Health significance of nanotechnologies

Gezondheidsraad
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport
PO Box 20350
2500 EJ The Hague, The Netherlands

Subject : Presentation of advisory report 'Health significance of nanotechnologies'
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Dear Minister,

Nanoscience and nanotechnologies have for sometime been a focal point of interest. They are making an entry in a wide range of fields throughout society. Not least among these are the fields on which the Health Council has long provided advice, namely public health, nutrition and the environment. Nanotechnologies have the potential to bring about major changes in human health and may result in considerable alterations in the entire healthcare system. The subject was therefore included in the Health Council's Work Programme for 2004. I hereby present the advisory report that resulted from this. It has been drafted by a Health Council Committee which I established especially for that purpose. It has been assessed by the Standing Committee on Medicine, the Standing Committee on Health and the Environment, and the Standing Committee on Medical Ethics and Health Law.

In its advisory report, the Committee discusses the opportunities and threats that nanotechnologies present for human health. Insofar as they are connected with health, broader social consequences are also discussed. Because I also consider this advisory report to be relevant for other policy areas, I have also presented it today to your colleagues at the Ministry of Agriculture, Nature and Food Quality and the Ministry of Economic Affairs, as well as to the state secretaries of Housing, Spatial Planning and the Environment and of Social Affairs & Employment.

Yours faithfully,

Professor M. de Visser,
Vice-President

P.O.Box 16052
NL-2500 BB The Hague
Telephone +31 (70) 340 74 51
Telefax +31 (70) 340 75 23
E-mail: hfg.van.dijk@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 VX The Hague
The Netherlands
www.healthcouncil.nl

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to:

the Minister of Health, Welfare and Sport

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

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

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

The Health Council of the Netherlands is a member of INAHTA, the international network of health technology assessment (HTA) agencies that promotes and facilitates information exchange and collaboration among HTA agencies.

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Contents

Executive summary

In the present advisory report, a Committee of the Health Council of the Netherlands explores the significance of nanoscience and nanotechnologies for human health. Addressing the associated opportunities and risks for individuals and society at large, the report suggests how to manage far-reaching developments in these areas.

Nanoscience and nanotechnologies

Nanoscience and nanotechnologies represent a field of study that is currently attracting a great deal of attention. The prefix ‘nano’ refers to the nanometre (nm), one billionth of a metre. The unusual mechanical, optical, electrical, and magnetic properties exhibited by materials with dimensions in the range 100 nm down to around 0.1 nm (the size of a single atom) can differ markedly from the properties of the same materials at larger dimensions. In recent years, researchers have become increasingly adept at manipulating the shape and size of materials at the nanometre scale and have therefore been able to study and exploit these unusual properties.

In a 1959 lecture, physicist Richard Feynman was the first person to predict the opportunities presented by the manipulation of matter at the level of individual atoms and molecules. Although the term ‘nanotechnology’ was coined in 1974 by a Japanese engineer named Norio Taniguchi, it was the invention of the

Scanning Tunnelling Microscope (STM) in the early 1980s that sparked the field's development.

This was the first time that scientists had been able to resolve individual atoms and to move them around on a solid surface. It offered the prospect of eventually being able to build structures atom by atom, a process dubbed the 'bottom-up' approach. However, assembling larger structures from individual atoms and molecules is currently too laborious for industrial applications. Researchers are instead focusing on self-assembly, in which the specific properties of individual building blocks lead them to automatically take up the correct positions in complex structures. Nature contains a huge variety of nanostructures created by bottom-up processes. Besides being a source of knowledge of the forces and design principles that play a role in self-organisation, they are a source of inspiration for the development of entirely new nanostructures with novel functions. Lithographic techniques are also being used to create ever finer structures on or in the silicon wafers used in chip production. This process has been dubbed the 'top-down' approach.

The boundaries between the traditional scientific disciplines are rather indistinct at the molecular and atomic level. Nanoscience and nanotechnologies therefore provide a perfect field for multidisciplinary research, characterised by increasing collaboration between physicists, chemists, biologists and engineers. Nanotechnologies are enabling technologies: they facilitate progress in other areas of technology.

An enormous amount of research involving nanotechnologies is underway at present. The extensive range of nanomaterials currently being developed is impressive: films that are just one to a few atoms thick; nanotubes of carbon or inorganic compounds; inorganic nanowires; organic nanofibres; biopolymers; nanoparticles made of metals and metal oxides; carbon black (synthetic soot); fullerenes (spherical C60 molecules); dendrimers (spherical, highly branched organic polymers); and quantum dots (nanocrystals of semiconductor material). In larger-scale materials it is also possible to create nanopores. Numerous applications are being developed for each of these materials in a wide range of fields. Some materials are already being used on a commercial scale. Carbon black, for instance, is used as a reinforcing-filler for rubber, while particles of titanium dioxide are used as UV reflectors in sunblock creams. However, most nanomaterials are not used routinely at present. Research and development account for most of the billions of euros spent on nanoscience and nanotechnologies around the world. Major efforts are under way in the Netherlands too, where various uni-

versities and companies are collaborating in government-funded research programmes, such as NanoNed, the country's national nanotechnology initiative.

Applications with health benefits

Nanotechnologies provide numerous new instruments for research into the basic biochemical and biophysical processes of both healthy and diseased cells. The resulting knowledge can be used as a basis for developing new prevention strategies and therapies. In addition, intensive research efforts are focusing on potential uses of nanotechnologies in practically every field of medicine. The current paucity of clinical applications is partially attributable to the strict safety requirements. Nevertheless, experts expect dramatic advances from 'nanomedicine' in the longer term (ten years or more).

The enormous increase in our knowledge of the human genome and proteins is making it easier to understand diseases in terms of anomalies at the molecular level. In theory, this provides opportunities for very early diagnosis and early treatment before the initial symptoms of the disease have appeared. Nanotechnologies offer the possibility of improving existing methods and instruments for *in vitro* detection of molecular biomarkers in patients' urine or tissue samples and for identifying pathogenic bacteria and viruses. These technologies are already leading to smaller, more compact and more sophisticated analytical instruments and cheap disposable components, thereby expanding opportunities for point-of-care applications involving simple tests that can be carried out in the doctor's surgery or the patient's home, even by patients themselves.

The use of novel contrast agents based on nanoparticles is improving existing imaging techniques for *in vivo* diagnosis. Iron oxide nanoparticles, for example, are currently being used in patients for both diagnosis and therapy. Nanotechnologies may lead to new, more effective medications, with fewer adverse effects. They may also prove useful in the search for new active substances. Since the 1970s, researchers have been trying to develop systems capable of transporting active substances to specific regions of the body. The small size of nanoparticles makes them perfect candidates for this. 'Stealth coatings', combined with targeted molecules and possibly contrast agents are expected to transform nanoparticles into 'magic bullets', which have been the goal of medical research for the past century. Although there is still a long way to go in this endeavour, the first anti-tumour and anti-fungal drugs using simple delivery systems are already being marketed.

Some nanoparticles can also function as active substances; tumour cells, for instance, can be killed by using an external energy source to heat injected nanoparticles. The effectiveness of this treatment is currently being assessed in patients.

Nanoparticles are also used to alter the physical and chemical properties of materials for medical applications ranging from wound dressings to implants. Silver nanoparticles for instance are antiseptic and are already used commercially in wound dressings. Attempts are being made to exploit similar properties in coatings for catheters, implants and bone cement. Passive implants, such as artificial hips, become more resistant to wear when their surfaces are given a nano-coating or nano-structure. These surface treatments improve the body's level of acceptance of the implants, as the modified surfaces more closely resemble the natural extra-cellular matrix, which has its own nanostructure. The nanostructured surface promotes surrounding tissue growth, which leads to improved and more durable bonding. Tissues cultured *in vitro* grow best on nanofibre scaffolds of collagen, for example. In laboratory animals, the injection of scaffold material has been shown to stimulate the *in vivo* regeneration of damaged nerve tissue. The same applies to active implants, such as cochlear implants, pacemakers and defibrillators. Nano-structuring of the electrode surface increases the area of contact with the surrounding tissue and prevents the formation of scar tissue, thereby facilitating a better and more sustainable signal transfer. Moreover, the energy storage capacity of the batteries used for the implants is steadily increasing, again thanks to nanotechnologies.

Human health could also benefit from the use of nanotechnologies in agriculture, the food sector, and environmental management. However, developments in this area are somewhat less advanced. Many possible applications are in keeping with those in the medical field, for example, the detection of pathogens and harmful substances, disinfection, and delivery systems for veterinary medicines and crop protection agents. Other uses include soil remediation and water purification.

Toxicological risks

The very properties that make nanoparticles so interesting from a technological perspective, such as their high degree of reactivity and ability to cross barriers, could also make them hazardous to humans and the environment. The present debate on the risks of nanotechnologies has largely focused on the potential dangers of nanoparticles.

Nanoparticles of various kinds occur naturally and ubiquitously in the environment. However, fossil-fuel combustion has considerably increased their vol-

ume in the air in recent centuries. It has been known for quite some time that fine air-borne dust particles can be harmful to human health. This applies not only to high concentrations in the workplace, but also to the relatively low air-borne concentrations in urban environments. Toxicological research has generated a great deal of knowledge of the relationship between the particles' physical and chemical properties and the mechanisms that underlie their adverse impact on health. However, our understanding of their interactions is still far from complete. With the rise of nanotechnologies, particle toxicologists have been increasingly focusing on the finest of dust particles, the nanoparticles. One concern is the extent to which our current knowledge of 'traditional' micro and nanoparticles is applicable when assessing the risks of newer types of synthetic nanoparticles. The latter category includes nanotubes, fullerenes, nanowires, quantum dots and particles used for drug delivery and diagnosis.

Research into 'traditional' particles has shown that fine dust particles readily penetrate deep into the lungs. Their minute size enables nanoparticles to bypass or damage the lungs' clearing mechanisms. Any such particles that are not readily dissolved or broken down tend to accumulate. Unlike larger particles, nanoparticles are capable of entering cells and disrupting cellular metabolism. From the lungs, they can enter the bloodstream, which then carries them to other organs. Nanoparticles may also be able to enter the brain via the nasal mucous membrane and the olfactory nerves. There is less clarity about the extent to which they are capable of entering the body through the skin (whether damaged or intact) and the digestive tract. Within the body, nanoparticles may promote the formation of harmful substances, such as reactive oxygen compounds. The particles also cause inflammatory reactions which, if chronic, can lead to elevated and harmful levels of immuno-reactive substances in the blood. These mechanisms may well be the reason for the observed relationship between the presence of fine dust in the air and disorders of the respiratory and circulatory systems in humans.

Initial toxicological studies of new synthetic nanoparticles indicate that these mechanisms also play a role in the particles' toxicity. However, there is currently only a slight risk of the general population being exposed to any such synthetic nanoparticles.

For the time being, the individuals at the greatest risk are those who work with the particles in various research centres. However, this situation may change when more products containing such particles start to appear on the market. It would therefore be appropriate to focus on the toxicological risks associated with nanomaterials.

Social implications and moral issues

The significance of nanotechnologies is not restricted to the health of individuals. There are beneficial as well as adverse consequences for society as a whole. Nanotechnologies are 'enabling technologies' par excellence. This explains why most of the related moral issues are neither new nor exclusive to nanotechnologies, certainly when considering the short to medium-term outlook. Issues of this kind have often arisen as a result of previous developments in other technological disciplines. However, now that nanotechnologies have led to progress in these disciplines, the existing moral issues have taken on a new dimension. They are gaining momentum and presenting themselves with ever increasing urgency. They are also growing in complexity, which makes it difficult to find suitable solutions. As an illustration of this, the Committee provides a few examples, which are all related to health, either directly or indirectly.

Nanotechnologies will affect how resources are used and how products and wealth are distributed. They could, therefore, potentially contribute to the creation of a more sustainable society, and benefit the living standards and health of future generations. Nanotechnologies could also help in the realisation of the United Nations' Millennium Development Goals, which aim to improve the living conditions of people in developing countries. However, progress in science and technology generally demands substantial levels of investment and is mainly restricted to those locations where adequate financial resources are available. Unless a conscious effort is made to translate these developments for use in third world situations, there is a risk that underdeveloped countries will not benefit as much or as quickly as they should from the fruits of nanotechnologies.

Comprehensive legislation exists at the national and European level to combat violations of individual privacy. This is particularly important in the health service. However, the progressive miniaturisation of equipment, combined with developments in information-communication technology (ICT), is increasing the risk of accidental disclosure and/or unethical uses of restricted information.

Nanotechnologies will affect doctor-patient relationships in various ways. On the one hand, they are likely to increase the gap between diagnostics and therapy, as developments in the former area are outpacing those in the latter. This will lead to questions regarding the right to know. On the other hand, advanced, easy-to-use equipment and breakthroughs in ICT have created a situation in which diagnosis and treatment can increasingly take place in the home. These activities can be performed by informal care providers or by patients themselves, possibly assisted by the manufacturer of the equipment in question. These developments

lend increasing weight to questions about what providing proper care and proper information entails.

In the future, nanotechnologies may offer new, far-reaching opportunities for healthy people to 'perfect' themselves in accordance with their own personal wishes. At present, such enhancement applications are either still in their infancy or are speculative in nature. Applications that involve the insertion of ICT implants into the brain touch the very core of our being. They give rise to questions about the possible implications for concepts such as what it means to be an individual, freedom, and responsibility. In this respect, the issues are the same as those concerned with the use of psycho-pharmaceuticals. In due course, new possibilities may arise with such far-reaching consequences that they raise entirely new moral issues. This could have major implications for society as a whole; for example, social divisions could arise between individuals with implants and those without. Many issues will also be raised as a result of military applications.

Conclusions and recommendations

The Committee has reached the following conclusions on the basis of the above:

- Intensive research efforts are focusing on the potential uses of nanotechnologies in practically every medical field (nanomedicine). To a lesser extent this also applies to the agricultural, food, and environmental sectors. As yet, only a few nanotechnology products are commercially available, but the Committee anticipates that this number will increase in the next few years. There will undoubtedly be new opportunities for the diagnosis and treatment of diseases. At the same time, the Committee cautions against unrealistic expectations. Stringent efficacy and safety requirements mean that it may take many years to develop new medications and medical devices. The environmental benefits still involve a degree of uncertainty.
- There is still a lack of understanding about the possible dangers of new, synthetic nanoparticles. This applies to the nature of possible health and environmental impacts as well as to their severity. The Committee believes there are good grounds for thoroughly investigating the toxicological properties of nanoparticles that do not readily dissolve or degrade. This should be done before the materials enter the mass-production stage and become commercially available. The Committee bases its view on current knowledge of 'traditional' particles, and on the initial results of research into novel nanoparticles.

- Aside from the immediate implications for human health, consideration should also be given to the social consequences of nanotechnologies, which may be beneficial as well as adverse. As enabling technologies, nanotechnologies are especially likely to reinforce issues that first arose in connection with other technological developments. In the longer term, entirely new moral issues may emerge, as would be the case with the development and use of ICT-based brain implants, for example.

In view of the numerous opportunities and risks, plus all of the uncertainties and differences in value judgements in a diverse society like that of the Netherlands, the Committee calls for appropriate caution to be exercised in the further development of nanoscience and nanotechnologies. To this end, it makes the following recommendations:

- The government can use financial incentives to encourage research in nanotechnology that it considers to be important for human health or for the environment. This is particularly important where such research is commercially unattractive. Nanotechnologies are by their very nature transdisciplinary. This aspect requires special attention since both teaching and research have been traditionally funded on a sector-specific or discipline-specific basis.
- However, the best way to stimulate nanoscience and nanotechnologies is to adopt a careful approach when considering the risks. Risk governance*, as recently defined by the International Risk Governance Council (IRGC), can be of use in this. Besides knowledge, value judgements are particularly important when defining the problem. The same applies when judging the acceptability of risks and the need for measures to curtail risks, and when selecting suitable risk management options. The Committee therefore recommends that the decision-making process should involve stakeholders, including the general public in certain cases.
- Early identification of any adverse or harmful effects of nanotechnologies on health, working conditions, the environment, ethics, and social relationships is essential. The Committee believes that this can best be achieved by a broad committee specifically appointed for that purpose and composed of independent scientific experts as well as stakeholders and representatives of the general public.
- The IRGC proposes the following categories for classifying risks: ‘simple’, ‘complex’, ‘uncertain’ and ‘ambiguous’. This classification system can also

* The term governance is used to refer to the structures and processes for collective decision-making, involving governmental and non-governmental actors.

be applied to the risks associated with nanotechnologies. It gives direction to the search for the best risk management strategy. The above sequence, from 'simple' to 'ambiguous', corresponds to the increasing importance in the decision-making process of involving stakeholders, including members of the public. According to the Committee, issues relating to privacy, self-testing, and the toxicity of readily degradable nanoparticles can best be classified as 'simple'. The 'complex' category covers issues concerned with the gap between rich and poor, and possibly those concerning sustainability. The question of the toxicity of synthetic nanoparticles that do not readily degrade is placed in the 'uncertain' category because the existing knowledge on this subject is incomplete. The Committee classifies issues involving the gap between diagnosis and therapy, advanced home care, enhancement, and military applications as 'ambiguous' because they involve value judgements which will differ from one individual to another or from one interest group to another.

- Classifying the issue of the toxicity of synthetic nanoparticles that do not readily degrade as 'uncertain' implies that the most suitable risk management strategy would be one based on precautionary measures. This can be given shape by:
  - performing life-cycle analyses on products that contain nanoparticles, to determine the extent to which such particles are released during the production, use and disposal phases; curtailing emissions from, and exposure within, research centres and factories; focusing on the risks associated with nanoparticles during (mandatory) safety assessments of applications (e.g. soil remediation) and products (e.g. medications) and only granting admission if the benefits counterbalance the risks.
  - as a result of their unique properties, the nano-forms of existing substances should be dealt with as if they were novel substances; there should be a lower production threshold or import threshold (or none at all) for nanomaterials in the new European regulations governing chemical substances (REACH);
  - more internationally coordinated (OECD's role) research into the toxicity of nanomaterials; modification of the current toxicity tests for substances to improve their suitability for use in nanomaterials; expressing the dosage administered in terms of the mass, surface area, and number of particles; an improved physicochemical characterisation of nanomaterials; energetically pursuing the recently proposed screening strategy for nanomaterials.

- Risk governance for nanotechnologies should take place at both the national and international level, partly in view of the international nature of many laws and regulations. The Committee cannot endorse the use of separate legislation for nanotechnologies. It considers that the best course of action would be to modify existing laws and rules as and when necessitated by developments in nanoscience and nanotechnologies.
- The concept of 'trust' is a critical factor in the dialogue between government, industry, directly affected groups and the general public. This also applies to the debate surrounding nanotechnologies. To win the public's trust it will be essential for institutions to subject their own performance to continual critical reflection. Besides expertise, decisiveness and integrity, openness and accountability are key concepts in this.

