Regulatory framework:** a review by the European Commission shows that, in principle, the present legislation covers the health, safety and environmental aspects of nanotechnology (EC, 2008). The documents which describe the implementation of the present legislation however need to be thoroughly evaluated and modified where necessary. Essential information on the risks of nanomaterials is still lacking for this;
- **Knowledge about risks:** although a great deal of knowledge is still missing, there is plenty of data available from research on fine particulates and medical applications. Despite the limitations that for fine particulates this relates only to particle toxicology further to inhalatory exposure, and that medical knowledge (mainly in the methodological area) is not shared, there is a knowledge base. This knowledge base was formed and is growing also through the research that has begun on various fronts. Besides national efforts, there are also international projects taking place, e.g., in the EU and OECD;
- **Risk assessment framework:** through the assessment of chemical substances not in nano form experience has been gained over the last decades which can provide a basis for the assessment of nanomaterials. For this, the application of these frameworks, such as the usual toxicological research methods, needs to be critically evaluated in terms of their suitability for nanomaterials. More knowledge is needed for this too;
- **Awareness and cooperation:** There appears to be greater awareness among the various stakeholders that the risks of nanotechnology need to be considered. Cooperation and dialogue between the various stakeholder and scientific disciplines is starting to emerge.

In essence there appears to be a sound basis to be able to obtain insight into the risks of nanomaterials to humans and the environment. There is a positive attitude towards the generation of knowledge and information based on the footing provided by the legislative framework. However, when it comes to the actual implementation and enforcement there are still a number of apparent gaps which are described below.

9.3 Observations: where are the knowledge gaps?

There are still a great many gaps in the knowledge necessary to be able to estimate the risks of exposure to nanomaterials for humans and the environment at a comparable level to that for chemical substances which are not in nano form.

The research required is very extensive and complex. The reasons for this include:

- The risks posed by a nanoparticle cannot simply be derived from the risk profile of substances, not in nano form or that of other nanoparticles. Apart from the chemical composition, characteristics such as form, surface and size are also important;
- One chemical substance may have a great many different sizes and forms of nanoparticles, each with its own unique properties and specific risks. For the time being, the risks need to be separately determined for each form of a nanomaterial;
- For chemical substances not in nano form there is often a body of knowledge on which to fall back on. Based on the physico-chemical properties of substances, the behaviour and toxicity of

a substance with similar properties can to some extent be predicted. This body of knowledge is not yet available for nanomaterials (including nanoparticles);
- Ideally for toxicological research the complete series of tests (including animal testing) would have to be carried out for every nanoparticle (i.e., for every particle size and form, et cetera). This is because it is not yet clear what criteria are essential to be able to characterise nanoparticles and indicate the dose. Such research is now only taking place for highly specific applications (e.g., pharmaceuticals) and for national and international research programmes;
- Apart from the ethical and economic drawbacks of such extensive toxicological research, it is to a certain extent uncertain whether the current testing methods can be applied to nanoparticles.

Observations concerning exposure, toxicology and ultimate risks are given per application area in Chapters 4 to 8. The most significant observations have been summarised below.

9.3.1 Lack of information on exposure

When we look more closely at what knowledge is missing, what immediately becomes apparent is that there is no clear overview of the degree to which nanomaterials are used. Most attention is devoted to the possible exposure of people working professionally with nanomaterials. It is, however, also insufficiently clear to what extent consumers and the environment are exposed to nanomaterials. The lack of adequately validated and accepted methods to be able to measure and characterise nanomaterials properly in various media plays an important part in this. As a result, it can also often hardly be determined whether (and in what form) nanomaterials can be found in the environment, the human body, and also in food, for example.

Although in employment situations there are already adopt ‘good practices’ in place, such as wearing protective clothing suitable for the working conditions. However there are knowledge gaps with regard to the effectiveness of such measures. For the environment and the consumer, however, there are hardly any pointers for protective measures when dealing with products containing nanomaterials.

9.3.2 Lack of information on possible toxicity

Apart from the lack of information on exposure there is also a lack of information about the possible toxicity of nanomaterials to humans and the environment. This makes it impossible to carry out a quantitative risk assessment. Such an assessment is necessary to substantiate threshold limit values and to estimate the risks to humans and the environment when these threshold values are exceeded. The information which is lacking is of a basic nature. For example, it is still unclear what parameter best describes a dose of nanomaterials. For chemical substances not in nano form a dose based on weight (e.g., gram) has been defined. For nanomaterials, however, this would not appear to be a good parameter for determining the relationship between dose and effects. This lack of a proper dose descriptor therefore constitutes an important hiatus with regard to both determining and exceeding threshold levels. The lack of data on actual exposure to and the toxicity of nanomaterials also stands in the way of a qualitative or relative risk assessment (such as a rough categorization of nanomaterials in various hazard groups).

9.3.3 Environmental risks difficult to estimate

Despite the rapid rise of nanotechnology, research on its environmental risks is still in its infancy. This means that even a basic estimate of these risks cannot be made. Given that nanoparticles are being used in ever greater numbers of applications, it may be expected that emissions to the environment will

increase. It is therefore urgently necessary to examine the entire life cycle of products (from manufacture to the waste stage). However, adequate information for this purpose is lacking in many areas (exposure and emissions during production, what particles are found in what products, how waste is handled, et cetera). And once nanoparticles end up in the environment, even less is known about their fate and behaviour. This makes it difficult to set up suitable testing systems to measure possible effects on ecosystems.

As the European Commission also concluded, the present regulatory framework provides a sound basis to guarantee the safety of humans and the environment to exposure to nanomaterials. However, there are some gaps in its implementation, in the area of enforcement, for example. Nanotechnology is often classified under converging technologies where, together with biotechnology, information technology and cognitive sciences (NBIC), it will lead to new applications. This convergence could mean that applications end up slipping between the regulations and legislative frameworks. As has already been observed for medical applications, it is not always clear whether a product should be viewed as a pharmaceutical or as a medical aid.

9.4 Conclusions

The phrase 'risks of nanotechnology to man and the environment' covers a very broad spectrum of research. It is important to bear in mind that there is no such thing as *the* risks of nanotechnology. The risks depend on the type of nanomaterial (form, size, et cetera), the application method and exposure, and the area of application, et cetera. Therefore we must always speak of the acknowledged and potential risks of certain types of nanomaterials in specific situations and applications.

Research and debate on the recognized and potential risks posed by nanotechnology to humans and the environment currently focus only on first generation nanomaterials; this report too. Here the concern, quite rightly, is with manufactured, free, non-degradable and insoluble nanoparticles. A great deal still remains unknown about the risks of these particles. To learn more about this, a good starting point would appear to be the way in which chemical substances not in nano form are assessed.
Key considerations for the coming years should be:

- Increasing and exchanging information and knowledge;
- Identifying solution areas and risk management;
- Making decisions;
- Research & Development;
- Cooperation.

9.4.1 Increasing and exchanging information and knowledge

A great deal of international attention is currently focused on drawing up research agendas. It is also very important to set up and maintain infrastructures to promote the exchange of knowledge and information between stakeholders, application domains and different scientific disciplines.

General concepts about the relationship between particle characteristics and their uptake in the body, for example, are for the time being still difficult to derive. This is because it is expected that relatively little research data will be generated in the coming years for each area of application. It is therefore necessary to integrate knowledge and experience from different application areas to be able to arrive at such concepts in the mid-term (five to ten years) at least. Knowledge about medical applications is

relatively thorough and thus from a methodological perspective, in particular, offers a good basis for other areas of application.