Chapter 1

Introduction

1.1 Background

Nanoscience and nanotechnologies represent a field of study that is currently attracting a great deal of attention. The prefix ‘nano’ comes from the Greek word ‘νανος’ (nanos), which means ‘dwarf’. In combination with a measure, it indicates a one billionth part of that measure. It fits in the series of prefixes that includes ‘milli’ (one thousandth) and ‘micro’ (one millionth). A nanometre, abbreviated to nm, is therefore one billionth of a metre. As an indication of how large (or rather how small) this is, consider that a human hair is around 80,000 nm thick. Animal cells generally have a diameter of between 10,000 and 20,000 nm. The terms nanoscience and nanotechnologies refer to the nanometre.

This raises the question of what is so extraordinary about the nanometre to warrant dedicating an entire branch of science to it. The answer is that materials in the nanometre range (between 100 nm and the size of a single atom, i.e. around 0.1 nm) can display unusual properties. Their properties can differ markedly from the properties of the same materials at larger dimensions. The nanoscale is the scale of macromolecules, molecules and atoms. Technical developments over the past two decades have made it possible to observe, study and even manipulate individual atoms and molecules, which is precisely the aim of nanoscience and nanotechnologies. The new techniques make it possible to study living as well as dead matter in a way that was impossible until only recently, namely at the level of the

individual building blocks. There are high expectations about possible applications of the new knowledge and that which still has to be gathered. The possibilities appear to be practically unlimited: faster and more powerful computers; new, better materials; more economic use and recycling of raw materials; and major progress in medicine. However, concerns have also recently been increasing. There are fears of accidents and misuse, and of a technique over which humans lose control. Some people are therefore calling for restraint, to prevent nanotechnologies from becoming a Pandora's box.

1.2 Nanotechnologies on the Health Council's work programme

Nanoscience and nanotechnologies are expected to have a dramatic impact on the whole of society. Not least, this also applies to public health and all kinds of policy fields on which the Health Council normally advises. New possibilities will emerge for prevention, diagnostics and therapy. New environmental-management opportunities will also arise for preventing pollution, tracing pollutants, and remediation operations. In the foods sector there will be new possibilities for preservation, detecting decay and for designing functional foods. For the purpose of developing government policy, the ability to anticipate all these developments properly entails having an insight into the possibilities, the time it will take to achieve them and any new risks that they may involve. Moreover, all these changes raise questions about the social consequences and possible ethical issues associated with the choices.

Taking all of the above into account, the Health Council's Work Programme for 2004 states that the Council will produce an advisory report on the health significance of nanoscience and nanotechnologies. As usual, the work programme was drawn up in consultation with various ministries and approved by the Minister of Health, Welfare and Sport. The passage concerned from the work programme is included as Annex A. The advisory report covers a broad range of subjects, which it places on the agenda. The focus is on identifying opportunities and threats, defining problems and outlining responsible approaches to policies.

1.3 Committee and working methods

The Vice-President of the Health Council established the 'Nanotechnologies and Health' Committee (hereinafter 'the Committee') on 15 December 2004 for the purposes of drafting the advisory report. Annex B provides details of the Committee's composition.

It was not necessary for the Committee to start from scratch. Various Dutch institutions have produced reports in recent years on nanoscience and nanotechnologies, which contained quite extensive discussions of the beneficial and adverse implications for health: the Rathenau Institute[1], the COGEM[2], the KNAW[3] and the RIVM[4,5]. Numerous foreign international bodies have also recently reported on the subject. These included the Swiss Zentrum für Technologiefolgen-Abschätzung[6], the European consortium Nanoforum[7,8], the German VDI Technologiezentrum[9], the British Royal Society, together with the Royal Academy of Engineering[10] and, in the United States, the Institute of Medicine[11]. Moreover, some environmental organisations have reported on nanotechnologies, such as the Canadian Action Group on Erosion, Technology and Concentration[12-14] and Greenpeace[15]. The Committee's advice is partially based on these publications; in particular, it has made extensive use of the report of the Royal Society and the Royal Academy of Engineering in support of its findings. The Committee has also based its findings on numerous publications in the scientific literature. To this end, it conducted searches in the life sciences and biomedical bibliographic database, Medline, for terms such as nanotechnology, nanoscience and the English names for various nanomaterials (see chapter 2). Finally, the Committee also consulted several experts. Their names are provided in Annex C.

Many definitions of nanoscience and nanotechnologies are used. The Committee uses the descriptions of the Royal Society:

> Nanoscience is the study of phenomena and manipulation of materials at atomic, molecular and macromolecular scales, where properties differ significantly from those at a larger scale.
>
> Nanotechnologies are concerned with the design, characterisation, production and application of structures, devices and systems by controlling shape and size at the nanometre scale.

The Committee's examination of the subject is limited to the parts of nanoscience and nanotechnologies that are of more or less direct importance to the policy fields concerned with health, the environment and nutrition. Developments that are of indirect importance, such as in the field of information and communication technology are only discussed briefly, if at all. Nor does the Committee discuss the economic significance of nanotechnologies. The Committee focuses on the health benefits as well as the risks and on the quality of the environment. It also examines the wider social implications, which involve both positive and negative aspects, and the associated ethical questions. With regard to new technologies, the Committee attempts to indicate the extent to which they

are already being used or the period within which they will probably be used. An indication is also provided of how realistic the Committee considers the risks to be. In all of these issues, wherever possible the Committee attempts to establish connections with previous Health Council reports.

1.4 Structure of this advisory report

The Committee first provides a general overview of developments in nano-science and nanotechnologies in chapter 2. In chapters 3 and 4 it focuses on the health opportunities and, in chapter 5, on the threats. This is followed in chapter 6 by a discussion of the broader social aspects of these developments. Chapter 7 contains a discussion of the possibilities that are available for properly regulating the development of nanoscience and nanotechnologies.

Chapter 2

An outline of nanoscience and nanotechnologies

In this chapter the Committee describes the emergence and development of nanoscience and nanotechnologies, from the very beginning of a visionary at the end of the nineteen-fifties up to the enormous research efforts in the field that are currently underway throughout the world, including in the Netherlands. The Committee also discusses the properties of matter at the atomic scale and the materials and applications that have been or are being developed to exploit those properties. The public's assessment of these developments is also discussed.

2.1 The start of nanoscience and nanotechnologies

The Los Angeles high school could send a pin to the Venice high school on which it says "How's this?". They get the pin back and in the dot of the "i" it says "Not so hot.".

Physicist and Nobel prize-winner Richard Feynman suggested in 1959 that high schools should enter a competition to see who could produce the smallest writing[16]. According to him, it ought to be possible at the level of molecules and atoms to write the entire works of the Encyclopaedia Britannica on a pin head. Taking this further, he even calculated that the contents of all the books in the world would fit into a single grain of matter hardly visible to the naked eye. He foresaw that manipulating matter at the level of individual molecules and atoms would, in time, present humankind with new, unprecedented possibilities. This

would apply all the more so because it would also then be possible to exploit the fact that matter at the atomic scale has completely different properties from that at the larger scale. The ratio of the surface area to the volume of a fragment of matter increases as the size of the fragment decreases. Moreover, at the atomic scale the laws of Newtonian mechanics are superseded by those of quantum mechanics.

Feynman expressed his ideas in a talk entitled *There is plenty of room at the bottom* during the annual meeting of the American Physical Society at the California Institute of Technology. This is why he is seen as the father of nanotechnologies. However, he never actually used the word nanotechnology. The term was first used in 1974 by Japanese engineer Norio Taniguchi[17]. A milestone in the development of nanotechnologies and considered by some to be the actual beginning[18,19], was the invention of the Scanning Tunnelling Microscope (STM) by the Swiss Heinrich Rohrer and the German Gerd Binnig in the early nineteen-eighties[20]. They received the Nobel prize for their invention in 1986. The STM uses an extremely fine needle to explore a surface that is being studied, thereby achieving such a high resolution that individual atoms become visible. It is also possible to use the instrument to exert forces on individual atoms or molecules and to relocate them. Using an STM in 1990, an American, Don Eigler, succeeded in writing his employer's name, IBM, with 35 xenon atoms on a nickel surface of a few nanometers[21]. Although this technique is far too laborious to enable the entire Encyclopaedia Britannica to be transcribed, he did put Feynman's idea of thirty years before into practice.

2.2 Strength through convergence

Various instruments, such as the atomic force microscope (AFM) and optical tweezers that enable individual atoms or molecules to be investigated and manipulated have since been developed. This gives rise to numerous new possibilities for scientific research; they are currently part of the standard set of instruments used in biology and physics. However, for the time being, using a set of instruments of this kind to construct larger structures from individual atoms or molecules – known as the bottom-up approach – is still too laborious for industrial applications. Consequently, a great deal of work is being conducted into what is known as self-assembly, in which the specific properties of individual building blocks lead them to automatically take up the correct positions in complex structures. Moreover, continued progress in miniaturisation is being achieved, especially in micro-electronics. Lithographic techniques are also being used to create ever finer structures on or in the silicon wafers used in chip production. The den-

sity of transistors on a chip has doubled every one and a half years for the past thirty years. This is known as Moore's law. The smallest structures that can be manufactured using this top-down approach are now equal to the largest structures that can currently be constructed using the bottom-up approach. This creates new possibilities for a combined approach.

Nanotechnologies are not new. Nature was billions of years ahead of humankind. Living cells are full of bottom-up constructed 'machines' and other structures with nanometre dimensions that are made of protein molecules. Physicists and technicians are therefore increasingly inspired by biotic systems in their research and designs for applications. On the other hand, they can use their own research methods, techniques and instruments to make a contribution to biological research[22]. The boundaries between the traditional scientific disciplines are rather indistinct at the molecular and atomic level. Nanoscience and nanotechnologies therefore provide a perfect field for multidisciplinary research, characterised by increasing collaboration between physicists, chemists, biologists and engineers. The differences in background and training provide mutual benefits. Nanotechnologies often make progress possible in other technologies. They are enabling technologies.

2.3 Nanoscience and nanotechnologies worldwide and in the Netherlands

Nanoscience and nanotechnologies have advanced rapidly in recent years. This is clear from the exponential growth in the number of scientific publications, for example. It should be remembered that scientists currently like to attach the nanoscience or nanotechnology label to their research because they think it will attract funding for their research. Some of the research was previously conducted under a different name. It is therefore more a question of evolution than revolution in many fields. An enormous amount of research involving nanotechnologies is underway at present and various directions have meanwhile been given their own name, such as nanoelectronics, bionanotechnology, nanobiotechnology, molecular nanotechnology and nanomedicine. The only common denominator is the scale of the objects being studied.

Besides this, the funding which governments around the world are providing for nanoscience and nanotechnologies has increased considerably. A total of $ 432 million was invested in 1997[22]. The figure in 2003 was almost $ 3 billion. The US, Japan, Switzerland and a number of EU countries are at the forefront. Germany, France and the United Kingdom are especially active in nanotechnology in the EU. On top of the national expenditure of EU countries, the EU Com-

mission has also provided money through the Sixth Framework Programme, which runs from 2002 to 2006. A total of € 1.3 billion has been provided for 'priority 3', 'Nanotechnology and nanosciences, materials and new production processes' (NMP). Around € 500 million of this was spent on nanotechnologies. The amount will probably be more than doubled in the Seventh Framework Programme[23]. This is all public money. The amounts the private sector and industry invest in nanotechnologies are estimated to be in the same order of magnitude[2]. An estimated $ 9 billion is currently being invested in these technologies worldwide[24].

The Dutch government has made € 130 million available for the field of 'Microsystems and nanotechnology' on the basis of a decree to subsidise investments in the knowledge infrastructure (Bsik). This subsidises three major research programmes: BiOMaDe, NanoNed and MicroNed. Prior to this, € 23 million had already been allocated to the NanoImpuls research programme, the predecessor of NanoNed. Because the subsidy often covers half the cost of the research concerned, total investments for the six-year period come to around € 300 million. BiOMaDe is mainly concerned with diagnostics and medical therapy. NanoNed has more of a basic scientific nature. It is the largest research programme and is divided into eleven flagship programmes and involves seven universities, the Industry and Technology division of the Dutch organisation for Applied Scientific Research (TNO), and Philips. There is also cooperation with various industrial partners. MicroNed focuses on microtechnologies and top-down nanotechnologies and is more application oriented. A total of around 135 institutions are active in the nanotechnology field in the Netherlands, including twelve universities and twelve research schools. The research involves around 420 researchers. In her Science Budget for 2004[25], the Minister of Education, Culture and Science designated nanotechnologies as a national priority, alongside ICT and genomics. Sources of extensive information on nanoscience and nanotechnology research include a report of the Commission on Genetic Modification (COGEM)[2], the website of the Netherlands Institute for Scientific Information Services (NIWI)* and the websites of the various research programmes**.

* NIWI: Nederlands Instituut voor Wetenschappelijke Informatiediensten van de Koninklijke Nederlandse Academie van Wetenschappen (Netherlands Institute for Scientific Information Services, an institute of the Royal Netherlands Academy of Arts and Sciences (KNAW)), www.niwi.knaw.nl/nl/over_niwi

** NanoNed: www.stw.nl/nanoned; www.micro ned.nl; www.biomade.nl

2.4 Nanomaterials and their applications

The special properties of materials at the nanometre scale are the result of two factors: their relatively large surface area in relation to their volume, and the occurrence of quantum effects. Because chemical reactions always take place on the surface of materials, as their structures become finer, they become more reactive. This is why iron filings, for example, are extremely flammable – they are able to react rapidly with oxygen – whereas a large piece of iron is not flammable but only rusts slowly. Quantum effects also start to dominate the material properties when the dimensions of materials approach a few nanometres. They no longer obey the laws of classical mechanics but those of quantum mechanics. Quantum mechanics is a collection of natural laws which describe the behaviour of subatomic particles, such as electrons, protons and neutrons. The term 'quantum' indicates that the particles can only exchange discrete amounts of energy. This has a major impact on the material's optical, electrical and magnetic properties. People have become more adept in recent years at also precisely controlling materials with small dimensions. This makes it possible to exploit the special properties of nanomaterials. A lot of research is currently underway in this field and many applications are now at the laboratory stage. However, commercial products that use or are based on nanomaterials are still scarce at the moment.

In line with the Royal Society and the Royal Academy of Engineering, the Committee classifies materials as nanomaterials if they are smaller than 100 nm in at least one dimension. They can be categorised as follows on the basis of the number of dimensions of less than 100 nm:

Nanoscale in one dimension

- Films, layers and surface coatings that are just one to a few atoms or molecules thick.

Nanoscale in two dimensions

- Carbon nanotubes (CNTs)
  Besides graphite and diamond, these tubes are a third form of pure carbon. They were discovered in 1991 by the Japanese researcher Sumio Iijima, and consist of a layer of graphite just one atom thick (known as graphene) which is rolled up into a seamless cylinder[26]. There are two types of CNTs: single-walled (one tube) and multi-walled (several concentric tubes). They are only a few nanometres in diameter but they can be several centimetres long. They

are extremely strong but flexible and have special electrical properties. All these properties mean that CNTs are one of the icons of nanotechnology.

- Inorganic nanotubes
  These tubes and fullerene-like structures of layered compounds, such as tungsten disulphide, molybdenum disulphide, boron nitride, nickel dichloride, niobium disulphide and titanium dioxide, were discovered shortly after CNTs. Their diameters range from one to a few tens of nanometres[27].
- Nanowires
  These are formed by linear self-assembly from nanoparticles of all kinds of inorganic materials, such as silicon, gallium nitride and indium phosphide. They have remarkable optical, electrical and magnetic properties.
- Nanofibres
  Fibres of tens to hundreds of nanometres thick, which can be made using various techniques from synthetic (e.g. polylactic acid, polyurethane) or natural (e.g. collagen) organic polymers[28].
- Biopolymers
  Biopolymers, such as DNA, can be used for the self-organisation of nanowires. DNA molecules can also be coated with metals, for example. They can also be joined to nanostructures, such as CNTs.
- Nanopores
  These include pores in solid materials[29,30] and pores formed by proteins or nanotubes in membranes of, for example, lipids[31]. Their size, shape and uniformity are precisely controlled.

Nanoscale in three dimensions

- Nanoparticles of bulk chemicals
  These are particles with a diameter of less than 100 nm which, in comparison with large particles of the same material, have new or stronger, size-dependent properties. Examples include nanoparticles of TiO_2, ZnO and some forms of carbon black*. They can be used as loose particles, in suspension, or fixed to or in other materials.
- Fullerenes
  Buckminsterfullerenes are named after the architect R. Buckminster Fuller, who was known for his striking domes. They are known for short as fullerenes or buckyballs. They are spherical molecules of pure carbon approximately

* Carbon black is an industrially produced carbon product similar to soot. However, unlike soot, it is composed of particles of a precisely determined size (smaller than 1000 nm) and contains hardly any contaminants, such as tar and ash.

one nanometre in size. The sixty carbon atoms from which they are constructed are arranged as twenty hexagons and twelve pentagons, the configuration of a football. They were discovered in 1985 by Richard Smalley[32] and it has been possible to produce them in large quantities since 1990[33]. There are also forms that exist with a wall made up of several layers wrapped around each other like the skin of an onion, in which some of the carbon atoms can be replaced by nitrogen atoms. These forms are known as nano-onions[34].

- Dendrimers
  The name is a contraction of dendritic polymers. The polymeric molecules are formed by hierarchical self-assembly from smaller molecules. They are highly branched from the inside out in all directions and their spherical shape is reminiscent of the crown of a tree. The size, shape, degree of branching and chemical surface structure can be very precisely controlled. Dendrimers are extremely suitable for transporting substances that are placed between there branches or attached to the surface. There are many types and sizes, the smallest only measure a few nanometres[35].
- Quantum dots
  Quantum dots are small nanocrystals of semiconductor material[36]. They range in size from one to several tens of nanometres in diameter. Their small size means that the electrons they contain display quantum behaviour. They can only exchange certain amounts of energy. This is expressed in the absorption and emission of very specific wavelengths (colours) of light. When producing quantum dots it is possible to precisely regulate their shape and size, and thereby the colour of light that they absorb and emit. These special optical properties make quantum dots suitable for numerous applications.

Some nanomaterials are already used commercially. For example titanium dioxide nanoparticles and zinc oxide are used as UV reflectors in sunblock creams, carbon black is used as a filler to reinforce car tyres, and naturally occurring nanoparticles of clay are used in car bumpers. Nanometre-thick coatings are used on opto-electronic equipment, catalytic surfaces and self-cleaning windows. Nanocrystals make cutting and drilling tools more resistant to wear and erosion.

Within a few years, nanoparticles and other nanomaterials will probably also be used in paints, fuel cells, TV/monitor screens, batteries, catalytic converters and as fuel additives. In the longer term, expectations include material reinforcement using carbon nanotubes, lubricants made of nanoballs, magnetic nanomaterials for data storage and more readily workable ceramic materials made of nanocrystals.

Medical and other applications that have a more or less direct importance for health are discussed in the next two chapters.

Shaping of public attitudes

American futurologist, Eric Drexler, published his book *Engines of Creation: the coming era of nanotechnology*[37] in 1986, thereby placing nanotechnology on the political agenda. The book provided an overview of the possibilities that nanotechnologies will offer the world in the future. He also described the negative consequences that the development of nanotechnology could have for the world. He outlined the *'gray goo'* scenario, in which self-replicating nanorobots escape our control and destroy all the life on the planet. The fear of nanorobots has again been stirred up over the past few years by science fiction stories[38]. Environmental organisations ETC group[12-14] and Greenpeace[15] recently demanded that attention be paid to the risks of nanotechnologies. The ETC group even called for a moratorium on new nanomaterials.

This has all led to the need to pay more attention to the social embedding of nanotechnologies than was the case in the past with biotechnology. All parties are therefore now endeavouring to gain an insight into the possible hazards at the earliest possible stage of the technological developments and to provide the public with – what they call – a realistic picture of the risks. Organisations such as COGEM and KNAW recently published reports[2,3] with this in mind. Calls are also becoming louder for some of the available research funds to be spent on research into the social consequences of nanotechnologies and the associated ethical questions[39]. The Rathenau Institute is currently working to inform members of the public and to involve them in a discussion of the subjects concerned[1]. Public knowledge of nanotechnologies is currently limited[10,40,41].

Chapter 3

Opportunities for medical care

Nanotechnologies may prove beneficial to human health in various ways. The Committee uses the word 'may' advisedly because the benefits are mainly concerned with applications that are the subject of – various stages of advanced – research. Only a few products are already on the market or being used in clinical practice. This chapter discusses applications in medical care. This is where developments are at the most advanced stage. The Committee discusses applications in the foodsector and in environmental management in the next chapter.

3.1 Scientific and application-oriented research

Living cells are full of complex and highly functional 'machines' at nanometre scale. They are composed of macromolecules, including proteins. They are involved in practically every process in the cell, such as information transfer, metabolism and the transport of substances. Nanotechnologies offer new instruments for observing the operation of these machines at the level of individual molecules, even in the living cell[42]. Using atomic force microscopes, it is possible, for example, to measure the bonding forces between trigger substances, such as hormones, and the associated receptor proteins that act as switches in the cell membrane. Biomolecules can be labelled using quantum dots. The intense light of a specific wavelength that these nanocrystals emit enables the path followed by the biomolecules in the cell to be precisely traced[43]. A great deal of this

research is concerned with obtaining information on basic biochemical and biophysical processes in healthy and diseased cells. This knowledge can provide the basis for the development of new prevention strategies and therapies.

Besides this primarily knowledge-broadening research, research is also underway into numerous possible applications for nanotechnologies in medicine. Research efforts are particularly intensive in the search for new methods and tools for diagnostics, screening and imaging and for drug delivery and gene therapy. More research is also underway into applications in fields such as disinfection, tissue engineering and medical implants. Clinical applications are currently scarce partly because of stringent safety requirements. Nevertheless, experts expect a great deal from nanomedicine[10,44], especially in the longer term (ten years or longer). The Committee refers to various recent general reports for further details[5,7,9].

3.2 Diagnostics

The enormous increase in knowledge of the human genome (*genomics*) and of expression products, proteins (*proteomics*), makes it possible in an increasing number of cases to trace diseases to abnormalities at the molecular level. In theory, this gives rise to the possibility of making a diagnosis at a very early stage – and of possibly starting treatment – even before the initial symptoms of the disease appear[45,46]. Attention in medicine is therefore increasingly focusing on prevention[9]. Neonatal screening (by means of a heel prick) for metabolic diseases is a good example of this[47]. The medical profession has an ever increasing number of technical tools at its disposal for detecting these molecular biomarkers. It is in this field that the impact of nanotechnologies will probably be noticed first (within five years)[6,44,48]. The diagnostic research can be conducted in the laboratory using samples taken from the human body (*in vitro* research) but it can also be carried out directly on the patient (*in vivo*). This distinction is important because, in the latter case, the tools/agents have to meet more stringent requirements. The Committee only illustrates the health significance of nanotechnologies for diagnostics on the basis of a few examples and refers to the references for further details[9,36].

3.2.1 In the laboratory

Research into patients' genetic material (DNA) can be conducted to measure gene expression – the degree of RNA production – in diseased tissue, or to ascertain which variant of a particular gene a person has. Many human genes exist in

several forms, which only differ in a single base pair. These are known as single-nucleotide polymorphisms (SNPs). The corresponding protein variants may differ from each other in a single amino acid and then display a considerable difference in functionality. SNPs are the root of all kinds of genetic disorders but also affect a person's sensitivity to chemical substances, including medicines. This refers to their therapeutic effect as well as their side effects. Genetic research offers major possibilities for identifying gene types that predispose a person to certain diseases and for achieving better matches between individual patients and the medicines they are prescribed. The Health Council published an advisory report on this subject several years ago[49].

DNA chips used for analysing DNA have been available for a few years now. They are currently widely used in scientific, biomedical research but they are rarely used in clinical practice. The chips comprise an inert support which carries micro-arrays of hundreds to thousands of single-strand DNA molecules with different base sequences. DNA from a tissue sample that has been labelled with a radioactive or fluorescent material can be identified on the basis of the place on the chip where it binds to the chip DNA. The Dutch Cancer Institute has been using a DNA chip since 2003 to predict the spread of breast tumours on the basis of gene expression profiles. This information makes it much easier than it was in the past to determine which patients would benefit from supplementary chemotherapy after the tumour has been surgically removed[50,51]. Similar chips are being developed for the diagnosis of leukaemias[52,53] and mouth and throat tumours[54]. DNA chips and other biochips were originally an achievement of microtechnology but miniaturisation is advancing here too, as with computer chips. Nanotechnologies are also increasingly playing a role in producing the chips and in increasing their detection sensitivity and reliability[9].

A new nanotechnological analytical method uses quantum dots. DNA in a sample is identified on the basis of its bonding to DNA molecules of a known composition embedded in micrometre-sized polymer spheres containing various mixtures of quantum dots, each of which provides a unique spectral bar code (colour code) [55]. American researchers have used this method to study SNPs in genes that code for enzymes of the cytochrome P450 family which are involved in the breakdown of substances (including medicines) in the body[56]. The method is very suitable for studying large quantities of samples on many SNPs simultaneously (multiplex analyses).

In theory, the composition of DNA molecules can also be ascertained by pulling them through nanopores in a membrane by means of an electric potential difference. The base sequence can be deduced from the time profile of the electric

current through the pores[57]. Researchers have now used this method to identify a mutation in an HIV gene that makes the virus resistant to a particular medicine[58]. If this method, which is still being developed, can be perfected, it will result in a much faster way of determining the base sequence of DNA than has thus far been available. This would involve having to place hundreds of pores on a chip.

The aforementioned techniques would, in principle, also be suitable for identifying other biopolymers, such as proteins and carbohydrates. The complex and unstable structure of proteins, which is extremely important for their functionality, means that the development of protein chips is five years behind that of DNA chips[9]. Nevertheless, American researchers have succeeded in developing a chip to detect prostate cancer. The chip contains around one hundred cantilever sensors (micrometre-sized, nanometres thick miniscule levers), which are coated on one side with antibodies to prostate-specific antigen (PSA), a biomarker for that disease. Bonding of PSA from a sample placed on the chip bends the cantilevers several nanometres, which can be detected optically. This enables clinically relevant concentrations of PSA to be measured[59,60]. Antibodies placed on nanowires can be used in a similar way to detect viruses, in a blood sample for example[61,62]. The bonding of a single virus particle to an antibody results in a change in the nanowire's electric conductance. The method is extremely sensitive, which means that an infection can be detected at a very early stage. It is also suitable for multiplex analyses. Work is also underway on sensors based on carbon nanotubes, for use in micro-arrays[63]. Detection methods based on cantilevers, nanowires or nanotubes offer the added advantage that it is not necessary to label the sample.

Labs-on-a-chip are pocket-sized laboratories. They can be used for analysing biopolymers but also for research and for manipulating cells. They are expected to play an important role in the further development of biosensors for the detection of pathogenic bacteria[64]. In due course there will also be possibilities for point-of-care applications, in which simple analyses can be made in the general practitioner's surgery or in the patients' homes and carried out by the patients themselves[9,65]. Researchers of the University of Twente are currently working on the development of a lab-on-a-chip for measuring lithium concentrations in the blood[66]. A chip of this kind would enable patients who use psychopharmaceuticals based on lithium to keep the lithium concentration in their blood at the right level. The ease of use would be comparable with that of current devices that enable diabetic patients to measure glucose levels in their blood.

Photonic explorers for bioanalysis with biologically localised embedding (PEBBLEs) are a final example. These sensors are a few hundreds of nanometres

in size and are composed of an inert capsule, made of polymers for example, containing an indicator colouring agent that emits light as soon as a substance being analysed diffuses through the capsule to the inside and binds with the colouring agent[67]. PEBBLEs were developed for measuring concentrations of small ions and molecules – such as ions of hydrogen, calcium, magnesium and zinc, or glucose – in living cells. Once the nanocapsules have been introduced into a cell, their light emission (and cessation of emission) can be monitored using a microscope. Tools of this kind are useful when studying certain diseases. For example, an abnormal zinc balance is a characteristic of brain disorders such as Alzheimer's disease and Parkinson's disease[68].

3.2.2 In vivo *diagnostics and imaging*

In the case of *in vivo* diagnostics, patients are given contrast agents or radiopharmaceuticals. Their specific properties mean that these agents are useful in imaging pathophysiological changes and functional changes such as changes in blood flow in cells, tissue and organs. The term molecular imaging is often used, as today's imaging techniques are increasingly concerned with making molecular biomarkers of disease processes visible, for instance a receptor protein on the surface of a cancer cell. To this end, besides being given a contrast agent (the imaging component), a carrier molecule or particle is also given a molecule that specifically binds to the biomarker, such as an antibody (the targeting component). Various techniques have been developed, each with its own contrast agents and imaging equipment: methods based on ultrasonic vibrations, radioactive substances (including positron emission tomography, PET), magnetic resonance imaging (MRI) and fluorescent substances. Each has its own possibilities for applications and its own restrictions[69]. Imaging that focuses on molecular biomarkers makes early detection of diseases possible and provides information on appropriate therapies. Imaging is also very suitable for monitoring, evaluating and optimising treatment that is being provided[45]. Nanotechnologies offer numerous possibilities for improving existing and designing new imaging techniques[9,70-72].

Nanoparticles of perfluorohydrocarbons combined with a lipid layer have multiple uses. They are suitable as an ultrasonic contrast agent[73]. If gadolinium compounds or radioactive substances such as technetium-99 are combined with the lipid layer of the nanoparticles, they are also suitable for MRI, or scintigraphic imaging[9,74]. Given the right targeting molecule, the particles can make pathogenic changes in blood vessels visible. The nanoparticles are currently being studied for use as a contrast agent for the diagnosis of atherosclerosis,

thrombosis and (tumour) angiogenesis. A clinical study is expected to start within a few years[69].

Superparamagnetic* nanoparticles of iron oxide are now being used clinically as an MRI contrast agent[46]. They accumulate after intravenous administration in the liver, the spleen and the lymph glands, thereby enabling studies of those organs[9,75]. Patient-based research has indicated that they can also increase detectability of tumour metastases in lymph glands[76]. Combined with dendrimers, the particles can be used for marking living cells. Magnetodendrimers of this kind make it possible to, for example, monitor the migration and division of transplanted cells in the body. The method, which has already been used successfully on laboratory animals[77], may prove to be of valuable assistance in the future in stem cell therapy. Gadolinium dendrimers are also being developed for use as contrast agents[35,78]. The first of these agents are almost ready for introduction on the market[46]. Depending on their size and solubility in water or fat, they are suitable for examining blood vessels, kidneys, liver or lymph glands[79,80].

Optical imaging techniques use fluorescent colouring agents which are taken orally or injected and then accumulate in a tumour, for example. The tumour cells fluoresce when irradiated with laser light. Because the laser light cannot penetrate deep into the body, this technique can only be used for imaging tumours in or just below the skin or in tissue that is accessible using an endoscope[9].

Intensive research has been underway for several years now into new optical methods based on the use of nanoparticles. Quantum dots are at the most advanced stage of development[81-84]. These nanocrystals have the advantage over colouring agents that they fade less quickly over time and do not react with cell components. Moreover, quantum dots of different colours can be made to fluoresce with laser light of the same wavelength, which makes multiplex applications possible. Nanoparticles have already been successfully used in cell cultures and laboratory animals to colour biomarkers on the surface of cancer cells[85], to monitor the development of cell lines in a frog embryo[86], to make blood vessels visible in mice[87] and lymph glands in pigs[88]. The hope is that the latter application will in due course improve the possibilities for tracing tumour metastases[89]. The quantum dots are provided with a layer of lipids or polymers, to prevent heavy metals from being released. However, before clinical applications can be considered, research will have to show that coatings of this sort are also effective in the long term[84].

Contrast agents can sometimes also act as a medicine. For example, under the influence of laser light of a certain wavelength and in the presence of oxygen,

* Superparamagnetic materials interact with a magnetic field, but cannot be made permanently magnetic[9].

some fluorescent colouring agents produce toxic substances that destroy tumour cells by oxidation. In addition, it is theoretically possible to combine diagnosis and therapy by providing nanoparticles not only with targeting molecules and contrast agents but also active substances. The nanoparticle then also acts as a drug delivery system.

3.3 Therapy

3.3.1 Drug delivery

Many substances that could, in theory, be used as medicines have the disadvantage that they are hardly, if at all, able to reach the diseased organs or tissues in the body. There are various possible reasons for this:

1 the substance is hardly, if at all, soluble in water
2 the substance is broken down in the body or inactivated before it reaches its target
3 the substance is hardly, if at all, capable of passing certain biological barriers (cell membranes, placenta, blood-brain barrier)
4 the substance distributes non-specifically to all kinds of tissues and organs.

Substances of this kind are therefore ineffective or lead to undesirable adverse side effects. As long as a hundred years ago, German microbiologist Paul Ehrlich conceived of the idea of using ‘magic bullets’ to direct medicines at their target more effectively[9,71]. This idea was taken up again at the end of the nineteen-sixties and researchers have since been developing such drug delivery systems[90]. Their miniscule dimensions mean that all kinds of nanoparticles are suitable for use in systems of this kind[7,9,71,91-94]. Depending on the type of particle, the active substance can be encapsulated or attached to the surface. This means that even if they dissolve poorly in water, they can be transported in an aqueous solution, such as blood and are better protected against degradation by enzymes, for example. A suitable coating on the nanoparticle can prevent identification and removal by the immune system[95,96].

Selective accumulation in the target organ or tissue can arise through various mechanisms. The first mechanism is passive. An example of this would be to use the high permeability of the walls of blood vessels and the reduced lymph drainage in tumour tissue[97]. However, it is also possible to provide nanoparticles with ‘targeting molecules’ (e.g. specific antibodies or folic acid), which ensure that the delivery system primarily bonds to the diseased tissue. However, this can aid detection by the immune system[98]. When provided with suitable targeting mole-

cules, some nanoparticles are able to transport medicines across the blood-brain barrier to treat brain tumours, for example[99,100]. The cells being treated can then take up the delivery system containing the active substance by means of endocytosis*. Combining the delivery systems with contrast agents, fluorescent or radioactive substances also makes it possible to use imaging techniques to monitor how successful the selective transport to the destination has been[101,102].

Once it has reached the target area, the active substance has to be released from the carrier at the correct rate. This can occur spontaneously by gradual diffusion, in combination with the delivery system's degradation or otherwise. It may also occur as a result of special conditions at the destination, such as a different acidity level[103], salt concentration, temperature or the presence of certain enzymes. The accumulation of the delivery system and/or the release of the active substance at the right place can also be controlled from outside by influencing conditions in the target organ or tissue by means of magnetic fields[104-106], near-infrared radiation[107], ultrasonic vibrations[108] or heat[109-111]. The delivery system used and the external treatment have to be precisely matched to each other for this purpose.

The requirements that delivery systems have to fulfil are:

1 their residence time in the blood must be long enough to enable accumulation in the target tissue
2 they must be capable of containing sufficient active substance
3 the systems or their degradation products must have a favourable toxicity profile
4 they must have a shelf life that is long enough to allow storage and distribution
5 the effectiveness must be in proportion to the costs.

Research into the suitability of a large variety of nanoparticles for use as a delivery system is currently underway[7,9,71,91-94]. Which particles are most suitable depends on the active substance that has to be transported, the target organ and the method of administration (oral, inhalation, dermal, by injection). Some particles, such as nanoparticles of polymer or of solid fat, appear to be usable for transporting a wide range of substances. The scope for using other, especially inorganic, nanoparticles is smaller. Most delivery systems are currently being developed for transporting anti-tumour agents, genetic material (gene therapy) and proteins and peptides.

* Endocytosis: a process in which cells absorb material from outside by engulfing it with their cell membrane. The material is then enclosed in the cell by a vesicle made of part of the cell's membrane.

Research using liposomes and nanoparticles of polymers as delivery systems for active substances has been taking place since the mid-nineteen-seventies. The usefulness of other systems, such as nanoparticles of solid fat, dendrimers, fullerenes and nanocrystals of the active substance, only began to be studied in the early or mid-nineteen-nineties. There are now various medicines with delivery systems on the market and many are in the clinical study phase[46,90].

The future for drug delivery systems is expected to be bright, even if significant obstacles still have to be overcome[90]. Obstacles include the development of methods to increase the specificity of delivery systems for target cells, to more precisely regulate the bio-availability of active substances in the target tissue and to get active substances to the destination within the cell more efficiently.