The development of safe applications can be promoted by considering the risk assessment and risk management aspects during the development phase. For this, researchers developing nanotechnology products can learn from researchers studying the toxicology of free, insoluble particles and vice versa. Because not only is knowledge and information lacking, but there is also a failure to exchange it. The worldwide consensus is that the above problem requires interdisciplinary cooperation and coordination to prevent the duplication of research. The Netherlands subscribes to this conclusion set out in the government paper on nanotechnologies (Netherlands' government, 2006). At present research on risks is insufficiently well organised within the Netherlands, partly because no umbrella activities have been set up for this by the government.

9.4.2 Identifying solution areas and risk management

A general analysis across the target groups and applications suggests a number of areas in which solutions may be sought to minimise these risks to humans and the environment. *Employees and those professionally involved in the application of nanoparticles* can apply the principles of 'good practice'. Some urgency in the development of such practices is therefore required. For *patients* the existing strict admittance requirements for medicines must be regularly evaluated in terms of their topicality. There are fewer opportunities available for ensuring that *consumers* are exposed as little as possible to nanomaterials in food and consumer products. Tightening up the legislation and providing information to consumers would appear to be the best options for this. The background to these pointers is given in Appendix 6.
For *the environment* the most obvious place to start is by limiting emissions. Nanoparticles are being used in ever greater quantities, in ever more applications. It may be expected that, parallel to these developments, emissions to the environment will increase and thus also their effects on ecosystems. Research on the fate and behaviour of nanomaterials in the environment and their possible impacts therefore also needs to be considered.

9.4.3 Making decisions

A great deal of basic information is still lacking to be able to arrive at proper quantitative risk estimates. The research questions are numerous and methodological in nature. Good national and international coordination of research can help to fill these knowledge gaps. It would be desirable for a vision to be developed on the basis of which the Netherlands can contribute to risk research. National and international government authorities must set priorities for this.

9.4.4 Research & Development

Both innovative and applied research for product development will be necessary to be able to determine the most suitable testing methods.

Research on risks should in the first instance be directed towards research which will make a significant contribution to a reliable risk assessment. From this perspective it is important to first demonstrate that nanomaterials are actually taken up by the body in that form. If this is the case, then full toxicological research must be carried out. If the nanomaterial degrades to the chemical substance not in nano form before uptake, existing toxicological data could possibly be used.

It is recommended that risk research in the area of nanotechnology be conducted on a more pro-active basis in future, particularly with a view to the risks posed by following generations of nanotechnologies. This requires a switch from reactive to anticipatory risk research.

9.4.5 Cooperation

In estimating the risks of nanotechnology there are three main groups of actors involved, i.e., the legislative bodies, the scientific community, and trade and industry. These three groups need to be aware of each others' questions. In this way a set of priorities can be created in terms of the activities required to fill the knowledge gaps as quickly and efficiently as possible.

Linking research on nano applications to their risks in various domains also offers good prospects: the unique properties of nanoparticles which are interesting for applications may also be relevant in identifying risks. What may be seen as an opportunity in one domain (e.g., drugs which can pass the blood/brain barrier) may in another domain be seen more as a risk (e.g., nanoparticles which unintentionally end up in the brain).

Given the advantages which nanotechnologies could bring to society, it would be to the benefit of the various stakeholders to subscribe to the same principle: *the implementation of nanotechnologies in society deserves to succeed, provided that the safety of man and the environment can be guaranteed.*

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Terms and definitions

Absorption	Uptake of substances by the body.
Accumulation	The build up of substances in the body or in organisms.
ADME	Absorption, Distribution, Metabolism, Excretion
Adsorption	The adhesion of substances to particles. In principle this may be dissolved particles (such as dissolved organic carbon), but this often refers to substances attaching to solid particles, such as soil particles.
Advection	The transport of substances from one environmental compartment to another through movement. An example is the transport of particles in water to sediment through surface water soaking into the substrate.
Aerosol	A suspension of microscopic particles, in solid or liquid form, in a gas.
Agglomeration	A group of particles which are held together by weak forces such as Van der Waals forces, some electrostatic forces and surface tension (SCENIHR, 2008).
Aggregation	A group of particles which are held together by strong forces such as covalent or metallic bonds (SCENIHR, 2008).
AMOLF	Institute for Atomic and Molecular Physics
ASTM	American Society for Testing and Materials
Behaviour	The behaviour of nanomaterials in a product, work environment or environmental compartment (air, water, soil or sediment) such as breakdown, dispersion within and between various compartments, sorption and aerosol formation. Also the behaviour of people with regard to a product or nanomaterial, e.g., the form of ingestion or use of a product, or another form of activity which could lead to internal or external exposure or exposure of the environment. The term exposure scenarios is used in this context.
Bioaccumulation	See accumulation.
Bioavailability	The degree to which a substance can be taken up by (is available to) organisms.
Biocompatibility	Property which indicates the extent to which a product or material has a desired interaction with the body.
Biomarker	Change in the physiology, biochemistry or histology which can be used to measure the development of a disease or the effect of a treatment.
Biotransformation	Conversion of substances by the body or by organisms in the environment into other (usually less harmful) substances.
BSI	British Standards Institute
Buckyballs	See fullerenes.
Bulk chemical/substance	Chemical/substance which is manufactured in large quantities.
CBG/MEB	College ter Beoordeling van Geneesmiddelen (Medicines Evaluation Board)
CEN	European Committee for Standardization (Comité Européen de Normalisation)
Clean room	An environment typically used for production or scientific research which is characterised by a low level of environmental

	contamination, such as dust, airborne microbes, aerosols and chemical fumes.
Coagulation	A process in colloid chemistry in which dispersed colloidal particles agglomerate.
Colloid chemistry	Branch of chemistry concerned with the study of the behaviour of dispersed particles. In relation to air this is mainly aerosols, for water it often relates to emulsions of particles in water (or more commonly: clusters of particles).
Concentration	The presence of nanomaterials in a product, working environment or environmental compartment (air, water, soil or sediment).
Converging technology	Technology in which the integration of various scientific disciplines takes place leading to new and innovative developments.
Cytotoxicity	Damage or destruction of body cells (cytes), usually caused by damage to the cell membrane.
Delivery container	Miniscule container which is used to selectively administer substances (e.g., medicines) to body cells.
Delivery systems	Applications in which useful ingredients can be precisely dosed and released in a controlled manner, for example, while eating (aromas) or in the body (nutrients). Encapsulation can be used to enhance the dispersion of nutrients in the body.
Dendrimer	Spherical macromolecule with an internal cavity or cavities comprising a core with radial branches with special end groups attached.
Dermal	Via the skin
Dispersion	Fine distribution of a solid substance in another solid substance.
Distribution	Dispersal of substances throughout the body or various environmental compartments.
DLVO theory	Derjaguin-Landau-Verwey-Overbeek theory
Dosimetry	The accurate and systematic determination of the dose.
Dose-effect relationship	Relationship between the total amount per time unit of a substance administered to or taken up by a human or an organism and the resulting effect.
Drug delivery	Release of pharmaceutical.
Drug targeting	Targeted pharmaceutical release (e.g., in a tumour)
Ecosystem	The entirety of organisms (animals and plants) present in the environmental compartments of air, water, groundwater, sediment and soil.
Ecotoxicity	Harmful effects of a substance on organisms or ecosystems.
EFSA	European Food Safety Authority
EMEA	European Medicines Evaluation Agency
Emission	The release of substances into the environment.
Encapsulation	The enclosure of a nanoparticle or nanoparticles in a case.
EPA	Environmental Protection Agency
EU	European Union
Excretion	The elimination of substances from the body.
Exposure	Degree to which humans/organisms come into contact with substances.
Exposure scenario	A set of facts and assumptions about how exposure takes place. These scenarios can be used to estimate exposure.