3.3.2 *Nanoparticles as medicines*

Besides acting as a delivery system, in some cases nanoparticles can act as an active substance. Once they have found their way through the bloodstream into a tumour, or have been injected directly into it, metal-containing nanoparticles can be heated using near-infrared radiation[112,113] or a rapidly oscillating magnetic field[114] so that the tumour cells die. As yet, this relates to research conducted using laboratory animals. It may also be possible to use single-wall carbon nanotubes in a similar way. *In vitro* studies have in fact shown that, if combined with folic acid as targeting molecules, the tubes are selectively taken up by cancer cells. These cells can then be killed by using near-infrared radiation to heat the tubes. Healthy cells appeared to take up few, if any, nanotubes and not to be affected by the near-infrared radiation.[115]

3.3.3 *Passive implants and tissue engineering*

Artificial joints, such as artificial hips, normally have a life of around ten to fifteen years, after which complications occur, such as wear or implant loosening, and further operations are required[9,116]. Nanotechnologies could help reduce these problems. The implants, which are usually made of titanium or alloys of cobalt and chromium, can be provided with a thin layer of a nanocrystalline structure, which is harder and smoother and consequently more resistant to wear. This would also result in less wear of the artificial socket, which is generally made of a special type of polyethylene. Moreover, the layer would ensure that the body better tolerates the implant (better biocompatibility).

The suitability of various materials for use as a coating is currently being studied: diamond, metal-ceramic and hydroxyapatite[117]. The latter material is a

natural component of bone, 70% of which consists of the mineral hydroxyapatite, with the remaining 30% consisting of organic fibres (collagen). Hydroxyapatite has been used as a coating in implants for some time but new production methods now make it possible to apply layers with a grain size in the nanometre, rather than the micrometre scale. This makes their structure more like that of natural hydroxyapatite in bone, which likewise has a nanocrystalline structure (grain size less than 50 nm). This aids biocompatibility. The layer can even encourage the growth and bonding of the surrounding bony tissue. *In vitro* research has shown that bone-forming cells (osteoblasts) adhere better and deposit more calcium on materials with a grain size in the nanometre range than on conventional materials with a grain size in the micrometre range[116,118-120]. This is presumably related to the higher absorption of proteins that stimulate cell adhesion[121]. Bone resorbent cells (osteoclasts) also function better on these nanomaterials. Proper, coordinated function of both types of cells is essential for the formation and maintenance of healthy bony tissue and, therefore, for strong bonding between the implant and the surrounding bone[116,122,123]. This is extremely important for implants that are attached without the use of bone cement. Implants provided with a hydroxyapatite layer with a nanostructure are currently being tested in patients; in 2000, a patient in the Maastricht University Hospital was the first to receive an artificial hip with such a coating[9]. Nanoparticles of hydroxyapatite can also be introduced directly into damaged bones to accelerate the repair of bony tissue. In recent years, a few medicines have been admitted that work according to this principle[9]. Implant coatings with a nanostructure based on diamond and metal-ceramic are still at the research stage. Their main benefits are hardness, smoothness, corrosion resistance and good bonding to the implant[117].

The mechanical properties and biocompatibility of implants can also be improved by providing the material that is used to make the implants with a nanostructure. This is possible by applying a thin layer of titanium dioxide with nanopores. An added advantage of this approach is that the layer can be made in a way that metal ions with an antiseptic effect such as copper ions are slowly released. This reduces the likelihood of bacterial infections, which are a frequent complication with implants[124]. Another possibility is to make the implants from nanopowders of titanium dioxide or aluminium oxide using a sinter process[9]. Promising alternative materials include organic polymers with a nanostructure and composite materials of organic polymers into which nanofibres of carbon or nanoparticles of titanium, aluminium or hydroxyapatite have been mixed[116,125,126]. The advantage of the organic polymers is that they dissolve grad-

ually while new bony tissue is being formed. Studies are also underway of the possibilities of generating bone with the help of scaffolds of carbon nanotubes[127].

The orthopaedic applications are closest to being used on patients[116], but biodegradable scaffolds of nanofibres consisting of natural or synthetic organic polymers are already used to cultivate other tissues, such as cartilage, muscle tissue, nerve tissue and vascular tissue *in vitro*[28]. Here too, the goal of the nanostructure is to imitate the natural extracellular matrix. Researchers recently succeeded in using nanofibres to regenerate brain tissue *in vivo*. Young and adult hamsters that had been blinded as a result of intentionally caused brain damage, had their sight restored within a few weeks of scaffold-forming nanomaterial being injected into the brain[128]. It may also be possible to use the method in the future to repair damaged human nerve tissue.

Stents are a completely different type of implant. They are small tubes of woven thread used to dilate blood vessels. Inflammatory reactions often occur and lead to the blood vessel closing again. This problem is dealt with using stents with a coating of aluminium oxide which is provided with nanopores. A radioactive substance can be applied to them, which prevents the stent from clogging. The pores ensure that sufficient radioactive material can be introduced and that it is released very gradually. The functionality and safety of these stents still has to be confirmed in animal trials. Research is also underway into the possibility of using the lotus effect: a coating of titanium compounds is used to prevent clotting reactions owing to conformation changes in proteins in the blood caused by their contact with the stent wall[9].

3.3.4 *Active implants*

Active implants are implants that contain a source of energy[7]. They can be divided into two groups on the basis of their function. The first category comprises implants for administering medicines, such as insulin pumps and morphine pumps. They have been in use for a long time. Work has also been underway for several years on implantable microchips for the storage and controlled release of active substances[129,130]. The benefits of this approach to administering medicines include the fact that the medicines go directly to the location where they are needed and can, if required, be administered at varying rates. The release could also be controlled by a biosensor that responds to physiological parameters. The first system of this kind is soon due to be tested on patients[9].

The second group comprises neural prostheses, which are intended to repair or take over nerve functions. For instance, they bridge damaged nerve paths, provide impulses for muscles or replace senses. This category includes cochlear

implants (for restoring hearing), pacemakers and defibrillators (for regulating the heart beat), bladder stimulators (for controlled emptying of the urinary bladder by spinal cord lesion patients), deep-brain stimulators (to combat tremor in patients with Parkinson's disease), peroneus stimulators (to combat drop foot). These are all currently used in patients and some have been in use for decades.

On the other hand, retinal implants to restore the sight in patients with a damaged retina are still in development. In recent years, a great deal of research has been conducted into this in the United States, Germany and Japan. Although considerable advances are being made and the first clinical tests are already underway, some major obstacles still have to be overcome. It will probably be years before 'artificial retinas' are as common as the other neural implants[9,131].

For some years now, various research groups in the United States have also been working on neuroprostheses that enable devices to be operated by thought[132-137]. To this end, one or more chips with electrodes are fitted to the motor cerebral cortex, which register the electrical signals associated with thoughts. These prostheses are also referred to as brain-machine interfaces. They have now succeeded in enabling rats to operate handles by 'brain power' and monkeys to operate the cursor of a computer or a robot arm[134,135]. A few years ago, an ALS* patient had an electrode implanted in the cerebral cortex, to enable him to operate a computer[138]. In 2004, a neuroprosthesis was fitted to a paralysed man. It enables him to operate the cursor of a computer by thought, play video games, operate a light switch and to select a television channel. The findings were presented at the annual meeting of the American Academy of Physical Medicine and Rehabilitation, in Phoenix in October 2004**. The ultimate goal, which is still far-off, is to enable patients to operate arm or leg prostheses or even to restore their control of their paralysed limbs[133,136].

Conversely, it also proved possible to control rats remotely by administering electrical stimuli in the parts of the brain involved in touch and in experiencing pleasant feelings[139,140]. These so-called 'robotrats' could be used to search for victims underneath the rubble of collapsed houses, to detect landmines or be used as mobile biosensors.

All these active implants are essentially products of microtechnologies but nanotechnologies may play an important role in their improvement and further development. Research is mainly concerned with increasing functionality, fixa-

* Amyotrophic lateral sclerosis: neurodegenerative disease which first leads to paralysis of the limbs and later to a loss of speech, while usually leaving the intellectual faculties intact.

** See press report of Brown University: *Pilot study of mind-to-movement device shows early promise.* (www.brown.edu/administration/news_bureau/2004-05/04-035.html, consulted on 1 April 2005.)

tion in the surrounding tissue and biocompatibility by modifying the surface at the nanoscale[141]. For example, electrodes with a nanoporous surface are being developed for retinal implants. This nanostructure increases the electrodes' surface area by a factor of one hundred, which is necessary for proper signal transfer from the electrodes to the tissue[9]. The micro-electrodes of neuroprostheses that register electrical signals in the brain often only work for a few weeks. They do not usually become defective but the surrounding tissue gets damaged and non-conductive scar glial-cell tissue grows. *In vitro* research has shown that a nanoporous surface structure reduces glial-cell adhesion and promotes the formation of outgrowths of nerve cells[142]. A possible explanation for the stimulating effect on the nerve cells is that they are naturally embedded in an extracellular matrix with a nanostructure of microtubuli and laminin. To combat rejection reactions or infections, coatings can be applied that release medicines gradually[7]. An antiseptic layer based on silver nanoparticles is already being used in Germany on cochlear implants[9]. Other examples of contributions made by nanotechnologies to active implants include the membranes with nanopores in micro chips for drug delivery and batteries with a higher energy-storage capacity[7].

3.4 Other applications

3.4.1 Disinfection

The disinfectant effect of silver has long been known but the use of silver in combating pathogenic micro-organisms decreased with the emergence of organic antibiotics. The increasing resistance of bacteria to antibiotics has resulted in renewed interest in silver as a disinfectant. The antiseptic effect is based on silver ions[9,143]. They block the enzymes required for oxygen metabolism, destabilise the cell membrane and block cell division. Bacteria are not expected to develop resistance to silver, owing to the diversity of the working mechanisms. Especially in the form of nanoparticles, silver is extremely effective thanks to the large contact area with the environment[144]. Moreover, the particles have the advantage that they can be readily integrated with other materials, such as polymers[145]. The nanoparticles then act as depots that continually release new silver ions. When applied to medical instruments or implants, antimicrobial layers of this kind can help reduce the number of infections. Current research is studying uses on catheters[145,146], cochlear implants[7,9] and in bone cement[147,148]. Antimicrobial wound dressings containing nanocrystalline silver are already on the market[149,150].

Titanium dioxide nanoparticles also have a bactericidal effect. This is based on a photo-catalytic effect. Under the influence of ultraviolet radiation and in the presence of water and oxygen, the particles form extremely reactive molecules (radicals), such as hydroxyl and perhydroxyl radicals, which kill micro-organisms[151]. Titanium dioxide can be used to produce antiseptic surfaces that only work in the presence of UV radiation. Fullerenes also have an antimicrobial effect in the presence of light[152]. Various antimicrobial products based on nano-particles are already on the market in Japan[9].

3.4.2 *Identification, security and logistics*

Radio Frequency Identification labels (RFID labels) consist of a microchip to which a radio antenna is attached. The chip can contain information on a product that contains it or to which it is attached. A scanning device can activate the chip by means of the antenna, which in turn transmits the information stored in the chip. The labels are used for identification and security purposes and for following flows of goods. They have been in use for some time, for locating stolen cars and bicycles, for example, and for identifying domestic pets and cattle. The labels are a product of microtechnology but nanotechnologies offer possibilities for making them smaller and cheaper. This is expected to increase their use considerably.

RFID labels are already used in hospitals and care institutions. They are used to prevent newborns from being abducted or confused or demented patients from wandering away unnoticed[153]. They are also increasingly being used for identifying patients or samples taken from patients, alongside or instead of labels with bar codes[153,154]. This is to enable an early response when the wrong patient is taken to an operating room, for example[155]. They are also expected to reduce the number of wrong blood transfusions[156]. The labels can also simplify the tracing and localisation of expensive hospital equipment, make it easier to trace medicines and to help in combating drug counterfeiting[153]. Implanting RFID labels in victims of disasters can facilitate their subsequent identification[157].

Meanwhile, RFID labels the size of a grain of rice are available for implantation under the skin. The Food and Drug Administration in the United States approved a label of this kind in 2004. A person's medical records can be stored on the chip. The idea behind this is that faster availability of the right medical information could save a person's life in an emergency. In the Netherlands, the same labels have been implanted for non-medical purposes in the frequent guests of a certain discotheque, who can then enter and pay automatically.

In summary, the Committee notes that a great deal of nanoscientific research is being conducted in almost every field of medicine. Few nanotechnological products are currently available on the market but the Committee expects the number to increase over the next few years. New possibilities for diagnosis and treatment will certainly appear. At the same time, the Committee cautions against unrealistic expectations. The high requirements that are set for efficacy and safety mean that the development of new medicines and medical devices will take years.

Chapter 4

Opportunities for healthier food and a cleaner environment

Proper nutrition and a clean environment promote human health. Nanotechnologies are only used to a limited extent at the moment for achieving these aims. Nevertheless, experts foresee opportunities in agriculture and the food industry[158-164]. Nanotechnologies are expected to prove useful in the environmental field for detecting and solving existing and preventing new problems[11,23,165]. In the latter case, considerations other than environmental issues, such as cost-savings, are often the main reason for the development of new applications. This increases their likelihood of success in the market because they combine environmental benefits with other benefits[23]. Most applications will only be completed in the medium-long term (five to twenty years) or the long term (more than twenty years)[23,160,166]. Many of the envisaged applications have a counterpart in the medical field. The Committee provides an overview of the possibilities in this chapter.

4.1 Possible applications in agriculture

If farm animals or agricultural crops become infected by a pathogen or become sick because of hazardous substances or a lack of nutrients, water or light, it can take a long time for the problem to become apparent. By then, a large part of the livestock or the crop may have been affected. In theory, nanosensors offer possibilities for (constant) monitoring of all the aforementioned aspects of environ-

mental quality. Molecular diagnostics can also provide information on the state of health of plants and animals, and indications of suboptimal conditions, long before the first symptoms of disease have appeared. For example, a multiple DNA test based on *micro-array* technology was recently marketed. It can determine the presence of fifty types of pathogenic fungi and bacteria in crop, soil and water samples all at once[167]. Treatment or preventive treatment of the entire livestock or field, which is currently the rule rather than the exception, can therefore be replaced by specific treatment of those animals or parts of the field that have been affected. Early detection is especially important in the case of infectious diseases, which can spread to other farms, and in the case of zoonoses, which threaten human health. Delivery systems can ensure that veterinary medicines, crop-protection agents and nutrients are targeted more specifically to the place where they are needed. For example, French researchers are attempting to improve the uptake of a non-water-soluble, systematically working insecticide by packaging it in nanospheres[168,169]. Nanotechnologies are expected to offer similar possibilities in veterinary medicine and crop protection as in human health care. More effective use of veterinary medicines and crop-protection agents will be beneficial for both the quality of the agricultural product and the environment.

The new possibilities which nanotechnologies create in the field of DNA and protein research may bear fruit in the refinement of plants and animals with a view to developing varieties that are highly productive or salt-resistant or drought-resistant. Research into active substances for the development of new veterinary medicines and crop-protection agents could benefit from nanotechnological instruments, such as the atomic force microscope, which enables direct measurement of interactions between active substances and receptor molecules. New possibilities are also arising for following product flows, which will make it easier to ascertain the origin of infected or contaminated agricultural products. Finally, new possibilities for processing agricultural waste products are also arising under the influence of nanotechnologies[159].

4.2 Possible applications in the food industry

The possibilities for applications in the food industry are even wider. The *'Roadmap microsystem- and nanotechnology in food and nutrition'*[170] was drawn up last year to engender change in the scarcity of applications[166] in the Netherlands. Nanotechnologies will be used to improve the health value, safety, taste and attractiveness of foods.

Delivery systems can ensure that biologically active substances that occur naturally in food or that are added in increased concentrations are not broken down prematurely but reach the right places in the body and remain available at the right concentrations[164]. The same systems can also be used to deliver flavourings. For example, it is conceivable that targeted delivery of salt could enable a product's salt level to be considerably reduced but that it would still taste as if the same amount of salt had been added. Reduced salt intake can be beneficial to health. The number of functional foodstuff delivery systems is expected to increase sharply over the next few years.

Many microbial safety problems in the food industry are attributable to equipment and surfaces that have been contaminated with bacteria or spores of bacteria or fungi. The adhesive properties of the bacteria and spores play an important role in this. They can be further studied using an atomic force microscope. Future strategies based on nanotechnologies for modifying the surface chemistry and structures may be used to prevent adhesion of bacteria and spores. Surfaces that come into contact with food can also be given active coatings that release antiseptic agents in a controlled manner. Decontamination of surfaces and equipment is also possible using new antimicrobial nano-emulsions. Finally, nanosensors can contribute to food safety by enabling early detection and identification of pathogens.

Nanocomposites, synthetic materials to which nanoparticles such as clay minerals (montmorillonite) have been added are a promising material for use as packaging. They are stronger, lighter, more heat-resistant and work better as a barrier against oxygen, carbon dioxide and volatile compounds[171]. Built-in nanosensors could provide an indication (by changing colour for example) of the freshness of a product and could warn the user of deterioration. This type of packaging is known as intelligent packaging. Another type of packaging known as active packaging, releases antiseptic agents. However these types of packaging must not endanger the consumer's health or cause unacceptable changes in the product's composition and must meet high safety requirements. They are consequently still in development and are not used commercially at present. All deterioration and freshness indicators have to comply with the legislation on food-contact materials and will soon have to comply with the new EU Directive on active and intelligent packaging[172].

The AFM can help provide greater understanding of the molecular forces and mechanisms that play a role in the formation and preservation of foams, gels and emulsions. Membranes with nanopores (based on polymers and nanotubes) provided with functional groups, could be used in the future to separate molecules/

biomolecules with a functional value (proteins, peptides, vitamins, minerals), for the production of functional foods or food supplements, for instance[159].

4.3 Preventing environmental damage

The most effective way of preventing environmental pollution is to tackle it at the source. More efficient use of raw materials, water and energy in production processes could reduce waste production. Nanotechnologies can help with this by providing better catalysts, better sensors for process control and better separation and filter techniques[165,173]. They are also increasingly helping to provide a better understanding of natural processes in living organisms, which may provide a source of inspiration for industrial production processes. The Committee has already mentioned the possibility of a more targeted use of water, fertilisers and crop-protection agents in agriculture.

Major possibilities exist in the energy sector in particular[174]. For example, quantum dots are used for improving the characteristics of light-emitting diodes (LEDs)[175,176]. LEDs with a higher light output per unit of electricity consumed may replace present-day incandescent lamps and fluorescent lamps in due course. This would lead to a considerable energy saving and lower carbon dioxide emissions. The use of lighter materials, such as composites of polymers and nanoparticles or carbon nanotubes in aviation would have a similar impact[10]. Savings could also be achieved by increasing the efficiency of combustion processes with the aid of nanoparticles or nanoporous catalytic converters and by using insulating and reflective glazing with nanocoatings[174].

Nanotechnologies also play an important role in the development of new, clean and sustainable energy sources. For example, nanocrystalline titanium dioxide is used in new types of solar cells[177] while quantum dots can help in improving their efficiency[178]. There is also the hope that nanotechnologies will push through the technological breakthroughs that are required for the switch to hydrogen as a fuel[179]. This applies to both the production of hydrogen gas and the storage and use of fuel cells for generating electricity. The switch to materials with nano-dimensions could lead to a considerable improvement in the properties of electrodes and electrolytes, which would improve the performance of batteries and fuel cells[180].

The British Royal Society and the Royal Academy of Engineering pointed out in their joint report that it still remains to be seen whether materials and products based on nanotechnologies actually prove to be good for the environment throughout their lifecycle[10]. It will be necessary to examine whether the energy yield of a solar cell offsets the energy costs involved in its production and its

treatment at the waste stage. Moreover, the energy savings gained from using lighter materials in aircraft construction could be lost, if people start to fly more because flights become cheaper. Likewise, the impact of more economical LED lamps could be lost on account of more excessive use of lighting.

4.4 Tracing environmental damage and its remediation

Humans have been using mammals and birds for centuries as sentinel species to issue a timely warning of the presence of fatal concentrations of gases and hazardous substances. The most familiar example is probably the use of the canary in mines. Extremely sensitive real-time sensors that could provide real-time information on the presence of hazardous substances or pathogenic micro-organisms in the environment or workplace, even before any animal used to provide a warning suffered damage, could play an important role in protecting human beings and ecosystems[11,165,181]. A great deal of work on sensors of this kind is underway in microtechnology. Researchers are using a wide variety of nanostructures, such as carbon nanotubes[182-184,] nanowires[61,62,185,186], nanoparticles[187,188], nanocrystals[189], cantilevers[190-192] and dendrimers[11,193,194], in attempt to achieve further miniaturisation and increased sensitivity. The fear has increased in recent years of terrorist attacks involving toxic substances, such as nerve gases[195] or pathogenic micro-organisms[196,197]. This appears to have given extra impetus to research into sensors[61,183,184,189].

Besides their use for detecting hazardous substances and pathogens, sensors may also start to play an important role in epidemiological and toxicological research[181,198,199]. A lack of accurate data on exposure is the greatest source of uncertainty in epidemiological research and restricts the possibilities for reaching definite conclusions on the relationship between exposure and disease. The small size, low cost and ease of use of the sensors currently being developed make them highly suitable for continuous registration of the external exposure of humans to individual compounds and to mixtures of substances. This applies not only at the level of the broader environment but also at the scale of the individual home, the workplace and the immediate personal environment or even at the level of the points of contact with the human body[199]. However, developments in the determination of personal, external exposure are progressing slowly. The sensors could also be used to provide information on personal activity patterns that affect the degree, frequency, duration and routes of exposures. Finally, sensors could also be used in quantitative detection and monitoring to determine internal exposure to substances in the human body. Sensors therefore offer numerous possibilities for reducing uncertainty when determining exposure. The large flow

of data that continuous monitoring produces will place high demands on data-processing systems.

Because poisoning is caused by interactions at the molecular level, nanotechnologies offer numerous new toxicological research possibilities[181,198]. For example, an AFM can be used to explore the cell surface to create an image of ultrastructural changes under the impact of toxins. The spatial and temporal dynamics in the release of chemical substances, such as neurotransmitters, hormones or cytokines, by individual cells, and the impact of toxic substances on them, can be examined using arrays of electrochemical detectors. Using optical nanofibre probes, it is possible to measure the concentrations of toxic substances or the activities of enzymes involved in the metabolism or programmed cell death (apoptosis) in individual cells[42,200]. Nanoelectromechanical systems (NEMS) based on cantilevers can be used to determine the weight of individual cells accurately. This makes it possible to measure weight changes in cells under the influence of toxic substances[181].

New DNA analysis techniques offer opportunities for studying the interaction between environmental factors and genetic factors when disease occurs. As the Committee has already indicated, a method based on quantum dots has been developed for studying single-nucleotide polymorphisms (SNPs) in genes. The method has been successfully tested on genes that code for enzymes from the cytochrome P450 family[56]. These enzymes play a role in the breakdown of chemical substances in the body. Various forms of an enzyme may differ in functionality and the type which a person has partly determines that person's sensitivity/lack of sensitivity to certain toxic substances.

Finally, a great deal of research is underway into the possibility of using nanotechnologies in environmental remediation operations. Nanoparticles in particular appear to be suitable for this because their small size and their relatively large surface area make them reactive and easy to manage[165]. A lot of research has especially been conducted using nanoparticles of metals, alloys and metal oxides, such as iron, iron/palladium, iron/silver, zinc/palladium, titanium dioxide and zinc oxide. The particles can be injected into the soil *in situ*, can be used *ex situ* in slurry reactors for cleaning soils or sediments, or they can be anchored to fixed carrier material, such as carbon or zeolite, or to membranes, for treatment of water or gases. The particles appear to be capable of reducing a wide variety of common environmental pollutants, such as PCB, organochlorine pesticides and halogenated solvents to harmless hydrocarbons. Nanoparticles of iron are also capable of reducing anions (perchlorate, nitrate and bichromate), heavy metals (nickel, mercury) and radionuclides (uranium dioxide)[165,201]. Carbon nanotubes

have a high affinity for dioxins, which in due course will offer prospects for removing these hazardous substances from water and air. Metal ions such as copper are readily removed from water through ultrafiltration after complexation with dendrimers[202]. A great deal of research is underway into possibilities for removing substances and micro-organisms from groundwater and surface water by means of nanofiltration to make it fit for drinking water production. The reliability of some applications has meanwhile been demonstrated and they are now established techniques. Others are being studied at the laboratory scale[203]. All these remediation techniques can be used in the field but it is advisable to integrate them in the waste flows or production processes as far as possible, thereby preventing foreign substances or organisms from being introduced into the environment[198].

The Committee concludes that a significant amount of nanotechnological research is being conducted in the agricultural, food and environmental sectors, but not as much as in the medical field. There are opportunities for promoting health but it still has to be shown whether materials and products based on nanotechnologies can actually provide environmental benefits.

Chapter 5

Health risks

It has become clear in recent years that nanotechnologies also involve risks. Like other experts[2,3,10], the Committee sees no indication that self-replicating nanorobots will become a reality within the foreseeable future. Present legislation and regulations appear to provide adequate control of the risk of modified existing life forms ('green goo'[204]) escaping at the interface between nanotechnologies and biotechnology[2]. The Committee therefore devotes this chapter to the toxicity of nanomaterials, especially that of free nanoparticles. After all, the same properties that make these particles so interesting from the technological point of view, such as their high reactivity and ability to pass through barriers, could also make them detrimental to humans and the environment. There is no danger from nanostructures that are inseparably joined to larger products, such as chips, because the likelihood of exposure is practically zero. The broader social implications of nanotechnologies that could also involve risks are discussed in the next chapter.

5.1 Types and sizes of particles

Nanoparticles are ubiquitous in the environment. They exist naturally in the soil, water, air and in living creatures[205-208]. They arise there through physico-chemical processes, either under the influence of micro-organisms or otherwise. Nanoparticles can enter the atmosphere during incineration processes (e.g. forest fires, volcanic eruptions) or they can be formed in the air from the gases it contains. The

amount of nanoparticles in the air has increased considerably in recent years through human activity. The combustion of diesel fuel forms a particularly important source. At the same time, nanoparticle scavenging has decreased, owing to lower emissions of larger particles[208,209].

It has been known for some time now that people who inhale fine particles in the workplace can suffer serious damage to their health. A well-known example of this is black lung disease (pneumoconiosis) that is prevalent among coal miners. However, it emerged more than ten years ago that exposure to much lower concentrations of fine particles in ambient air of urban areas can be harmful as well. This involves exposure to particles with a diameter of less than 10 μm, known as PM10[210]. Interest in the toxicity of particles increased sharply with this discovery. A great deal of epidemiological and animal-based research has been conducted in recent years into the health impact of fine particles and fibres*. Besides the aforementioned 'combustion particles', this also includes quartz, asbestos, carbon black and titanium dioxide. Large amounts of ultra-fine forms (particles smaller than 100 nm) of the latter two materials have been produced for decades and are added to plastic and rubber, for example, to improve the material characteristics or as a filler and pigment.

Particle toxicology has now developed into a separate field of toxicology[211]. It focuses mainly on exposure through the respiratory tract. A few modes of action and particle properties that are important in biological activity of particles have been clarified but the details are far from complete. The emergence of nanotechnologies has led particle toxicologists to focus increasingly on nanoparticles[4,208,212-215]. They now have to determine the extent to which available knowledge of 'traditional' particles/nanoparticles can be used for assessing the risks of newer types of synthetic nanoparticles, such as nanotubes and fullerenes, nanowires, quantum dots and particles for drug delivery (see figure 1)[208,212,215,216]. The Committee summarises its findings below in discussions of exposure to nanoparticles, the body's uptake of nanoparticles and their distribution through the body (toxicokinetics), the modes of action and resulting impact on laboratory animals and humans (toxicodynamics) and, finally, the environmental risks.

* Particles with a length at least three times their diameter.

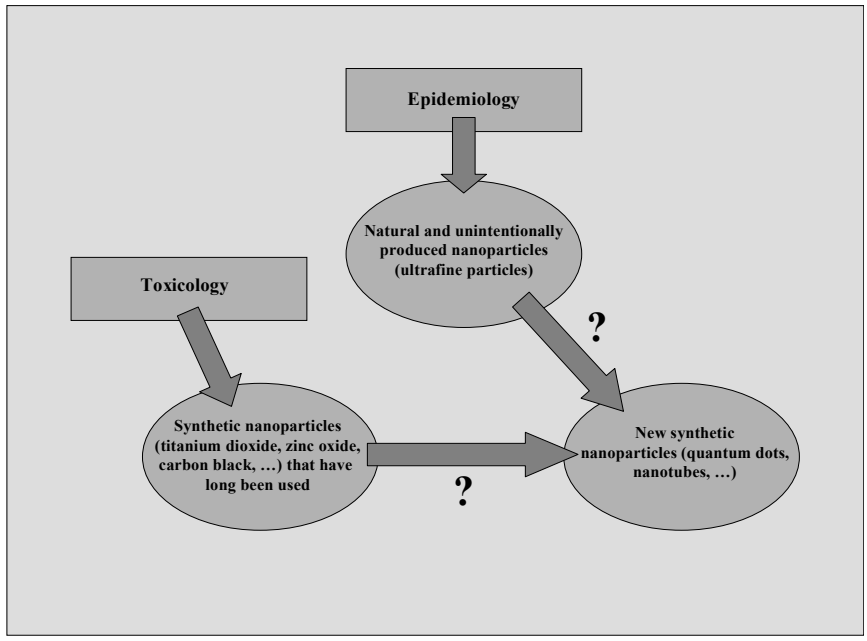

Figure 1 Epidemiological research has demonstrated acute effects on human health of unintentionally produced nanoparticles. Toxicological research has ascertained the existence of chronic effects on laboratory animals as a result of exposure to synthetic nanoparticles that have long been in use (carbon black, TiO_2). The question is: to what extent can these findings be extended to new, synthetic nanoparticles? This is indicated by the question marks.

5.2 Exposure

Exposure to nanoparticles can occur through the respiratory tract, the digestive tract or the skin. Nanoparticles are often also injected directly into the bloodstream for medical purposes (imaging, diagnostics or therapy). Particles can also be released into the body from wearing implants[214,217].

In terms of numbers of particles, exposure to natural and unintentionally produced nanoparticles (such as diesel combustion particles) is high. Although ultrafine particles may account for a small fraction of the total mass of particulate matter in the atmosphere, they account for a large majority of the number of total particles[205]. Around four million of these particles are inhaled with each breath of air and more than half of them remain in the lungs[10]. Westerners are estimated to have an intake of 10^{12}-10^{14} microparticles and nanoparticles per person, per day through food. These particles are mainly silicates, which are found in foodstuffs, medicines and toothpaste as contaminants or additives (pigments and anti-

caking agents). Particles also occur in our intestinal tract because calcium and phosphate coprecipitate in the intestines[218,219].

In comparison with this, the general population's exposure to synthetic nanoparticles is still very low at present. Only a few materials, such as titanium dioxide, zinc oxide and carbon black, are already produced on a commercial scale and used as nanoparticles. The first two of these are used as UV filters in sunblock creams. However, the number of uses is expected to rise rapidly and other nanoparticles are also expected to go into production on a commercial scale in the future[10,220]. For example, various types of nanoparticles are being studied closely for their usefulness as delivery systems for medicines. There are also plans to use delivery systems in functional foods (see chapter 3). Some trial production plants for carbon nanotubes already exist[10]. A factory also exists that produces fullerenes[217]. For the time being, people are most likely to come into contact with synthetic nanoparticles at industrial and university research centres. The level of contact will depend a lot on the production techniques and the safety measures taken.

It is currently not possible to produce carbon nanotubes as individual tubes; they always agglomerate. They are therefore unlikely to occur as individual fibres in the air. Provisional research at locations where these particles are produced appears to confirm this finding[221]. If nanotubes agglomerate, they can probably be inhaled as a 'normal' fine particles, provided they are smaller than 10 µm. If the tubes group into very short 'strands', the risk will be similar to those of conventional fibres. Although there is a possibility of individual nanotubes separating from the agglomerate in the lungs under the influence of lung surfactants, it seems unlikely to occur, owing to the large adhesive forces between the nanoparticles. Large non-inhalable agglomerates may land on uncovered skin. This results in exposure through the dermal route. Many synthetic nanomaterials are produced and incorporated in liquids. This is also why direct dermal absorption and oral ingestion are more relevant exposure routes[217].

5.3 Uptake and kinetics

Humans have always been exposed to fine particles throughout evolution. Up to a point, the body has been able to adapt by developing various mechanisms to keep out the particles or to remove them from the body before they can cause damage. These are the same mechanisms as the ones the body uses to combat microorganisms. For example, the upper airways are lined with fine cilia, which transport the inhaled and deposited particles back to the throat. Particles that reach the deeper airways and alveolar sacs are taken up by phagocytic macrophages, which

transport them back up or remove them through lymphatic vessels and blood vessels. The outer layer of human skin, the epidermis, is covered with a layer of dead, keratinised cells. As long as this horny layer (stratum corneum) is undamaged, it forms an impenetrable barrier for particles and micro-organisms. Finally, although the function of the intestinal epithelium is to allow the passage or to absorb substances, it is impermeable to larger molecules, such as proteins, and to particles.

Research into 'traditional' fine particles has made it clear that they sometimes succeed in circumventing or damaging the defence mechanisms. They are then able to enter the body and spread. This particularly applies to particles with nano-dimensions[208,222]. Many uptake and transport routes in the body have now been shown to exist. Others are hypothetical and require further research. However, little is known about transport rates, or accumulation and retention in organs.

Nanoparticles can readily penetrate the body through the airways. The physical dimensions and surface characteristics of the particles play an important role in this. Provided they do not form excessively large agglomerates, nanoparticles can easily reach the alveolar region. Here, owing to their small size, and depending on their surface characteristics, they are not so readily identified and removed by phagocytic macrophages. Moreover, if the particles are not readily soluble and degradable, they can accumulate to harmful levels. Nanoparticles are taken up passively and actively by cells, such as macrophages or cells of the lung epithelium. This is likewise largely dependent on the surface characteristics of the particles. They may end up in the mitochondria, which could disrupt cellular processes[208]. From the lung epithelium they can reach the underlying interstitium and the blood vessels it contains. This has been demonstrated through research involving both volunteers and laboratory animals[208]. However, the results are ambiguous with regard to the degree to which nanoparticles can gain access in this way to the bloodstream and other organs in the body[213]. On the other hand, the pharmaceutical industry is developing drug delivery systems based on nanoparticles that can pass the blood-brain barrier (see chapter 3). This implies that nanoparticles may also be able to pass this barrier and reach the brain unintentionally. It was recently discovered that inhaled carbon nanoparticles can move to the brain via the mucous membrane of the olfactory tract and the olfactory nerves, as is the case with the poliovirus[223]. Earlier it was shown that gold nanoparticles can reach the brain via the same route. These findings concern laboratory animals (monkeys and rodents) but it is likely that the same transport mechanism operates in humans. The translocation of solid particles along nerve

paths is specific for nanoparticles and is determined by the properties of the particles, such as their size, shape, surface chemistry and surface charge[208].

Conditions in the intestines differ considerably from those in the airways. The constant death and regeneration of the intestinal epithelium and the relatively rapid passage of food through the digestive tract mean that the nanoparticles present in food do not generally stay in the intestines for long. On the other hand, there is a constant new supply of particles. The intestine contains a complex mixture of digested food, bacteria and enzymes, which can affect the properties of nanoparticles[213]. It has emerged that some nanoparticles can move from the intestine via the cells of the small intestine's mucous membrane (the enterocytes) or via lymphatic intestinal tissue (Peyer's patches) to enter the bloodstream and thereby other organs. The size of the particles and the nature of functional groups on the surface of the particles play a role in this[224,225]. For example, particles of polystyrene administered orally to rats only entered the bloodstream through the intestines if the particles were smaller than 300 nm. Moreover, more particles of 50 nm were absorbed than particles of 100 nm. In humans, titanium dioxide nanoparticles were found in the blood of volunteers after oral administration[226]. On the other hand, rats absorbed no iridium nanoparticles (of 18 and 80 nm) from the digestive tract[227].

Relatively little is known about the ability of nanoparticles to enter the body via the skin. The scarce information that is available indicates that nanoparticles are more likely than larger particles to penetrate deeper into the skin. However, there are no indications at present that particles can enter the circulatory system via the skin[213]. The European Commission’s Scientific Committee on Cosmetic and Non-Food Products (SCCNFP) has concluded, on the basis of a confidential dossier, that the titanium oxide nanoparticles used in some sunblock creams do not penetrate deeper than the stratum corneum and that the use of any size of these particles is safe[228]. These products are intended for use on intact skin. Hardly any research has been conducted into whether or not titanium dioxide particles can penetrate deeper into skin that has been damaged, for example by sunburn or eczema. There are indications that nanoparticles can enter lymphatic vessels and blood vessels through the skin at places where the skin is regularly bent, such as the wrist[208]. The SCCNFP does not deem zinc oxide nanoparticles, which are also used as UV filters, to be safe[229]. Before an opinion can be given, more information is required on the skin's absorption of these nanoparticles. On the other hand, the FDA in the United States has approved the use of zinc oxide as a UV filter in sunblock creams. It is unclear whether particle size was taken into account in the decision[10].