External dose/exposure	External exposure: the dose (amount of nanomaterial) which people or organisms come into contact with per time unit.
Fate and behaviour	Fate refers to the distribution and behaviour of substances in the environment. After an emission has taken place, a substance will be distributed over the various environmental compartments. The substance could also be broken down. All the distribution and breakdown processes define the fate and behaviour of a substance in the environment.
FOM	Foundation for Fundamental Research on Matter
Fullerenes	A family of carbon allotropes, molecules composed entirely of carbon, in the form of a hollow sphere, ellipsoid, tube or plane. Spherical fullerenes are also called buckyballs and cylindrical ones are called carbon nanotubes or buckytubes.
Functional Foods	Food which may have health benefits beyond its normal nutritional value.
Half-life	The time interval required for the original amount to be reduced by exactly half. Measure for the rate at which a substance disappears from a medium.
Harmful effects	Adverse effects on various endpoints (e.g., mortality, reproduction) for humans and the environment further to short (acute) and/or long-term (chronic) exposure.
HSE	Health, Safety and Environment
ICON	International Council On Nanotechnology
ICT	Information and Communication Technology
I.m.	Intramuscular, in a muscle.
In vitro	In a test tube, not in living organisms.
In vivo	In the intact organism.
Inhalatory	Via the airways
Internal dose/exposure	Internal exposure: the dose (amount of nanomaterial) which is actually taken up by the body or organisms per time unit.
Intravenous	See I.v.
IoN	Institute of Nanotechnology
I.p.	Intraperitoneal, in the stomach cavity.
ISO	International Organization for Standardization
I.v.	Intravenous, in the blood circulation.
IVAM	Research and Consultancy on Sustainability organisation (IVAM) of the University of Amsterdam
KEMA	(formerly Keuring Electrotechnisch Materieel Arnhem): a multinational organisation for consultancy, quality assurance and product certification.
Kinetics	Analysis of the rates of absorption, distribution, metabolism and excretion (ADME) of substances.
KIR nano	Risks of Nanotechnology Knowledge and Information Centre (KIR nano)
KIWA	Institute for Water Research, Water Quality and Public Health
Lab-on-a-chip	Total analysis system comprising functions for sample processing, combined with reagents and detection with all the necessary electronics integrated in a chip.
LAREB	Netherlands Pharmacovigilance Centre

LCA	Life Cycle Analysis
LCIA	Life Cycle Impact Analysis
Life Cycle Analysis	The analysis of all substance and energy flows involved in the production, use and emission of products.
Liposome	Fat cell
LNV	Ministry of Agriculture, Nature and Food Quality
Manufactured nanomaterial/nanoparticle	Every material/every particle that is deliberately manufactured such that it is made up of separate functional parts (both internally and on the surface) many of which have one or more dimensions in the order of 100 nanometres or less (SCENIHR, 2008).
Micro-	Prefix used for a millionth of a unit (10^{-6}, e.g., micrometre or microgram). Also used to indicate that something is in the order of a micrometre in size (e.g., microtechnology).
N&ET WG	New and Emerging Technologies in Medical Devices. Working Group of the European Commission.
Nano-	Prefix used for a billionth of a unit (10^{-9}, e.g., nanometre or nanogram). Also used to indicate that something is in the order of a nanometre in size (e.g., nanotechnology).
Nanotube	An individual, hollow entity with two dimensions in the order of 100 nanometres or less and one longer dimension (SCENIHR, 2008).
Nanoparticle (free/bonded)	An individual entity with three dimensions in the order of 100 nanometres or less (SCENIHR, 2008). Unlike free nanoparticles (e.g., in cosmetics and cleaning products) bonded particles are fixed in or on a medium (e.g., in textile or as a coating on a surface).
Nanomedicines	Pharmaceuticals made from new or existing substances applied on a nanometre scale. These may consist of nanoparticles of the active ingredient, nanoparticles as a carrier material or porous material from which the active ingredient is released in a controlled manner.
Nanostructured materials	See nanostructure.
Nanocrystal	Crystal of nanoscale dimensions.
Nanomaterial	Any form of a material that is made up of separate functional parts many of which have one or more dimensions in the order of 100 nanometres or less (SCENIHR, 2008).
Nanomedicine	Application of nanotechnology in healthcare.
Nanometre	A billionth of a metre (10^{-9} m).
NanoNed	NanoNed was set up in 2002 by MESA+, the Kavli Institute in Delft and BioMaDe in Grongingen, and is a consortium of seven universities, TNO and Philips. NanoNed has 11 flagship programmes (aimed at scientific research) a technology assessment programme and a virtual nano lab (a sophisticated nanotechnology infrastructure). Under NanoNed some 200 research programmes have been facilitated.
Nano crop protection products	These are pesticides and herbicides made of new or existing substances applied on a nanometre scale. They may consist of nanoparticles of the active ingredient, nanoparticles as a carrier material or porous material from which the active ingredient is released in a controlled manner.

Nanoscale	A feature characterised by dimensions in the order of 100 nanometres or less (SCENIHR, 2008).
Nanostructure	Any structure that is made up of separate functional parts, both internally and on the surface, many of which have one or more dimensions in the order of 100 nanometres or less (SCENIHR, 2008).
Nanotechnology	There is, as yet, no generally accepted definition of this. In this report the ISO proposal is used: - Understanding and control of materials and processes on a nanoscale, usually but not exclusively, smaller than 100 nanometres in one or more dimensions, where size-dependent phenomena begin to play a role which generally makes new applications possible. -Use of the properties of nanomaterials, other than those of individual atoms, molecules and bulk substances, to make improved materials, equipment and systems. The Royal Society and The Royal Academy of Engineering (2004) defined it as follows: The design, characterisation, production and application of structures, devices and systems by controlling form and size at nanometre scale.
Nano food products	Food products which contain nanomaterials or which have been produced with the aid of nanotechnology.
Nanoscience	The study of phenomena and manipulation of materials at atomic, molecular and macromolecular scales, where properties differ significantly from those at a larger scale (The Royal Society and The Royal Academy of Engineering (2004)).
NIOSH	National Institute for Occupational Safety and Health
Non-food consumer products	Products which are not food and which are bought by consumers for personal use.
Novel food	Foodstuffs and ingredients which were not used in significant amounts for human consumption in the European Community before 15 May 1997.
OECD	Organisation for Economic Co-operation and Development
Oral	Via the mouth
Partition coefficient	The ratio of the concentration of a substance in air or in water to the concentration of that substance in particles where sorption or adsorption has taken place. Examples include the sediment-water and the soil-water partition coefficients, but a partition coefficient for water and the carbon dissolved in the water can also be defined. A partition coefficient can also be defined for water and certain compounds found in the soil or sediment. A commonly used example for hydrophobic organic substances is the partition coefficient of a substance between water and the organic carbon present in the soil or sediment.
PEC/PNEC	The ratio between the predicted concentration of a substance in the environment (on the basis of known information on the emission and behaviour of a substance in the environment) and the predicted concentration of a substance in the environment where no undesirable effects on the ecosystem may be expected from the substance. PEC is the abbreviation of Predicted Environmental Concentration, PNEC is the abbreviation of Predicted No Effect

	Concentration. A PEC/PNEC ratio of less than 1 means that no unwanted effects of the substance may be expected in the environment.
Persistent	Non-degradable.
Physico-chemical properties	Chemical properties of a substance become visible during a chemical reaction (e.g., pH, flammability), while the physical properties of a substance can be seen without changing the identity of the substance (e.g., solubility, density).
Point of entry	The place in the body where nanomaterials are taken up. When a substance passes a point of entry internal exposure or uptake is said to have occurred. Possible points of entry include the airways (inhalatory), the skin (dermal) and the gastro-intestinal tract (oral).
Quantum dot	Minute structure which due to its small dimensions exhibits special quantum properties (e.g., the direction in which an elementary nanoparticle spins on its axis) and where the addition or removal of a single electron can result in a significant change.
R&D	Research and Development
REACH	Registration, Evaluation, Authorization and restriction of CHemicals
RES	Reticulo Endothelial System: the system in the body which filters out and destroys bacteria, dead tissue and harmful substances.
Research and Development	often abbreviated to R&D
RFID	Radio Frequency IDentification, identification with radio waves.
RIKILT	Netherlands Institute of Food Safety
Risk	In the context of toxicology the term risk is considered as a combination of toxicity and exposure to a substance. A certain dose of a substance (in this case, nanoparticles) will lead to harmful effects (toxicity). Thus to actually be at risk, an organism must first actually be exposed to such a dose.
Risk assessment	The estimation of the risk to humans or the environment, including the associated uncertainties, further to exposure to a substance.
Risk management	Decision-making process in which political, social, economic and technical considerations are balanced against relevant information from the risk assessment in order to arrive at suitable measures to manage the risk.
RIVM	National Institute for Public Health and the Environment
RIZA	Institute for Inland Water Management and Waste Water Treatment (merged into the Water Service of the Directorate-General for Public Works and Water Management (RWS) in November 2007)
Roadmap	A detailed plan for a process in which goals and steps of action are set out in a schedule.
SCCP	Scientific Committee on Consumer Protection
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
Sediment	Bed of river, sea or other body of water.
Sedimentation	The deposition or settling of particles out of the air onto the soil or to water, or from water onto the watercourse bed. Sediment is the soil on the bed of the watercourse or body of water.
SETAC	Society of Environmental Toxicology and Chemistry
SME	Small and medium-sized enterprises

Source	The source of exposure to nanomaterials, such as a consumer product, a medicine, the environment or the workplace (in the context of human risks) and a production facility or waste (in the context of environmental risks).
Substance	Chemical element and its compounds in a natural state or obtained through some kind of production process, including any additives necessary to maintain stability and impurities originating from the procedure, but excluding solvents which can be removed without affecting the stability or changing the composition.
Systemic / local toxicity	Harmful effects of a substance which occur in a different location than where the body came into contact with the substance, which implies that the substance has been absorbed by the body. This is unlike local toxicity where effects occur at the place where the body was exposed to the substance.
SZW	Ministry of Social Affairs and Employment
TI Pharma	Top Institute Pharma
Tissue engineering	The production of natural or synthetic organs and tissues which can be implanted as fully functional units or which further to implantation grow to become units which perform essential functions.
TNO	Netherlands Organization for Applied Scientific Research
Toxicity	Harmful effects of a substance.
Toxicokinetic	See kinetic
TU Delft	Delft University of Technology
Ultrafine particles	Particles with a size of 0.1 – 100 micrometres (μm) in one or more dimensions.
VWA	Netherlands Food and Consumer Product Safety Authority
VWS	Ministry of Health, Welfare and Sport
WPMN	Working Party on Manufactured Nanomaterials. OECD Working Group looking at the risks of nanotechnology.
WPN	Working Party on Nanotechnology. OECD Working Group looking at the applications of nanotechnology.
WUR	Wageningen University and Research Centre

Annex 1: Research on applications

Application areas

Many different application areas for nanotechnology can be identified, including materials science, energy supply, environmental technology (e.g., water treatment), electronics, pharmaceuticals, medical technology, foodstuffs and military applications. A large proportion of the potential nanotechnology applications are currently still in the research and development phase and are not yet actually in use. Nevertheless, there are already nanotechnology applications on the market. These include the improvement of materials (e.g., scratch-resistant and anti-bacterial coatings), electronic components and products such as sunscreen creams. The Woodrow Wilson Institute in America has a public database of products in which manufactured nanoparticles have been used (www.nanotechproject.org). This database provides an extensive overview of available products, but is not exhaustive.

In general, it may be said that specific market applications of nanotechnology are difficult to identify. The designation 'nano' is regularly used in product names, although this does not necessarily mean that nanoparticles have been deliberately used. This form of marketing using the term 'nano' is now declining. But it is also possible that nanoparticles are included in products while this is not stated on the packaging. Consultants are doing research on the current status in terms of the development and market applications of nanotechnology. In general, the cost of such research and the resulting reports is expensive, while the quality is unclear. Mandatory labelling of products in which nanomaterials have been incorporated is a possible way of providing consumers with better information. The government in France intends to introduce labelling for nano products (that include nanomaterials with at least one dimension <100 nm). There are no such initiatives in other countries at this time.

Nanotechnology research and development now and in the future

Nanotechnology is developing in overlapping phases of research, development and application. The products made with the aid of nanotechnology can be divided into four generations.

The *first generation* nanotechnology is now already available. This generation of nanotechnologies covers passive nanostructures: materials with fixed structures and functions which are often used as a component in a product. The first generation nanoparticles currently on the market are often particles which have been added to already existing products (e.g., consumer products). These include nanocoatings, nanostructured metals, metal oxides, polymers, carbon nanotubes and ceramic materials.

Certain products which fall under *second generation* nanotechnology are also currently on the market. This generation covers active nanostructures with properties which change during use, such as size, form or conductivity. Examples of these are 3D transistors, amplifiers and targeted drug delivery.

Third generation nanotechnology, which is expected to come onto the market after 2010, consists of integrated nanosystems or 'systems of nanosystems'. It is expected that this generation of synthesis and assembly techniques will enable multi-scale chemical and bio-assembly, nanoscale networks and hierarchical architectures (IRGC, 2006).

Fourth generation nanotechnology is expected to appear on the market after 2015. In this generation nanotechnology will include heterogenous molecular nanosystems. In these systems or networks, the components are reduced to molecular and supramolecular structures which operate as separate devices.

Computers and robots could be reduced to extremely small dimensions and new types of genetic therapies could be developed.

The nanomaterials used in products that are now already on the market mainly come under the first generation of nanotechnologies. It is estimated that in 2007 there were more than 600 consumer products on the market in which nanotechnology had been used and more than 1000 intermediary materials and components. While R&D is already engaged in the development of fourth generation nanotechnology, risk research is still mainly aimed at the first generation. The risk research in this respect therefore clearly lags behind the research and development of nanotechnology itself.

Research and development in the Netherlands

The government paper on nanotechnologies (Netherlands' government, 2006) states that the Netherlands plays an 'important leading role in the field of nanotechnologies'. There is superior scientific knowledge available in the Netherlands, for example, and a number of companies based in the Netherlands, including AKZO-Nobel, ASML, DSM, FEI and Philips, play an important part in the field of nanotechnology. In the food industry this includes companies such as Friesland Foods, Campina, Numico and Unilever.

A considerable proportion of the large companies undertaking major R&D work in the Netherlands (at least 13 out of the top 20) are involved in research in the field of nanotechnology. Besides these large companies there are also a number of start-ups and SMEs occupied with nanotechnology (Netherlands' government, 2006). To some extent, these are spin-offs from research programmes and research institutes. MESA+ (University of Twente), for example, has 30 spin-offs.

Besides nanotechnology research and development in industry and research institutes, research and development has also taken place under the auspices of the Netherlands Organisation for Scientific Research (NWO) and NanoNed, for example (NanoNed, 2008).