In connection with the development of drug delivery systems, the pharmaceutical industry conducts a great deal of research into the uptake of nanoparticles and their distribution through the body. By choosing the right particles and by means of coatings and other surface modifications, the industry endeavours to find the most effective and selective way possible of ensuring that the particles reach the places in the body where the active substance they carry is required. A lot of this knowledge can also be used in assessing the risks of unintended exposure to hazardous nanoparticles. However, data exchanges between pharmacologists and toxicologists are limited[212]. Carbon nanotubes and fullerenes are seen as highly promising drug delivery systems[230]. The behaviour of water-soluble fullerenes in mice was investigated with this aim in mind[231]. They were not efficiently absorbed when administered orally and were excreted within 48 hours, primarily via the faeces. However, when fullerenes were injected intravenously, 90 percent of the dose was still in the body after one week. Within three hours of their administration, the particles were found in the liver, the spleen, the lungs, the heart and the brain. In a similar study, carbon nanotubes, which were first made water soluble through hydroxylation, soon reached the bones and all the organs except the brain, regardless of the method of administration (oral or via subcutaneous, intravenous or intraperitoneal injection)[232]. Around 80 percent of the dose was excreted within eleven days[208]. Such information is essential for the development of drug delivery systems based on these particles but also for assessing the health risks, if the particles get into the environment. The unique biokinetic properties of nanoparticles, which make them so suitable for medical purposes, are precisely why they can lead to toxic effects.

5.4 Effects on laboratory animals and on cells cultivated *in vitro*

Animal-based research using substances that are hardly, if at all, toxic such as titanium dioxide and carbon black in particle form has shown that exposure to the particles through the respiratory tract can cause inflammation and tumours in the lungs. It also emerged that nanoparticles have a larger effect than the same mass of larger particles of the same substance[233,234]. Nevertheless, there are major differences in harmfulness between (nanoparticles of) various substances[235,236]. This probably also depends on the particles' surface characteristics (charge and reactivity), which determine the interaction with structures and processes in or on the cells (the toxicodynamics). Some particles, such as quartz, have a reactive surface that forms free radicals (extremely reactive atoms or molecules). Other types of particles have transition metals (such as iron, nickel or cobalt) on their surface. These can also promote the production of radicals. Some particles form

radicals in a way that is not yet understood. The resulting oxidative stress can cause changes in gene expression and signal transfer in cells[208]. However, less intrinsically toxic particles with a less reactive surface can also damage health, if inhaled in sufficiently large quantities. For example, nanoparticles with positive or negative charges on their surface can adhere to biomolecules (receptors, effectors, enzymes) on or in the cells and disrupt their functioning. The size of the particles plays an important role in all cases. After all, the smaller the particles, the greater their surface area per unit volume that is available to interact with cells and tissues. This explains why the effects observed in animal trials (inflammation and tumours) often correlated most strongly with the total surface area of the particles[208,236].

A permanent presence of a large surface area of particles/nanoparticles in a rat's lungs can cause lung tumours. Impairment of the macrophage-mediated clearance by nanoparticles results in rapid accumulation of particles in the lungs (known as rat lung overload) and in chronic inflammation. The lung tumours are attributed to the mutagenic activity of the reactive substances excreted by cells from the immune system that have been attracted. Moreover, the radicals that are produced on the surface of the nanoparticles may contribute directly to the emergence of mutations and thereby to the formation of tumours[237].

Initial results of research into the effect of single-wall and multi-wall carbon nanotubes on the lungs of rats and mice after intratracheal injection of high doses (1-20 mg/kg) indicate that the tubes can also damage the lungs[238-240]. However, the nature and location of the damage and effects differ from what was expected on the basis of present toxicological knowledge of particles, and this makes it difficult to interpret the results[217]. The high dose of nanotubes in combination with the method of administration (intratracheal instillation*) resulted in obstruction of the airways and atypical connective tissue formation in the form of granulomas. Inhalation tests with realistic exposure levels should provide more clarity about the relevance of the observed damage to health[208,239,241]. Very recent research, in which mice were administered nanotubes via pharyngeal aspiration** (0.5-2 mg/kg), also revealed inflammatory reactions, oxidative stress and connective tissue formation in the lungs[242]. The effects were more severe than those for comparable doses of quartz and ultrafine carbon black. Moreover, the nanotubes had a negative effect on the removal of bacteria from the lungs.

* Intratracheal instillation involves injecting a suspension of nanoparticles directly into the trachea.

** In the case of pharyngeal aspiration, a drop of a suspension of nanoparticles is placed on the base of the extended tongue of an anaesthetised laboratory animal. The particles are then sucked into the lungs by the passing inhaled air.

Carbon nanotubes are often contaminated with traces of iron, nickel and other metals, which are used in their manufacture. These traces could promote the formation of free radicals[243,244]. However, Lam and colleagues found the same type of severe lung damage for tubes containing extremely varied concentrations of metal[238]. Radical formation by metals therefore appears not to be the only reason for the effects observed in this study[243]. However, the high dose and the method of administration (intratracheal instillation) may completely overshadow other effects. Nevertheless, research into the influence of single-wall carbon nanotubes on cultivated human epidermal cells did put forward radical formation under the influence of the iron that was present as the main reason for the observed cytotoxicity[10,245]. Multi-wall carbon nanotubes proved capable of penetrating cultured human epidermal cells and causing inflammatory reactions there[246]. Bonding of chemical groups (phenyl sulphite groups or phenyl carboxyl groups) to the surface of nanotubes resulted in a sharp reduction in the cytotoxicity[247].

Because of their promising medical applications, the toxicity of fullerenes and fullerene derivatives has been studied in greater detail. Their dermal and oral toxicity is low but intravenous administration can lead to acute symptoms of poisoning[217]. Their cytotoxicity is likewise based on oxidative stress. This has been demonstrated by *in vitro* research using various human cell lines[248,249]. In an aqueous environment, fullerenes form oxygen radicals. They oxidise the lipids in the cell membranes, which causes the membranes to leak and the cells to die. Toxicity is greater in the presence of light[217]. The harmful effect of fullerenes can be reduced or prevented by simultaneously administering antioxidants and by derivatisation of the surface with hydroxyl or carboxyl groups. In addition to this, their solubility in water increases sharply. There are indications that fullerenes may also affect the structure, stability and function of DNA molecules[250].

In vitro research using hamster cells revealed major differences in cytotoxicity (measured on the basis of the activity of the enzyme mitochondrial dehydrogenase) between single-wall nanotubes, multi-wall nanotubes and fullerenes[251]. The first of the aforementioned particles were the most toxic and the latter the least. In the same order, they also inhibited phagocytosis by alveolar macrophages. The researchers concluded that carbon nanomaterials with different geometrical structures can display considerable differences in cytotoxicity and bioactivity *in vitro*. It has to be demonstrated whether the same applies *in vivo*. The toxicity or the differences in toxicity may be partly attributable to the pres-

ence of contaminants (amorphous carbon and metals). New tests using ultra-pure tubes should provide a decisive answer.

Some toxicological information has also been collected on dendrimers in connection with their promising possibilities for medical applications[252]. Owing to the wide variety of types, it is difficult to make any general statements. Their cytotoxicity *in vitro* depends on the chemical composition of the core but even more so on the nature of the surface and the degree of branching. Dendrimers with negatively charged groups or with biocompatible polymers on their surface are less toxic than those with positive groups. Toxicity also decreases as the degree of branching increases. This provides a starting point for designing safe dendrimers. Dendrimers can also cause lysis and clotting of red blood cells, and can lead to immunoreactions. Repeated exposure to types that are not readily degradable can result in their accumulation in the body's cells, leading to symptoms of disease. Thorough studies of the biokinetics of dendrimers have been conducted in connection with their possible use as a contrast agent or drug delivery system. However, still relatively little animal-based research into their toxicity has been conducted. It is clear that *in vivo* applications in particular require careful toxicological study, tailored to the nature of the intended medical use.

Various *in vitro* studies have demonstrated the cytotoxicity of quantum dots of cadmium selenide (CdSe) or cadmium telluride (CdTe)[253-256]. The toxicity may be the result of the release of free cadmium ions[253,255], but may also be produced by the formation of oxygen radicals (ROS)[256,257]. On a mass basis, smaller green quantum dots appear to be more toxic than larger red ones[254,255]. This may be explained by differences in the distribution of the nanoparticles in the cell and the larger surface area of a similar mass of green quantum dots. Suitable coatings, such as zinc sulphide or proteins (BSA), can considerably reduce toxicity and may even remove it completely[253]. However, the long-term stability of any such coatings under *in vivo* conditions still has to be investigated[222]. Moreover, some coating materials are themselves cytotoxic[258]. Serious attention must therefore be paid to the risks that quantum dots pose to human health[259].

5.5 Effects on humans

A lot of our current knowledge of the human health hazards posed by fine particles is based on epidemiological research into the consequences of exposure to quartz or asbestos in the workplace and to fine particles in polluted ambient air[208,212]. The Health Council has frequently provided advice in the past on the health impacts of exposure to particles in the workplace or the environment[260-262]. These particles are particularly harmful when inhaled. High exposure to

micrometre-size quartz particles for a few years appears to be capable of causing pulmonary fibrosis (connective tissue formation) and lung tumours. Inhalation of asbestos can cause asbestosis (connective tissue formation), lung cancer or mesothelioma (cancer of the pleural membrane). Numerous epidemiological studies have shown a clear link between the presence of fine particles (smaller than 10 μm or smaller than 2.5 μm) in ambient air and death caused by heart and lung diseases[210,263]. Although the particles mainly comprise chemicals which are thought to be non-toxic, such as carbon and ammonium salts, extremely low levels of exposure appear to have a measurable impact on death rates[212]. Particularly people with weak health are affected. The idea was put forward on the basis of the findings of toxicological research that the ultrafine particles (particles smaller than 100 nm) in the particulate fraction of air pollution may be responsible for the health damage[264-266]. Hardly any epidemiological research to test this hypothesis has been conducted and the available data appear to indicate that both fine particles and ultrafine particles are harmful and that they produce partly different effects[267-269]. A recent study in which healthy and asthmatic volunteers were exposed to ultrafine carbon via the airways did not reveal any noteworthy impact on health[270]. Epidemiological data suggest that fine/ultrafine particles can cause lung cancer in humans[271-273].

The immune system plays an important role in the occurrence of the aforementioned effects. The particles damage macrophages, epithelial cells and possibly other cells in the lung, which results in inflammatory reactions. These responses are indeed part of the normal defence mechanisms in healthy people. However, in individuals with weak health and, depending on the duration and level of exposure and the nature of the particles, even in people in good health, the particles can cause temporary or permanent damage to the airways and can also cause or exacerbate systemic reactions. Some substances that are released during inflammatory reactions can increase the permeability of the respiratory epithelium and the endothelium[274-278]. This facilitates the translocation of nanoparticles to the interstitium and blood vessels. This means that inhaled nanoparticles can have an impact elsewhere in the body, such as the cardiovascular system. However, effects on the circulatory system, such as hypercoagulation[264] and the progression of atherosclerosis[279,280], may also be related to increased levels of reactive substances of the immune system in the blood, which are the result of chronic inflammation in the lungs.

There is a lack of information on the harmful consequences of oral exposure to nanoparticles. A relationship has been suggested between the presence of fine

and ultrafine particles in food and Crohn's disease, a chronic inflammation of the intestinal wall[218]. However, recent research has failed to confirm this[219,281].

Man-made mineral fibres with diameters of a few micro-metres, such as glass wool and rock wool, can cause skin inflammation (dermatitis) through mechanical irritation. There are no indications in scientific references that thinner fibres with diameters of less than 100 nm require special attention in this respect[213].

Titanium dioxide, particularly the mineral form, anatase, is photoactive and can form free radicals in the presence of UV radiation[282]. The free radicals could cause local damage to the skin. To reduce the possible phototoxicity of nanoparticles of titanium dioxide in sunblock creams, the particles are often provided with a coating. This also ensures that the nanoparticles are properly dispersed through the cream. Other substances present in the creams, such as solvents and antioxidants, may also convert the radicals to less harmful substances. Nevertheless, research has shown that various commercial sunburn products form free radicals (ROS) under the influence of UV radiation[282,283]. These can damage DNA and RNA molecules[282]. According to some researchers, the biological significance of this still has to be determined[284]. However, the European Commission's Scientific Committee on Cosmetic and Non-food Products has concluded – on the basis of a confidential dossier – that the use of such substances in sunblock creams with or without a coating is safe[228].

Wear and corrosion of prostheses, such as artificial hips, form another way in which particles of a few tens of a micrometre to a few micrometres in size can enter the body[214,217]. They may consist of, amongst other things, hydroxyapatite or replacement materials, such as metal or polyethylene. These particles can be cytotoxic and cause inflammatory reactions. This can lead to loss of bone and implant loosening[285,286]. The underlying working mechanism still has to be clarified. The particles can spread through the body via lymphatic vessels and possibly also via blood vessels, to ultimately reach the spleen or liver[287,288]. The long-term consequences of this are unknown.

The pharmaceutical industry conducts a great deal of research into the possibility of using nanoparticles for drug delivery (see chapter 3). The research pays a lot of attention to the biocompatibility of the particles. The most frequently observed adverse effects after intravenous administration are hypersensitivity reactions[90]. Extra caution is required in the development of delivery systems based on nanoparticles because the patient groups that are intended to use them[289] are partially made up of people who have been judged by particle toxicologists as the most susceptible to fine/ultrafine particles, namely people with cardiovascular and lung diseases[212].

5.6 Environmental risks of synthetic nanoparticles

Synthetic nanoparticles can enter the environment through waste flows from factories and research laboratories or from products during their life or waste phase. Nanoparticles in medicine and cosmetics can enter the environment through the sewage system, thereby forming a diffuse source of pollution. Moreover, synthetic nanoparticles may be released into the environment intentionally for the purpose of soil remediation or as delivery systems for fertilisers.

Hardly anything is known about the behaviour of nanoparticles in the environment and about possible toxic effects in the environment[290]. For example, it is not known whether they aggregate to form larger particles or where they accumulate and how this affects their toxicity. In the case of fullerenes, which are essentially lipophilic, aggregate formation in water goes together with increased solubility (up to 10 ppm)[217,291]. However, under the influence of salts, the aggregates readily precipitate, which reduces the likelihood of exposure of organisms under natural circumstances[292]. Some information has been obtained from studies of the possibilities of using nanoparticles in soil remediation operations. Iron nanoparticles proved capable of travelling with the groundwater twenty metres into the soil and of remaining reactive for four to eight weeks[201].

There is almost a complete lack of data on how toxic nanoparticles are for organisms other than humans and some species of laboratory animals. Research into the significance of air pollution for ecosystems has thus far focused on gases, such as ozone, sulphur dioxide, nitrogen oxides and ammonia, rather than on particulate matter. A recent small-scale study found that exposure to 0.5 ppm solubilised fullerenes caused a significant increase in lipid peroxidation (fat oxidation) in the brains of juvenile largemouth bass. However, the increase was not significant at an exposure level of 1 ppm. The water in the aquarium also appeared to be cleaner, which indicates an effect of the nanoparticles on the micro-organisms that were present[293]. The antiseptic properties of fullerenes were recently confirmed[291]. The median lethal concentration (48 hours LC_{50}) of colloidal fullerene aggregates was recently established for the water flea at 800 ppb[208]. Nanoparticles can be removed from water by water-filtering organisms, such as mussels. However, they can also precipitate in soils or on sediments[292,294,295] and then be taken up by soil-eating and sediment-eating organisms. Some particles, such as fullerenes, are lipophilic and may therefore accumulate in the fatty tissue of organisms. They could then move up the food chain to humans again[208]. Recent research demonstrated that nanoparticles can

also be harmful to plants. Aluminium nanoparticles were observed to impede root growth of five species of plants[296].

Nanoparticles may be able to influence the biological availability of other environmental contaminants and thereby promote their breakdown by bacteria or cause them to be more widely dispersed or diluted. This means they could also be used in soil remediation operations. However, therein lies a danger too: the availability of the contaminants for plants and animals could also increase and the substances could be transported to vulnerable ecosystems.

In summary, the Committee concludes that information on the harmfulness of new, synthetic nanoparticles is still limited. This applies to both the nature and the severity of possible health and environmental impacts. On the grounds of the available knowledge of 'traditional' particles and the initial research results relating to new nanoparticles, the Committee believes that there are grounds for conducting thorough studies of the toxicological properties of synthetic nanoparticles that are not readily soluble and that are persistent before any mass production and marketing takes place.

Chapter 6

Social implications and ethical issues

The Committee devoted chapters 3 and 4 to an extensive discussion of the technical possibilities that nanotechnologies offer now, or that will be available soon, to promote human health and improve the quality of the environment. The preceding chapter discussed the risks that nanoparticles pose. In the present chapter, the Committee discusses a number of broader consequences of the nanotechnology applications that arise for society and the ethical issues they involve. The Committee also stresses the enabling character of nanotechnologies.

6.1 Old issues, new dimensions

Nanotechnology applications have currently only been realised to a small extent. Most of them are still only concepts in the minds of scientists and engineers. It is difficult to predict which of the applications will eventually become reality and when. Because of increasing convergence, this will partly depend on developments within other branches of science and technology, such as ICT, physics, chemistry, biology/biotechnology, neurosciences and medicine.

It is often difficult to foresee precisely what the social consequences of developments in science and technology will be. Relatively minor technological changes have sometimes had unexpected major consequences. The change from the fixed line to mobile telephone is an example of this. However, if the technological developments themselves are still highly uncertain, as is the case with nan-

otechnologies, it is impossible to predict their precise social implications. The uncertainty explains the many visions and spectres that nanotechnologies conjure up in people's minds. The Rathenau Institute recently provided a fine overview of these images[1].

Nanotechnologies are *enabling* technologies par excellence. This means that they do not form a technological discipline of their own alongside other technological disciplines, such as medical technology, environmental technology, agricultural technology or information and communication technology. They often intersect other disciplines and make progress in each of them possible. Progress of this kind does not usually involve a revolutionary new development but evolution, even if the evolution appears to be increasingly accelerating. This explains why most ethical questions concerning nanotechnologies are neither new nor typical of nanotechnologies. This certainly applies in the short and medium term. They are often raised by previous developments in the aforementioned technological disciplines. When they progress under the influence of nanotechnologies, the existing ethical questions take on a new dimension. They loom larger and more forcefully and their urgency increases. At the same time, they become more complex, which makes it more difficult to find a fitting answer. The Committee illustrates this below on the basis of a few examples that are directly or indirectly connected with human health. In the longer term, new possibilities of such a nature may arise that they constitute a break with the past and society may be faced with completely new moral questions.