- Netherlands Organisation for Scientific Research (NWO): In the NWO Strategy Document 2007-2010 nanotechnology is referred to as one of the spearheads for Dutch scientific research. The FOM Institute for Fundamental Research on Matter and Technology Foundation STW are investing in nanotechnology research (mainly fundamental research). NWO is also taking part in European research.
- NanoNed was set up in 2002 by MESA+, the Kavli Institute in Delft and BioMaDe in Grongingen, and is a consortium of seven universities, TNO and Philips. NanoNed has 11 flagship programmes (aimed at scientific research) a technology assessment programme and a virtual nano lab (a sophisticated nanotechnology infrastructure). Under NanoNed some 200 research programmes have been facilitated.

There are also a large number of public-private initiatives in which various stakeholders (government, industry, academia) work together.

The nanotechnology strategic research agenda of the NNI (Netherlands Nano Initiative) will be published in the autumn of 2008. NNI is the successor to the NanoNed research programme. The NNI agenda will indicate how investment in research and development will take place in the coming years. The NNI agenda (in preparation) will be dedicated to the following themes:

- Beyond Moore (micro-electronics on a nanoscale);
- Nanomedicine;
- Energy supply;
- Food and healthcare;

- Water treatment;
- Nanomaterials;
- Risks and toxicology of nanotechnology.

The first five areas correspond with the priority research themes referred to in the government paper on nanotechnologies (Netherlands' government, 2006). The government paper also mentioned the topic of 'functional nanoparticle surfaces with nanoscale patterns' as a main research priority.

In 2003 the Netherlands ranked sixth worldwide in the area of government spending on nanotechnologies per capita population. Partly because of 'considerable government investment' this country has a highly sophisticated research infrastructure. Research by Borm et al. (2008) identified the number of companies in the Netherlands working with nanotechnology.

International research and development

Nanotechnologies cover a very wide area which is developing rapidly. This makes it difficult to estimate the present and future size of the worldwide nanotechnology market and investment in nanotechnology research and development. The extent of the research, development, market and other applications of nanotechnology are an important economic factor which will be considered by NNI. Governments worldwide and the EU too, are investing in it.

Annex 2: Nanotechnology and 'Coping rationally with risks'

The government paper entitled 'Kabinetsvisie nanotechnologieën - van klein naar groots' [The Dutch government's vision on nanotechnologies - from small to great] (Netherlands' government, 2006) sets out the course that the government wishes to take in the innovation and development of nanotechnologies, as well as in relation to dealing with the risks of nanotechnologies. The government's vision on the subject can be summarised as follows:

> *Nanotechnologies are new technologies on which a great deal of research is already being carried out worldwide and which are increasingly being applied. It is important that the Netherlands be a part of this and thus not only tries to keep up in terms of knowledge but is also among those at the vanguard. Furthermore we must bear in mind the potential risks attached to nanotechnologies. Only by carefully dealing with the risks can the Netherlands take full benefit from the opportunities (Netherlands' government, 2006).*

As this vision suggests, these opportunities lie in the area of promoting a good research climate, strengthening the ability of industry to compete, and for society in areas such as healthcare, safety (protection), and the environment. The aim of the government paper is to 'indicate whether the frameworks which are necessary for responsible development are adequate, or whether they should be modified or updated' (Netherlands' government, 2006).

One of the main themes in the government paper is the topic of 'coping with risks'. For which, among other things, the current legislation in force was considered. As the government sees it, the general principles of the current regulatory framework also apply to the risks of manufactured nanoparticles (see Annex 4). However, for the purposes of supervision and enforcement the knowledge gaps are still too great. As long as there are no suitable and manageable measuring methods in place, for example, supervision, compliance and enforcement remain difficult to implement. According to the government paper, both government and industry need to have more information available, a common framework of understanding needs to be developed, standardisation needs to take place and standard methods for measurement and risk evaluation need to be developed. For the purpose of developing and exchanging knowledge and expertise, an internationally coordinated research effort will be required.

For policy in the area of risk management the Ministry of Housing, Spatial Planning and the Environment (VROM) policy document 'Coping Rationally with Risks' provides a starting point. This policy document deals with 'risk governance' in the context of the Netherlands. In Coping Rationally with Risks a number of problems are referred to concerning political decision-making about risks, including the assignment of responsibilities and the role of risk perception. In its efforts to manage the risks of nanotechnologies, the government will apply the principles in the VROM policy document (2004) (see also Chapter 1).

In addition, a number of international Codes of Conduct are being or have now been formulated for various target groups (EC, 2007; ICCA, 2007; Responsible Nano Code, 2008; VCI/BAUA, 2008). In Coping Rationally with Risks reference is made to the precautionary principle as set out in the Rio Declaration (Agenda 21):

The precautionary principle was incorporated in Principle 15 of the Rio Declaration: 'In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation'. The precautionary principle is also seen as 'a strategy for risk management, if there are reasonable grounds for concern that potential hazards may affect the environment or human, animal and plant health, and when at the same time the available data preclude a detailed risk evaluation' (VROM, 2004).

This policy document also makes reference to the principles formulated by the EU for the application of the precautionary principle:

'The implementation of an approach based on the precautionary principle must be based on three specific principles:

- the application of the principle must be based on a scientific evaluation which is as complete as possible. This should, where possible, identify the degree of scientific uncertainty at each stage;
- every decision on whether or not to act on the basis of the precautionary principle must be preceded by an examination of the risk and the potential consequences of inaction;
- as soon as the results of the scientific evaluation and/or risk evaluation are available, all the interested parties should be involved in the study of the various options and the procedure should be as transparent as possible' (VROM, 2004).

The government paper on nanotechnologies listed the following points for the 'risk management agenda':

1. Expanding knowledge on the applications and risks of nanoparticles (based on a common and international risk management process, together with industry and the scientific community);
2. The application of the precautionary principle with a sense of proportion. A moratorium on nanotechnology and nanoscience would be undesirable from the point of view of proportion. For each application it must be determined whether extensive research is necessary prior to market introduction or whether other measures are necessary;
3. Metrology and standardisation. These are matters which are seen as essential by the government to be able to enforce legislation.

The theme of 'coping with risks' was further elaborated on in the letter which the Minister of Housing, Spatial Planning and the Environment, Mrs. Jacqueline Cramer, submitted to the Lower House of Netherlands' Parliament in February 2008. The government's aim, as set out in this letter, is 'ultimately to reach a situation in which humans and the environment run little or no risk due to the use of nanotechnology'. To achieve this, an approach will be adopted which was described as 'nanoparticles will be treated with caution, care and common sense' (Lower House of Netherlands' Parliament, 2008). The letter referred, among other things, to the following activities which have been initiated in the Netherlands or to which the Netherlands is actively contributing:

- Drawing up a global knowledge agenda on assessment methods in the context of the OECD-WPMN. The international knowledge gaps are being identified by some eight working groups. The knowledge agenda will be published in September 2008. One of the topics which this will cover is regulation (both mandatory and voluntary) to obtain information on products;

- The compilation of the global knowledge agenda on standardisation will take place in the context of the ISO;
- In the EU context, efforts will be made to make the regulatory framework more enforceable and easier to implement. A national legislation survey will also be started to look at how substances and nanosubstances can be assessed and regulated;
- Investment in national surveys and research on the risks of nanotechnology;
- Publication of the Nanotechnology Action Plan (Lower House of Netherlands' Parliament, 2008);
- Setting up a stakeholder consultative body:
    - Consultation with trade and industry about the way in which the private sector meets its responsibilities in relation to the safety of processes and products, as well as to arrive at a joint approach to making the risks manageable;
    - The government is counting on reaching agreement with the private sector about generating and sharing information and knowledge. The government also hopes to reach agreement with the private sector on openness, and expects that the private sector will commit to investing in risk research and risk communication with third parties;
    - Consultation with civil organisations (which are currently often still in a start-up phase and are still defining their position and mission);
- The publication of the Coping with the Risks of Nanoparticles policy document in the second half of 2008.

Annex 3: European policy

The essence of the EU nanotechnology policy is an 'integrated, safe and responsible approach'. The EU strategy in the area of nanotechnology is set out in 'Nanosciences and nanotechnologies:
An action plan for Europe 2005-2009'. The EU strategy covers the following main areas (EC, 2007):

- *Research, development and innovation.* The EU invests in research and development in the field of nanotechnology, also in the context of European Framework Programmes;
- *Infrastructure and European poles of excellence.* Under Framework Programme 7 (FP7) access to and the development of research infrastructures will be supported. One of the projects of the European Strategy Forum on Research Infrastructures (ESFRI) is to set up a Pan-European Infrastructure for Nanostructures and Nanoelectronics. An infrastructure for nanobiotechnology may also be set up;
- *Interdisciplinary human resources*. Nanotechnologies will benefit from an interdisciplinary approach. Such an approach will mean that changes in certain traditional forms of education and training will be necessary. The Commission is active in the area of new education programmes and activities aimed at promoting the mobility and training of researchers. Attention will be devoted to education and training in nanotechnology in various ways;
- *Industrial innovation*. The Commission's aim is to enhance the competitive strength of European industry. In the first place, this should take place through knowledge generation in order to make the shift from being a 'resource intensive' industry to a 'knowledge intensive' industry. Research and support for the development of new applications generated by interaction between different technologies and disciplines should also contribute to this. The Commission will encourage industry, and in particular SMEs, to take part in R&D cooperation projects under FP7. Under FP7 there is more focus on the R&D needs of companies. Further, various other measures are being taken to foster innovation, including the creation of financial facilities for nanotechnology research and development by companies, to set up programmes to support innovation, and to support the development of roadmaps which lead to industrial applications. Standardisation is an important area for industrial innovation. The Commission plays an important part in the CEN and ISO standardisation bodies. In the European context, existing standards are evaluated and pre-normative research is promoted;
- *Integrating the societal dimension.* The Commission considers public acceptance as an important aspect of the development of nanotechnology. Nanotechnologies should be applied in a safe manner and lead to useful products and services, but, the Commission states, there must also be consensus on the overall impact of nanotechnologies. The benefits, risks and necessary measures should be fully and accurately presented and public debate should be encouraged. The Commission has taken a number of steps in this respect. For example, information material has been published, a 'survival kit for scientists' on the subject of communication has been published, a method for public debate has been investigated and calls have been made to set up a European network to look at the ethical aspects of *nanomedicine*;
- *Public health, safety and environmental and consumer protection.* The aim of the Commission in this area is to enable the safe development and safe use of nanotechnologies and to ensure that the public can exploit the benefits but is also protected from undesirable effects of nanotechnologies. To achieve this steps are being taken in the following areas:
    - Drawing up an overview of the current regulatory framework to establish whether changes need to be made to it in order to cover the risks of nanomaterials. The options

available to authorities to be able to intervene if it appears that products already on the market lead to risks, will also be considered as part of this process;
    - The identification of knowledge gaps in the area of the potential risks, exposure during the life cycle, research methods and methods for measuring and characterising nanomaterials. SCENIHR has adopted an opinion document which indicates that there are a number of gaps in the area of methods for the risk assessment of nanomaterials;
    - Research on safety aspects, with the aim of supporting risk assessment at an early stage, the closing of knowledge gaps and providing a basis to be able to meet the regulatory requirements in this area;
    - International cooperation in the fields of health and the environment, as well as in the contexts of ISO and OECD-WPMN.
- *International cooperation (general),* also in the area of international economic relations.

One of the current FP7 projects is setting up the 'EU Nano Observatory': a European Observatory for scientific and economic analysis of nanotechnologies to promote exchange among the relevant stakeholders on the benefits and opportunities offered by nanotechnologies (bearing in mind the barriers and risks). The purpose of this Observatory is to establish a permanent European Observatory on nanotechnologies to provide constant and independent support to decision-makers. The Observatory will, in due course, provide data on and analysis of scientific and economic trends, market analyses, assessments of ethical and societal matters, information on environmental and health risks and information on legislation and standardisation. The British IoN (Institute of Nanotechnology) will coordinate the setting up of the Observatory (www.observatorynano.eu).

Annex 4: The regulatory framework

In the government paper on nanotechnologies it was stated that: 'the general principles in the area of relevant legislation for dealing with risks apply in full to the risks of manufactured nanoparticles', (Netherlands' government, 2006). Further to the report 'Health significance of nanotechnologies' by the Health Council of the Netherlands (2006), the government will 'as far as possible apply the existing legislation and continually review whether changes to the regulatory framework are necessary to manage the potential risks.' Besides the European REACH legislation, in the Netherlands the following legislation applies to nanotechnologies:

- The Health and Safety Act (Arbowet). This prescribes that the employer must provide a safe and healthy workplace;
- The Consumer Goods Act (for food and non-food);
- Pesticides act;
- Animal Feed Act;
- Medicines Act and other legislation on drugs and pharmaceuticals.

The European Commission has evaluated the present regulatory framework in light of the potential risks of nanotechnologies (EC, 2008). An initial finding is that, in principle, the present legislation addresses concerns about the possible impact of nanotechnologies on health and the environment. Changes to the legislation may be proposed on the basis of scientific developments, or if there is a clear need for this in specific areas. The Commission states however that improving the implementation of the present regulatory framework will be the primary means of guaranteeing health, safety and the environment. The Commission recommends that in the meantime existing methods for risk assessment should be applied on a case-by-case basis (given the constant stream of data which is being generated). If necessary existing regulatory mechanisms can be applied 'in relation to thresholds, authorisation of substances and ingredients, qualification of waste as hazardous, reinforcing conformity assessment procedures, introducing restrictions on the marketing and use of chemical substances and preparations, and so on' (EC, 2007).

Classification and labelling

In general, the classification and labelling (C&L) of substances is based on the potential 'hazard' (toxicity). On the basis of the C&L of substances a certain form of risk management is applied in the production, storage and transport of these substances. Labelling is a powerful tool for risk management. There is, at present, no separate label for nanoparticles and it is still unclear how nanoparticles can be labelled under the present classification and labelling system (the Global Harmonized System). To be able to classify and label nanomaterials information is required, among other things, on the toxicological properties. Such information is currently often available for the same chemical substances not in nano form, but once in nano form these substances could have different toxicological properties and potential. Because the present toxicity tests may not be adequate to determine the hazard of nanoparticles and engineered nanoparticles, for the time being classification and labelling would appear to be difficult to substantiate.

General regulatory principles: REACH

REACH (Registration, Evaluation, Authorization and restriction of Chemicals), the European legislation in the area of chemical substances, provides an overarching framework for the regulation of substances. Substances in nano form are essentially also covered by REACH. The basic principle is

therefore that the production, risk assessment and regulation of nanomaterials will take place in accordance with REACH methods. At present it is open to question whether, in their present form, the tests and methods which can currently be used for REACH are appropriate and suitable enough to apply to nanomaterials. Under REACH, depending on tonnage level and use, the producer or importer must ensure that a separate dossier is supplied to the European Chemicals Agency (ECHA) for each substance. The present level of production of nanoparticles, however, will probably often remain below the REACH tonnage thresholds, and therefore registration will not be required. There are also questions relating to the classification of nanoparticles, not least because particles of the same substance in different sizes may well have different properties (toxic or otherwise). The possibility of making nanomaterials subject to REACH is currently being evaluated in consultation by the competent authorities.