6.2 A just distribution

Economic considerations are a powerful driving force behind the development of nanotechnologies. Some economists and industrialists believe that technological modernisation is the only opportunity for wealthy western countries to survive in the competitive battle with emerging economic powers such as India, China and Brazil. They even think that nanotechnologies place the western world at the start of a new economic growth curve[297]. However, the question is, who will reap the fruits of the new technological opportunities and the increase in welfare that will accompany them? And who will pay the costs? There are two sides to the issue of a fair distribution of the benefits and disadvantages. On the one hand, it involves a comparison between current and future generations. This has to do with sustainability. Applications could potentially lead to a more economical use of natural resources and energy sources, the availability of new, cleaner energy sources, a reduction in the impact on the environment and the removal of old pollutants from the environment. Assessments of nanotechnological products in

terms of their contribution to sustainable development should take into account their entire lifecycle. Because most technologies are still in their infancy, the future will have to show the extent to which they actually increase sustainability. Constant reflection on the significance of nanotechnologies during their further development will enable timely adjustments, if required.

On the other hand, it involves a comparison between current generations. In 2000, the United Nations defined eight quantitative goals, the Millennium Development Goals, to improve the lives of poor people in developing countries*. The intention is for the goals to have been realised by 2015. In theory, nanotechnologies offer numerous opportunities for contributing towards the achievement of the goals[298,299]. For example, some issues, such as the detection of diseases and the treatment of water will become cheaper and therefore more widely available. However, time will tell whether developing countries are actually able to reap the benefits. Vaccination against some infectious diseases is also relatively cheap but is nevertheless not becoming prevalent. Technological solutions presented from outside only seem to be effective if they are in line with the customs, standards, aspirations, legislation and knowledge base of the countries where they are introduced[299]. Meanwhile, some developing countries (China, India, Brazil, Mexico and South Africa) are developing their own initiatives in the field of nanotechnologies[298,300]. However, many countries lack suitable regulations in the area of environment, health and working conditions or the structures required for enforcing the regulations[299].

However, scientific and technical progress generally demand considerable investment and therefore mainly take place where the funds are available. They therefore tend to reinforce differences in competitive strength and wealth. This applies to both the gap between developed and developing countries and to differences between the poor and rich in the same community. There is a risk that this will also prove to be the case with nanotechnologies. Although some developing countries succeed in narrowing the 'nano gap' with western countries, many developing countries, such as those in sub-Saharan Africa, remain behind and the gap between the developing countries themselves appears to be widening[300]. Moreover, there is a danger that nanotechnological efforts, even those in developing countries, will mainly focus on commercially interesting products for wealthy consumers in the West rather than on products that are important for people in developing countries. Furthermore, many new 'nano-high-tech' medicines, implants and crop-protection agents will probably be too expensive for poor countries and poor citizens in wealthy countries, especially in

* ttp://www.un.org/millenniumgoals/ (consulted on 6 June 2005)

the short term. Some people fear that sensor technology and other high-tech applications for precision farming will primarily benefit large agricultural businesses and will lead to increases in scale, to the disadvantage of smaller farming businesses[163]. Demand for natural raw materials, such as cotton and rubber from developing countries, may also decrease, owing to the development of nanofibres and making rubber more resistant to wear with the addition of nanoparticles or nanotubes[163]. On the other hand, nanotechnologies offer opportunities for modifying natural starting materials to suit requirements. This would be more likely to increase demand for raw materials.

6.3 Privacy

Nanotechnological developments will make increasingly smaller, cheaper and highly efficient analytical techniques available that make it possible to collect large volumes of data in all kinds of fields. At the same time, developments in information and communication technology will simplify data storage, processing and distribution. This will offer benefits in many areas, such as material and product-flow logistics, safety and security, and diagnostics and customised healthcare. However, the same systems can also be used to observe people secretly or to gather and distribute personal details without proper consent. This will be made even easier if RFID labels are placed on or in the human body. In the latter case, individuals will find it difficult to escape unwanted observation. This all offers unprecedented possibilities for identifying, classifying and evaluating individuals on the grounds of increasingly refined data. To combat the infringement of individual privacy, extensive national and European legislation has been implemented that regulates who is entitled to gather information, the purpose for which it may be used, the conditions under which it may be gathered, who is responsible for its processing and what that person's obligations are. This applies not least in healthcare. Nevertheless, advancing miniaturisation of equipment makes it easier to evade the rules.

6.4 The gap between diagnostics and therapy

However, questions may still arise, even if people specifically consent to data being collected. An illustration of this is the introduction of new and better analytical techniques, such as the tandem mass spectrometer (which is not based on nanotechnology) in heel-prick neonatal screening for congenital metabolic diseases. The Health Council has reported on this in the past[47,301]. Research conducted in the Netherlands and elsewhere in recent years has made it clear that

using tandem mass spectrometry will enable heel-prick blood to be examined for dozens of rare metabolic diseases (multiplex screening). Because newborns with treatable metabolic diseases can benefit considerably from early detection, expanding the possibilities for this could be extremely worthwhile. However, there is a downside. Until recently, there was a broad consensus that neonatal screening should focus on disorders that can be treated (effectively) or prevented. However, this starting point is coming under pressure because of the continually widening gap between possibilities for early detection and the availability of therapies. In the Netherlands, participation in the screening is voluntary, on the basis of informed consent. It will not become any easier to provide proper information when screening covers more disorders at the same time. Moreover, information could become available unintentionally, for instance concerning disorders for which people did not want to be screened, owing to no treatment being available. The likelihood of this increases with the number of parameters measured. The question arises of whether medical practitioners should be permitted to deny parents this information. How can this be squared with the 'right to know' or even the 'right not to know'? Finally, the starting point of voluntary participation may come under pressure from the increasing technical possibilities. Some people fear that introducing the tandem mass spectrometer into neonatal screening will turn out to be a technological development on which it is difficult to impose limits. This issue will not become any easier with the introduction of even newer nanotechnology-based analytical and diagnostic tools.

6.5 The doctor-patient relationship

Medical technology is increasingly shifting from the hospital to the home. The emergence of home-care technology is taking place against various backgrounds. In the first place, there is the desire of patients and their families to stay at home for as long as possible, even in the case of severe or life-threatening diseases. Besides this, there is the political desire to call as much as possible on self-care and volunteer aid. The arguments that play a role in this are possible cost savings and shorter waiting lists. Finally, advanced home-care technology forms a new market for companies in the field of medical technology. The transfer of medical technology is not a new development but actually began with the use of the clinical thermometer in the home at the end of the nineteenth century. This trend is expected to increase as a result of the aging population, further opportunities for extending the lives of people with severe diseases, and growing technical possibilities. Home-care technology can focus on monitoring – following the physical functions such as respiration, body temperature, pulse and blood pressure and

forwarding the data to professional healthcare workers – or on treatment, such as kidney dialysis, intravenous administration of antibiotics, and artificial respiration[302-304].

There are undeniable positive aspects to the development of advanced home-care technology but it also raises ethical issues. The Health Council and the Council for Public Health and Health Care (RVZ) reported on this recently[305,306]. Amongst other things, it concerns the shift of responsibilities to patients' family members, the relationship between the patient and the professional providing the treatment and the role of the supplier of the technical equipment. The availability of cheap and sensitive sensors will increase under the influence of nanotechnologies and equipment will become steadily smaller, handier and easier to use for non-professionals. In combination with other technologies, such as communication and information processing technologies, nanotechnologies will therefore act as an impulse for these developments in home-care technology.

Technological developments combined with growing information requirements of patients who are becoming more independent and demanding, are resulting in self-diagnostics gaining ground[307]. The pregnancy test is an example of a test that has been generally accepted for years and is so reliable that physicians no longer repeat it as a rule. Hundreds of other medical self-tests are now also available through the Internet[308]. The simplest tests can be carried out by people at home using a sample of their own blood, urine or faeces. For the more complex tests, the samples have to be sent to a laboratory and the results are sent back to the person concerned. There are tests for screening that provide a provisional diagnosis which has to be confirmed (e.g. for prostate cancer, intestinal cancer, osteoporosis and diabetes). Diagnostic tests provide a definite answer (e.g. for food intolerances and Chlamydia). Monitoring tests are those which follow the course of a disease or the response to therapy, and, finally, predictive tests indicate, on the basis of genetic or other information, whether a healthy person has an increased likelihood of developing a given disease (such as cardiovascular diseases). The latter category also includes tests conducted with the intention of providing lifestyle advice based on genetic information.

Companies often supply the tests directly to consumers, without any intervention by a physician or other specialist. This raises questions about the safety of the tests, their reliability (error positive and error negative results) and the connection between the results and the disease being tested[308,309]. Other questions concern the information and instructions provided in advance for correct use. An important point is also that most people will need help with interpreting the results and advice on any follow-up steps that may need to be taken. A positive

test result may involve enormous psychosocial consequences, not only for the test subject but also that person's blood relatives in the case of genetic tests. Conducting tests of a highly predictive nature for extremely severe diseases, such as breast cancer, is widely only considered to be a good idea if combined with professional advice and support. There is still no consensus about the level of support required for less severe disorders[308]. A positive result could also have consequences for insurance (life insurance and disability insurance). It is unclear as yet whether self-tests will have a positive or negative impact on the workload of physicians. Test providers claim that cost savings will result from early detection and treatment of diseases that would often otherwise go unnoticed, such as diabetes. However, this has not yet been established[310]. In theory, legislation (In vitro Diagnostics Decree) is in place but its enforcement is difficult because of self-tests provided through foreign websites.

It is clear from the above that technological developments, especially in the field of ICT and nanotechnology, will start a trend towards decentralisation in health care, which will gradually break down the monopolies physicians currently have in the area of diagnosis and treatment, and that the business community will increasingly directly contact patients, who prefer to see themselves as customers. This could give rise to a growing need in healthcare for restructuring and amended or new regulations[311].

6.6 Human enhancement

In the future, nanotechnologies may offer healthy people ways of perfecting themselves according to their own tastes. Improvements may concern outer appearance, performance capabilities or personality characteristics. This is known as enhancement. Artificial retinas, which are currently being developed to restore the sight of blind people or improve that of the poorly sighted could, in theory, also be used to enable people to see infrared radiation. Changes to cochlear implants could enable users to hear sound frequencies or levels that the normal human ear is incapable of hearing[312]. Connecting the human brain to electronic systems for data storage and processing could drastically improve the performance of the human brain in a number of respects. In the United States in particular, there is discussion about the radical human enhancement that will become possible if nano, bio and information technologies and cognitive science increasingly converge in the future[313]. In Europe too, there is growing interest in the opportunities and threats that arise from converging technologies[314].

Enhancement applications using nanotechnologies are still in their infancy at the moment or are entirely speculative. On the other hand, other forms of

enhancement are already commonplace. These include cosmetic surgery, liposuction, piercings, tattoos and the use of anabolic steroids for increasing muscle size. According to some people, this also includes the use (outside the normal indication) of medication to combat impotence, depression and attention deficit hyperactivity disorder (ADHD).[315,316]. They mainly play a role in the achievement of a certain lifestyle or in dealing with the consequences of aging.

An ethical debate has arisen around the term enhancement over the past few years and is being conducted on two fronts: the ethics of self-improvement and the delineation of medicine[315,317]. Both are closely connected with each other. After all, in many cases the enhancement is achieved through the action or cooperation of a physician. There is a complex relationship between treatment and enhancement. When speaking in general, it is therefore hardly tenable that physicians must refrain from cooperating in enhancement. However, an important moral condition is that the intervention must lead to an increase in the well-being of the person concerned. In connection with the health risks associated with the intervention, it is important to determine whether the means and the end are in proportion with each other. In the case of new types of enhancement, too little is known about the adverse side effects, especially in the longer term. The autonomy of the individual is another important consideration. People are generally expected to be able to determine their own needs. This does not affect the fact that physicians have their own responsibility too and can refuse to cooperate, if they are concerned that the result may be serious health damage.

The consequences for society as a whole should also be taken into account, if certain types of enhancements become common practice. Enhancement could contribute to a less desirable cultural change. The pressure to meet certain dominant social standards, such as idealised concepts of what constitutes beauty, could increase at the expense of social multiformity. Our sense of vulnerability and imperfection, which is considered a moral good, could also decline. Enhancement could also put pressure on the opinion that the way in which a person strives to achieve a goal can have an intrinsic value of its own, which is separate from the achievement of the goal. Finally, there is the possibility that enhancement could undermine feelings of sympathy and solidarity towards the people who cannot or do not wish to make use of enhancements of this kind, which would therefore contribute to increasing social differences. After all, many forms of enhancements provide their recipients with social and economic competitive advantages.

The Committee believes that these ethical considerations can generally be extended to future forms of enhancement. Even more types of enhancement will

become available under the influence of nanotechnologies and they will be used more often, be more fundamental and, above all, come closer to the essence of our being. Moor recently stated that it is not a question of whether we should become cyborgs (part human, part computer) but which cyborgs we should become[312]. The identified ethical questions will become all the more frequent and forceful but it will become more difficult to find suitable answers. The same applies in particular to questions in the field of neuro-ethics concerning the possible implications of enhancement for terms such as 'being an individual', 'freedom' and 'responsibility' that also arise through the use of psychopharmaceuticals. Active neuro-implants may be able to restore (some of a) patient's independence – consider for example a spinal cord lesion patient able to operate equipment by brainpower – but they could also be used to deny people their independence; consider the aforementioned 'robotrat'[312] (see section 3.3.4). Forms of enhancements involving the use of implanted computer chips also raise questions about privacy. Implants of this kind could give the carrier access to the databases they contain or that are externally stored but also transmit information to the outside world on that person's identity, location and condition. Entirely new possibilities may exist in the somewhat more distant future. Moor outlines a scenario in which it is also possible, with the right brain implants and computer software to wirelessly enable sections of the brains of different people to work together, as currently happens naturally with the various sections of an individual's brain[312]. This would then give rise to a sort of 'group person' who would present us with entirely new ethical and legal questions.

6.7 Military applications

Nanotechnologies appear to offer new possibilities in the field of defence[10,318,319]. The United States in particular is spending a great deal of money on research in this field. Owing to rapid developments both in sensor technology (cheap, handy and extremely sensitive sensors) and in ICT, the first major impact of nanotechnologies will be on information supplies for national security. Sensors of this kind will also be useful in the early detection of hazardous biological or chemical agents. There are also numerous other applications on the horizon in the field of clothing, camouflage, armour-plating and weaponry. For example, work is underway in the US on a high-tech battle suit that is lightweight, comfortable and protective, and that can even apply pressure on wounds to close them or administer medication. Some applications, such as those to protect soldiers' health or to trace biological or chemical weapons, will raise very few ethical objections. However, others will, such as implants for enhancements

(e.g. for increasing resistance to stress or for decreasing response times), new weapons that use the special properties of materials at the nanoscale, autonomous combat vehicles and killer robots[318]. Many applications may be available within ten to twenty years.

Some applications will be developed for civil as well as military purposes. Especially when there is a large sales market, the driving force behind the developments will be civil applications. In other cases, research and technological development will be for military purposes. However, these developments sometimes clear the way for subsequent civil applications. The similarity between military and civil applications and the fact that equipment is getting smaller all the time make it more difficult to prevent undesirable proliferation of weapons systems. Some people fear that applications will get into the hands of criminal or terrorist groups or individuals[10]. Nanotechnologies could also give the arms race a new impulse. Finally, there is a real possibility that closely intertwining nanotechnologies and military applications will completely undermine public acceptance of nanotechnologies. This could also jeopardise beneficial applications in health care and the environment.

The Committee concludes that, besides the direct consequences for human health, attention should also be paid to the broader social consequences of nanotechnologies. They may be desirable or otherwise. As enabling technologies, nanotechnologies tend to reinforce questions that are raised by other technological developments. In the longer term, entirely new issues may also arise, owing to the development and use of ICT implants in the brain, for example.

Chapter 7

Further with appropriate caution

In this final chapter, the Committee summarises the findings of the preceding chapters and discusses the question of how nanoscience and nanotechnologies can best be socially embedded to achieve optimum use of the benefits while at the same time limiting the risks. The Committee believes that risk governance offers good opportunities for this. The Committee pays special attention to the issue of the toxicity of nanomaterials.

7.1 Nanotechnologies as highly promising, risky and uncertain scientific/technological developments

Nanotechnologies appear to offer major technical and socio-economic opportunities, not in the least in the field of public health, nutrition and the environment. The Committee has summarised some of the opportunities in table 1. However, these are mainly only ideas and concepts at the moment, which provide a strong impulse for nanoscientific research. It is difficult to predict which opportunities will pay off and when, and which of them will ultimately lead to nothing. Very few nanotechnological products are on the market at present. Nevertheless, the Committee expects the number to increase considerably and that nanotechnologies will have a beneficial effect on human health in the coming years. However, the Committee cautions against having unrealistic expectations.

Table 1 A few important applications for nanotechnologies, the present state of development, anticipated benefits and points that require attention.