The underlying principle of REACH is that industry itself is primarily responsible for the safety of the production, import and use of substances. REACH is therefore primarily based on the mechanism of market regulation. This means that companies themselves are responsible for the classification and labelling of the substances which they produce, assessment of the risks related to the use of these substances and taking adequate measures to manage these risks. Depending on the type of particle and the volume, certain requirements have been set with regard to the information which must be provided by companies and any other measures which should be taken. This information is recorded in a dossier which is held by the ECHA. The ECHA makes relevant information public and certain confidential information is made available to national authorities. The manufacturer or importer must indicate what the substance is used for (including downstream). This can mean that specific applications of nanotechnology must also be registered as such. The use and exposure scenarios (with and without risk assessment, depending on tonnage level and hazard) thus offer a possible starting point for the authorities to obtain more information. It is debatable how detailed and specific exposure scenarios provided by manufacturers can be (given that in general, little is yet known about exposure). For example: if two nanoparticles have a different size (but the same chemical composition), does this mean that the manufacturer must also make a distinction between them? At present, however, there is still too little known about the toxicity and other characteristics (including physico-chemical properties) of nanoparticles with different sizes.

If it turns out that in certain cases the mechanism of market regulation does not lead to an adequate level of safety, or if substances (or certain applications of substances) are not desirable from a safety point of view, then the competent authorities can introduce measures. These could be measures such as legal requirements or banning provisions, or harmonisation of the classification and labelling of substances. Under REACH the government has the option of proposing and justifying measures (through the use of ‘Annex XV’ procedures).

The private sector is primarily responsible for safe practices, but it is a government task to indicate what possible risks of substances should be determined: the question of whether and in what way regulation should take place is a political / societal one. The question of whether nanoparticles fit within the present framework and whether this framework may need modification is also ultimately a matter of political consideration about how we wish to deal with risks.

Annex 5: Public acceptance

In the area of nanotechnology there are fundamental questions at stake which have an inherent public interest attached to them. These questions relate to the opportunities as well as the potential risks of nanotechnology. Given that the future impact on society of nanotechnologies is expected to be great but that at the moment they are surrounded by many uncertainties, governments attach great importance to the pursuit of dialogue with the general public and stakeholders in society on the developments taking place in the field of nanotechnology. Past experience with the public debate on genetically modified organisms, for example, has shown that the early involvement of stakeholders and the general public in the development of possibly controversial technologies is desirable, not least from the point of view of public acceptance.

European research dating from 2005 pointed out that at that time 44% of the population in Europe had heard of the term 'nanotechnology' (Gaskell et al., 2006). Nanotechnology is predominantly found to be morally acceptable and useful, and the majority of respondents indicated that they did not see nanotechnology as something risky. Given the strong growth in the field and the fact that the public debate has just started to get going, it is quite possible that this view could change in the future. Civil organisations are currently still defining their position and mission (Lower House of Netherlands' Parliament, 2008), but critical comments on the subject of nanotechnology appear to be on the increase. Civil organisations, including NGOs, are increasingly demanding transparency about the risks of nanotechnology.

The Dutch government in its government paper on nanotechnologies indicated that it 'intends to work on public acceptance of nanotechnologies through entering into dialogue with the general public' (Netherlands' government, 2006). Also in line with the findings and recommendations of the Rathenau Institute (http://www.rathenau.nl/) and the Health Council of the Netherlands (2006), as well as the principles of risk management (transparency, clear allocation of responsibilities, early involvement of stakeholders; see also Chapter 7), the government intends to initiate a stakeholder process in the near future.

For this purpose a broad representation of stakeholders needs to be involved. The aim of such a process is to gain insight into potential problems in the area of public acceptance and identify ways of increasing public confidence. Private citizens can also contribute relevant information for policy and future research. The following possible topics to be addressed were indicated in the government paper (Netherlands' government, 2006):

- the toxicity and ecotoxicity of nanoparticles and their risks in the areas of occupational safety, food, consumer products, healthcare and the environment;
- issues relating to medical ethics, as referred to in the report of the Health Council of the Netherlands 'Health significance of nanotechnologies' (Health Council of the Netherlands, 2006);
- privacy and civil rights in relation to the increased monitoring possibilities, issues concerning military applications, long term impact on the gap between rich and poor and the unpredictable effects of convergence between nanotechnologies, ICT and biotechnology.

First and second generation nanotechnologies will probably raise relatively few ethical questions. It may be expected that third and fourth generation nanotechnologies (e.g., bio-assembly, minute robots

and computers, and genetic therapies) will be more likely to raise ethical questions, for example, on privacy and in the area of medical ethics. In the Netherlands the Rathenau Institute (http://www.rathenau.nl/) is active in the area of the societal aspects and public opinion on the subject of nanotechnology. This institute will be initiating a public dialogue on this topic in the future. The European Commission has also indicated that it attaches value to starting a dialogue process in society at large: 'With the intention to strengthen a culture of responsibility, the EC has launched a public consultation to contribute to the definition of some basic principles for the responsible governance of nanotechnology research.' (EC 2007, 2008).

Annex 6: Exposure aspects of nanomaterials

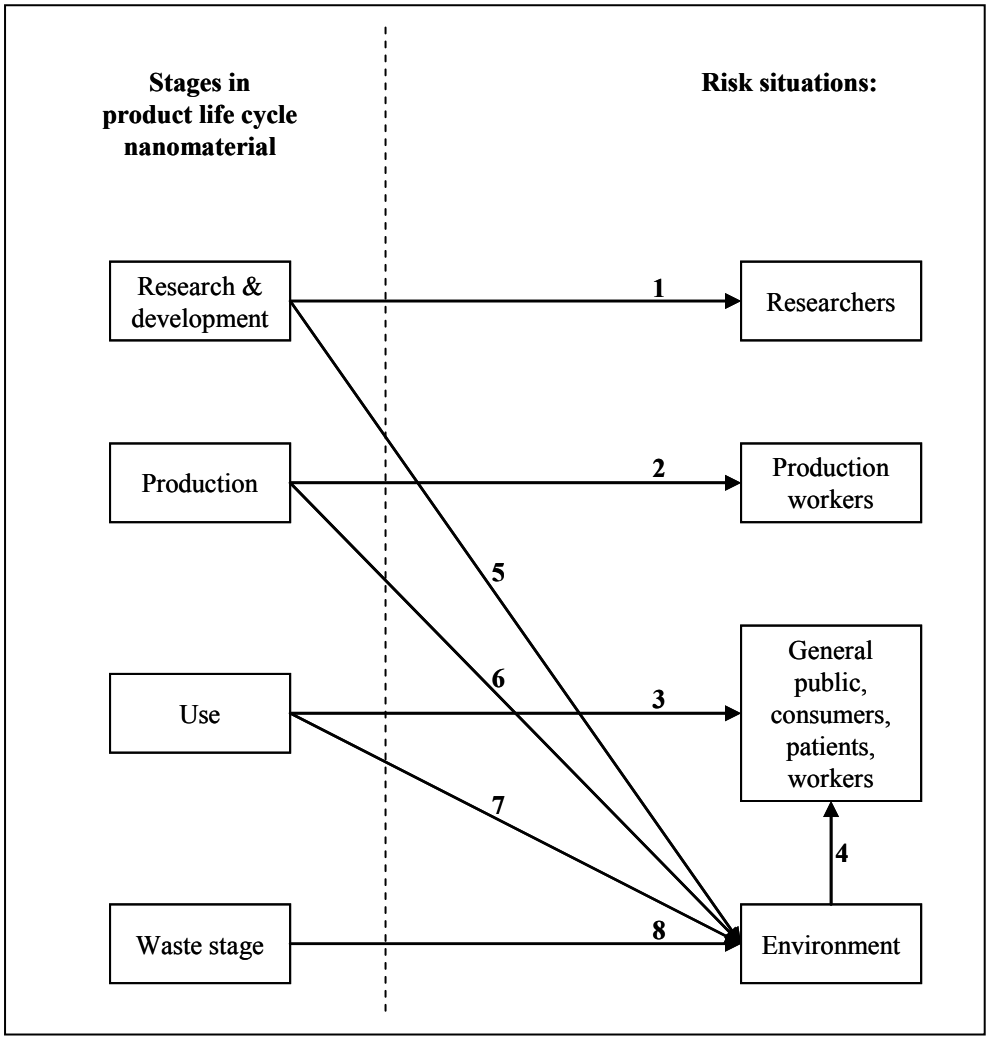

Figure B6.1: Risk situations in relation to the stages (phases) in the product life cycle of a nanomaterial. Different types of risk situations can occur per phase. Eight exposure routes have been identified, 4 of which are human (1-4) and 4 environmental (5-8). This system has been applied in Table B6.1.

Table B6.1: Qualitative estimate of human *exposure* per risk situation and application area

Risk situation	Occurrence / concentration	Behaviour (what is done with the substance or product)	External dose (external exposure)
1 (researchers)	- Nanoparticles can occur in the working environment and in work and production processes. - This could in principle relate to all types of particles in all possible media. - This could involve less well defined and controlled and potentially risky particles (also when risk research is carried out).	- Laboratory research for the purposes of R&D and risk research - Experimental and other manufacture of nanoparticles - Frequent and long term contact are essentially possible	- Potentially high - Exposure may be oral, inhalatory, and dermal. - Dose is not necessarily controlled
2 (production workers)		- Production of nanoparticles (control/implementation of production processes) - Application of nanoparticles in production processes / products - Frequent and long term contact are essentially possible	- Potentially high, particularly in packaging, transfer and cleaning. - Exposure may be oral, inhalatory, and dermal. - Dose is not necessarily controlled
3 (general public)	Pharmaceuticals: - Nanoparticles are used in various types of medicines, including drug delivery and in nanocrystal form, in liquid and solid media. - These are clearly defined nanomaterials in a controlled form due to strict admittance procedures which should be followed.	-Nanomedicines are intentionally ingested or administered. - Frequency and duration of contact may be high, depending on prescription. - Behaviour component is less important compared to other consumer applications	- Dose is highly controlled /measured and may be high. - Exposure may be oral, inhalatory, dermal and via injection.
	Medical technology: - Application of free particles, e.g., in wound dressings, biosensors, contrast media and therapies: generally solid media - Admittance of possibly risky applications takes place only after following a strict procedure. Particles in these applications are clearly defined and controlled. - Admittance of less risky applications is more decentralised and less strictly controlled	- Intentionally introduced into the body or applied externally. - Contact may be very long lasting in the case of implants (from which free particles could be released). - Contact for other applications is relatively shorter with a relatively low frequency	Dose / exposure to free nanoparticles will generally be small for medical technologies, except in the event of deliberate introduction into the body of free particles. - Exposure may be oral, dermal, via injection and implantation. - Dose is relatively controlled.

Table B6.1 - Continued

Risk situation	Occurrence / concentration	Behaviour (what is done with the substance or product)	External dose (external exposure)
3. (general public) (continued)	Food applications: - Free and insoluble nanoparticles are used as an additive in food, and could end up in food from packaging or sensors. - Particles can occur in liquid and solid media - Unwanted nanomaterials such as nano crop protection products could occur in food - In general, it is relatively unclear on what products these are used and what particles they contain - Particles in food are often not clearly defined or strictly controlled	Foods with nanoparticles are deliberately ingested, albeit that it is not always clear what particles can be found in what product (less deliberate than for medicines) - Consumers could unintentionally come into contact with nanoparticles through packaging with nanoparticles and nanoparticles from other applications which are not intended for consumption. - Frequent and long lasting contact is possible.	Mainly oral exposure - Potentially high in the case of nanoparticles added to food. - Exposure to nano crop protection agents on / in food could possibly occur - Exposure to particles from packaging or sensors is possible, but this will generally not be high - Dose is not controlled
	Consumer products: - Nanoparticles are used in all sorts of products, in fluid and solid media, and in sprays - In general, it is relatively unclear in which products these are used and what particles they contain - Particles are often not clearly defined or strictly controlled (in any case there is no information on this)	- All kinds of application methods, such as application to skin (cosmetics and sunscreen cream), hair colouring, use of toothpaste, use of cleaning agents, use of spray - Very frequent contact is possible, duration of contact will often be limited but can also be high (e.g., in the case of cosmetics)	Exposure may be oral, inhalatory, and dermal, depending on the application. - With certain applications potentially high doses may be involved, e.g., when sprays and creams are used. - Dose is not controlled
	Professional applications	- Use of products containing nanomaterials in the working environment - Frequent and long lasting contact are essentially possible	Potentially high - Exposure may be oral, inhalatory, and dermal. - Dose is essentially not controlled.
4 (via the environment)	- Deliberately manufactured nanoparticles can occur in the environment in air, water, soil and sediment - Particles are not controlled / defined - Actual occurrence of these nanoparticles in the environment is unknown - Occurrence in air, water and soil is relevant for potential human risks - Concentrations are expected to be low	- Breathing in air with nanoparticles - Swallowing water with nanoparticles - Eating produce grown in soil in which there were nanoparticles - Frequent and long lasting contact are essentially possible	- Mainly oral and inhalatory exposure are possible - At present only low or very low doses are expected in relation to deliberately manufactured nanoparticles - Dose is not controlled

Table B6.2: Qualitative estimate of environmental *risks* per risk situation and application area (see Figure B6.1 for routes 5-8).

risk situation	Emission		Occurence/concentration in air, water, soil and sediment	Behaviour (of a compound in the environment)	Dose (external exposure)	Internal exposure	Effect
5 (R&D)	Unclear, probably low	**air**	Actual occurence in the environment is unknown: no standard monitoring of nanoparticles in the environment	- Little known - Possible aerosol forming and then distribution over great distances	Little or nothing known		
6 (production)	Possibly through water, waste water and air, not expected to be relatively high. Probably comparatively high emissions of free nanoparticles						
7 (use)	Emissions to air (and thereafter to other compartments): e.g., as additive to fuel	**water**		- Nanoparticles are persistent contaminants - Small particles hardly settle - Flocculation behaviour is still difficult to predict	Possible effects on aquatic organisms		
	Consumer products and professionally applied products (such as sunscreen, cleaning products and cosmetics): relatively high emissions to water expected	**soil**		- Nanoparticles in the soil will be subject to the processes of degradation and adsorption - Nanoparticles could be responsible for adsorption of other substances	- Direct effects on soil organisms possible - Possible effects due to degradation products of nanoparticles		
	Products which are deliberately introduced into the environment (e.g., catalysts for water treatment): emsision to water and soil						
8 (waste)	Possible emissions to water and thereafter to other compartments, e.g., in anti-bacterial applications and (to a limited extent) in packaging	**sediment**		- Adsorption - Degradation - Possible further dispersion due to advection	Possible effects on bottom-dwelling and sediment organisms		

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