Nanotechnological applications in	State of development	Possible benefits	Points of attention
Medicine			
Scientific research	Already fully underway	New research possibilities	Nanoparticles possibly toxic for humans and the environment
Pharmacological research	Not much yet	More efficient screening candidate substances, fewer laboratory animals required	
Antiseptic surfaces	First (clinical) applications	More effective disinfection, resistance less likely, fewer chemicals required	Nanoparticles possibly toxic for humans and the environment
Diagnostics *in vitro*	First clinical applications	High sensitivity, earlier detection, cheaper	Nanoparticles possibly toxic for humans and the environment, Increase in gap between detection and therapy, Privacy, Doctor-patient relationship
Diagnostics *in vivo* (imaging)	First applications in patients	High sensitivity, earlier detection	Nanoparticles possibly toxic for humans and the environment, Increase in gap between detection and therapy, Privacy
Drug delivery systems	First (still relatively simple) systems already used on patients	More effective medicines, fewer side effects	Nanoparticles possibly toxic for humans and the environment, Just distribution
Therapy using nanoparticles	First applications in patients (antibiotics, experimental treatment of brain tumours)	More effective medicines	Nanoparticles possibly toxic for humans and the environment, Just distribution
Tissue engineering	First simple products on the market (bone formation, artificial skin)	More rapid repair of broken bones and skin wounds, new organs	Nanoparticles possibly toxic for humans and the environment, Just distribution
Coatings on passive implants	Still in development, partially in clinical test phase	More wear resistant, smoother and more biocompatible	Nanoparticles possibly toxic for humans and the environment
Active implants	Already used clinically (e.g. pacemaker, cochlear implant)	Better function, more biocompatible	Nanoparticles possibly toxic for humans and the environment, Ethical questions concerning autonomy and enhancement, Just distribution, Arms race
Foods and agriculture			
Precision farming	First products already on the market	More targeted fertilisation and pest control at an early stage	Nanoparticles possibly toxic for humans and the environment, Just distribution
Structure improvers for food products	First products on the way	Better structure of food product	Nanoparticles possibly toxic for humans and the environment, Just distribution
Delivery systems for nutrients and flavourings	First products on the way	More nutritional and tastier product	Nanoparticles possibly toxic for humans and the environment, Just distribution

Smart packaging	First products on the way	Fewer cases of food infection	Nanoparticles possibly toxic for humans and the environment
Environment			
Toxicological and epidemiological research	First applications in toxicology	Better toxicological characterisation of substances, better determination of exposure	Nanoparticles possibly toxic for humans and the environment
Detection of chemical substances and pathogens	First commercial products already on the market	Better detection of low concentrations of substances and pathogenic micro-organisms	Nanoparticles possibly toxic for humans and the environment
Soil remediation and water treatment	First applications in development	Restoration of environmental quality	Nanoparticles possibly toxic for humans and the environment
Energy sector	First applications already on the market	More economic use of fossil fuels, alternative fuels, lower CO_2 emissions	Nanoparticles possibly toxic for humans and the environment

The recent plethora of scientific publications on medical applications for nanotechnologies has created the impression that all the world's medical problems will soon be solved. Some people are hoping, for example, that the suffering and death associated with cancer will be a thing of the past within ten years, thanks to nanotechnologies[320]. The Committee thinks this is unrealistic. After all, most research is still *in vitro* and animal-based research, and is investigating whether a particular technique would work in principle. Applications for humans and benefits in health care still have to be demonstrated. It takes ten years to develop a new medicine, owing to the strict requirements that are set for efficacy and safety. This will not be essentially different for new medicines based on nanotechnologies. The same applies to contrast agents and in vivo diagnostics.

Many nanotechnology applications are commercially interesting and the business community would also like to develop them further without government intervention. Nevertheless, the government could provide extra incentives by providing public funds for research that it considers important for human health or the quality of the environment. This is especially important for technological research with a social significance but which is not being developed sufficiently owing to a lack of economic interests. However, research encouragement is often sector or discipline based, owing to the historical compartmentalisation of the flow of subsidies. Nanotechnologies actually need transdisciplinary encouragement from education and research[46], as now takes place in many national nanotechnology initiatives including the Dutch initiative, NanoNed.

As with other technological developments, nanotechnologies also involve new risks. For example, free nanoparticles may be toxic. Attention also needs to be paid to the wider social consequences (table 1). The latter will partially be perceived as benefits but also partially as undesirable and, therefore, as risks. Opinions on this may also differ markedly in a multiform society like ours. It is

currently difficult to estimate the precise nature and extent of the risks. On the one hand, it is unclear which specific products will be marketed; this will also depend on how convergence with other branches of science and technology develops. On the other hand, the influence products have on society is often difficult to predict.

It is precisely in such situations, when a lack of scientific knowledge and differences in value assessments make it difficult to balance the benefits and risks, that it is important to adopt responsible procedures that can facilitate democratic, scientifically-informed control and decision-making. The Committee believes that risk governance offers good opportunities for proceeding with due caution. The Committee discusses this in greater detail below.

7.2 Risk governance

Social scientists have made great use of the term 'governance' in recent years but not everyone interprets it in the same way. The Committee adopts the description used by the International Risk Governance Council (IRGC) in Geneva. In this interpretation 'governance' means the structures and processes for collective decision-making, which involves government as well as private-sector institutions and bodies[321]. These include companies for example, or sector umbrella organisations, employer and employee organisations, professional groups, consumer and patient organisations and organisations concerned with nature, the environment and animal welfare. This all reflects the fact that decisions in modern society are no longer taken top-down by governments but that they are arrived at in networks of all the parties concerned. When these ideas are applied to risks and risk-related decision-making, the term risk governance is used.

The IRGC recently presented a general framework for risk governance[321]. It corresponds closely with our national ideas on dealing with risks[322-325] and the Committee believes it can also be used for dealing with the risks of nanotechnologies. Risk governance has to be given shape at different times in the risk handling chain (figure 2). The risk appraisal and characterisation should initially be conducted by independent scientific experts, including those from the humanities and social sciences (including economists). Interested parties can be involved in this to ensure they contribute their specific knowledge and angles of approach. Value judgements play an increasingly important role in the subsequent steps. What do we deem to be a risk? When is a risk acceptable (no risk-reduction measures required), tolerable (risk-reduction measures required) or intolerable (prohibition or replacement of risk-causing activity required)? Is efficiency the principle element in a risk-management option or do justice and sustainability

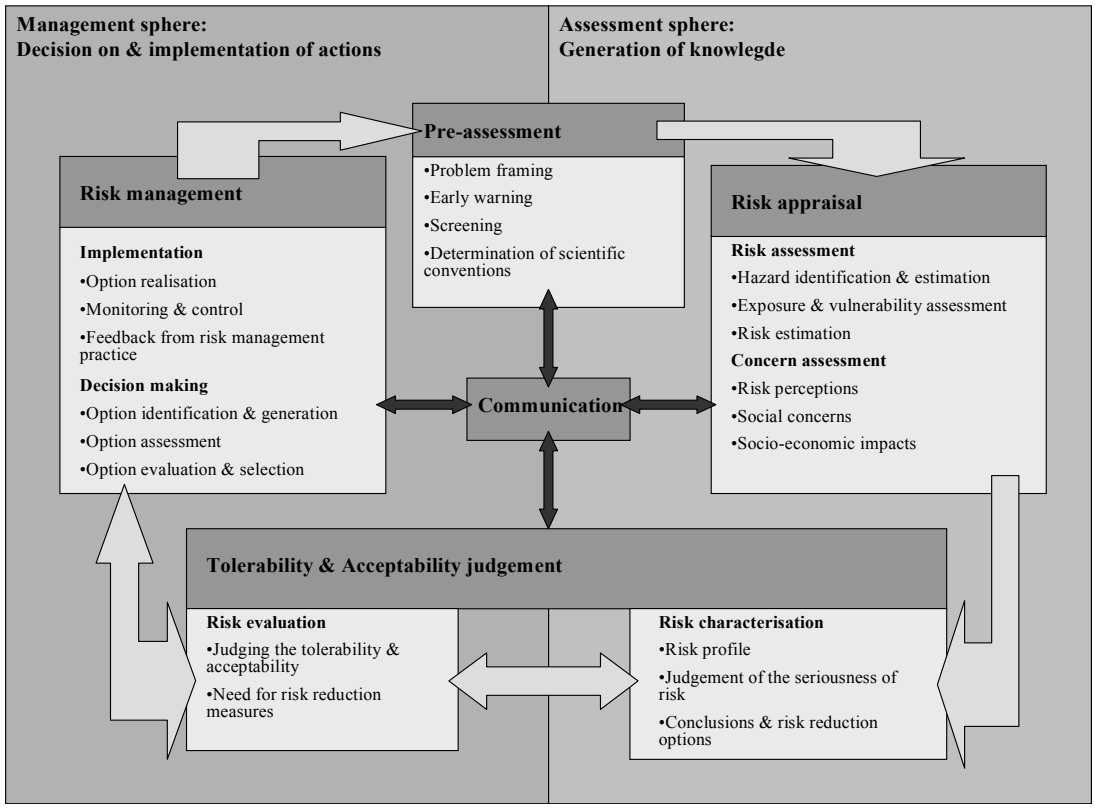

Figure 2 The risk handling chain[321].

also play a role? The success of these steps in the chain requires the involvement of stakeholders with a direct interest and possibly representatives of the public as well. Communication between those who execute the various steps and all the interested parties plays a key role in the risk governance chain. Communication creates an understanding of opposite standpoints, forms the basis for their solutions and engenders trust in the institutional resources for dealing with risks.

Three problems may present a challenge to dealing with risks: complexity, uncertainty and ambiguity[321]. Complexity refers to the difficulty of identifying and quantifying causal links between a multitude of potential causal agents and specific observed effects. Uncertainty refers to a lack of knowledge. Ambiguity indicates differences in the interpretation of the same information or differences in value judgements. The IRGC recognises four risk categories ('simple', 'complex', 'uncertain' and 'ambiguous') depending on which problem dominates.

This does not suggest in any way that risk problems are only characterised by one of the stated problems. For example, ambiguous problems may also involve complexity or uncertainty. None of these issues play an important role in problems in the first category, which does not imply that they are only minor, insignificant problems. They are problems that can be managed using a 'routine-based' strategy. The IRGC indicates what constitutes suitable risk-management strategies for each category, which instruments can be used and what the level and type of consultation should be with stakeholders (table 2). A risk problem's category should be determined at the start of the risk handling chain (pre-assessment phase), as it determines the further approach.

7.3 Risk governance in nanotechnologies

As the Committee has already indicated, nanotechnologies do not form a single, more or less sharply definable technology, such as biotechnology and ICT. Nanotechnologies are rather a collection of extremely varied technologies and applications with very little relationship between each other and which often have nothing more in common than the scale at which the material is studied and manipulated, and the unusual properties that the material can display at that scale. Moreover, nanotechnologies are at widely varying stages. They are also largely 'enabling technologies', which aid progress in technological developments in a wide variety of fields but thereby also strengthen the associated problems they involve. To achieve effective risk governance, it is therefore important not to treat nanotechnologies as a single group but as individual (types of) applications, each with its own specific risks.

To enable nanotechnologies to be developed along the right lines, it is important to identify at an early stage any actual, or indications of, undesirable or hazardous impacts on health, working conditions, the environment, ethics and social relationships. This is in fact concerned with the selection of risk issues that have to be dealt with according to the risk handling chain (figure 2). The Committee believes this can best be done by a broad-based committee, appointed especially for that purpose, which is composed not only of independent scientific experts but also stakeholders with a direct interest and representatives of the public. After all, what constitutes a risk cannot only be determined on the basis of scientific data; different parties may have different points of view on this. Proper agreements on selection criteria and the procedures to be followed are essential for this. Given the pace at which nanoscience and nanotechnologies are developing, the Committee believes it would be advisable for a monitoring committee of this kind to report every two years to the government and parliament.

Table 2 Categorisation of risk problems with an indication of the associated risk management strategies, suitable instruments and types of consultations with stakeholders[321].

Risk Problem Characterisation	Management Strategy	Appropriate Instruments	Nature of consultation and stakeholders
Simple	Routine-based: (tolerability/ acceptability judgement)	⇒ Applying 'traditional' decision-making • Risk-benefit analysis • Risk-risk trade-offs	Instrumental discourse • Staff of authority (authorities) concerned
	(risk reduction)	• Trial and error • Technical standards • Economic incentives • Education, labelling, information • Voluntary agreements	
Complex	Risk-informed: (risk agent and causal chain)	⇒ Characterising the available evidence • Expert consensus seeking tools: • Delphi or consensus conferencing • Meta analysis • Scenario construction, etc. • Results fed into routine operation	Epistemiological discourse • Staff of authority (authorities) concerned • External experts
	Robustness-focussed: (risk-absorbing system)	⇒ Improving buffer capacity of risk target through: • Additional safety factors • Redundancy and diversity in designing safety devices • Improving coping capacity • Establishing high reliability organisations	
Uncertain	Precaution-based: (risk agent)	⇒ Using hazard characteristics such as persistence, ubiquity etc. as proxies for risk estimates Tools include: • Containment • ALARA (as low as reasonably achievable) • BACT (best available control technology), etc.	Reflective discourse • Staff of authority (authorities) concerned • External experts • Stakeholders • Industry • Groups directly concerned
	Resilience-focussed: (risk absorbing system)	⇒ Improving capability to cope with surprises • Diversity of means to accomplish desired benefits • Avoiding high vulnerability • Allowing for flexible responses • Preparedness for adaptation	
Ambiguous	Discourse-based:	⇒ Application of conflict resolution methods for reaching consensus or tolerance for risk evaluation results and management option selection • Integration of stakeholder involvement in reaching closure • Emphasis on communication and social discourse	Participative discourse • Staff of authority (authorities) concerned • External experts • Stakeholders • Industry • Groups directly concerned • General public

Once a risk problem has been identified, its risk category should be determined. All the parties concerned should strive to reach agreement on this. The process can be intensive and time-consuming. The chosen category indicates the management strategy that can best be followed, the instruments that are most suitable and the shape that should be given to consultations with stakeholders (see table 2).

The Committee thinks that the IRGC's proposed categorisation of risk problems can be used for previously identified problems that arise from (or are reinforced by) nanotechnology applications (table 3).

Simple problems

The Committee believes that the privacy problem, which will increase with nanotechnology applications, belongs in the 'simple' category. The potential negative consequences are clear, the applicable value judgements are hardly controversial and there is little scientific uncertainty. Insofar as it is already necessary to involve stakeholders, the discussion should mainly be about the question of which instruments could best be deployed to solve the problem. There is, of course, always the chance of an apparently simple risk problem proving to be more complex, uncertain or ambiguous than it first appeared to be. For example, value judgements can still play a role if the aspect of privacy has to be balanced against the importance of combating terrorism. It is therefore essential to review risk problems regularly. The problem of the risks of diagnostic self-tests is probably also covered by this category. The legislation is clear and it is mainly a question of enforcing the law. The toxicity of readily degradable, synthetic nanoparticles, such as those of gelatine used for drug delivery, is another risk problem that the Committee believes is covered by the 'simple' category. There is little scientific

Table 3 Categorisation of risk problems that arise from or are reinforced by nanotechnology applications in the risk categories recognised by the IRGC[321].

Risk category	Risk problem
Simple	Privacy problem
	Self-tests (?)
	Toxicity of readily degradable nanoparticles
Complex	Sustainability (?)
	Gap between rich and poor
Uncertain	Toxicity of poorly degradable nanoparticles
Ambiguous	Gap between diagnostics and therapy
	Advanced home-care technology
	Enhancement
	Some military applications of nanotechnologies

uncertainty and existing procedures appear to be adequate for controlling the possible risks (e.g. of toxic degradation products).

Complex problems

The problem that nanotechnologies may increase the gap between rich and poor and especially between rich and poor countries comes into the 'complex' category, owing to the large number of factors that affect the size of the gap. The discussion is mainly a scientific problem in which the focus is on solving cognitive conflicts. Participation in the debate by various parties is based on their claim to contribute specific knowledge to the debate. The Meridian Institute recently identified options for controlling the risk of the 'nanodivide'. One option is that countries are called up to link their development aid programmes to programmes for developing nanotechnologies in Third World countries[299]. However, the efforts have to focus on applications that meet the needs of the local population and not those of wealthy consumers in the West[300].

The sustainability problem possibly also comes into this category. However, besides complexity, there is also uncertainty. After all, it is difficult to see at the moment whether savings on raw materials and fuels achieved by nanotechnologies will be cancelled out by changes in consumer behaviour. There are therefore also arguments in favour of categorisation in the following category.

Uncertain problems

The problem of the toxicity of free, not readily degradable, synthetic nanoparticles is characterised by a great deal of uncertainty about the question of how these particles' special properties will influence their behaviour in the environment, their uptake and distribution in the body and their ability to cause or exacerbate disease symptoms. A precautionary approach should form the starting point for managing risks that are characterised by a high level of uncertainty. Reflective consultation with all the stakeholders is therefore essential. The aim is to find a proper balance between the possibilities of over-protection and under-protection. The way in which the precautionary approach should be employed when dealing with nanomaterials that may be toxic has been the subject of intense international debate in recent years. The Committee therefore discusses this in greater detail in a separate section.

Ambiguous problems

The increasing gap between diagnostics and therapy, advanced home-care technology, enhancement (e.g. with ICT implants in the brain), and certain military applications of nanotechnologies are risk problems that the Committee believes should be categorised as 'ambiguous problems'. The problem is dominated by differences in convictions, opinions on what is worthy of protection, visions of what good care entails and ideas of the future. Questions such as 'Should we allow everything that is possible?' and 'How far do we want to go?' play a role here. In multiform Western societies, questions of this kind unavoidably lead to discussions, as demonstrated in the past by technology debates concerning nuclear energy, biotechnology in agriculture and the use of embryonic stem cells. For example, some people consider cyborgs to be the ideal further development of humans. However, others fear that this will affect the essence of being human. Problems of this kind require the most extensive type of participation involving not only stakeholders with a direct interest but also the public. The aim of the consultation is to identify common values, create an understanding of conflicting viewpoints and to find options that enable people to put their own vision of 'a good life' into practice, without detriment to the views of others. The Committee discusses public involvement in greater detail below.

The International Risk Governance Council has meanwhile started its own *risk governance in nanotechnologies* project. The project will conclude in the coming summer with a conference. The organisation hopes to achieve consensus there between all the parties involved on the right approach to risk governance for nanotechnologies[326].

Each technology's final impact is a co-production of all kinds of influences (stakeholders, public, media, insurance companies, their value judgements and their interactions) and the characteristics of the technology itself. (Constructive) technology assessment ((C)TA) is concerned with how these co-production processes progress and what the possibilities are for influencing them. The aim is to find possibilities for giving shape to a technology's development at an early stage, in such a way that it meets the social conditions in which it has to operate. A great deal of attention is paid to the technology's ethical, scientific, social, economic and environmental aspects. Part of the budget of NanoNed, the major Dutch national research programme, has been reserved for a (C)TA subprogramme. The Committee thinks that such a subprogramme could provide very useful information for risk governance. The Committee also recommends that

funds should be provided for CTA activities in future national nanotechnology programmes.

7.4 Nanoparticles and precaution

As the Committee indicated above, it believes that the problem of the toxicity of free, not readily degradable, synthetic nanoparticles should be placed in the category for issues that are characterised by a great deal of uncertainty. A risk management strategy based on the precautionary principle is appropriate for this category (see table 2). This principle has been described in various ways. The Committee uses the description set out at the Rio Summit in 1992, because it is one of the most commonly used:

> 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.

However, a description like this does not stipulate when and how the precautionary principle should be applied. This requires separate rules and procedures. A lot of scientific research and legal consultations are currently concentrating on this question, in the Netherlands as well as elsewhere. Another Health Council committee is currently examining this topic.

Reduction of emissions and exposure

The Committee believes that the decision to declare the precautionary principle applicable to free nanoparticles that are not readily degradable actually ensues automatically from the decision to place the problem of particle toxicity in the 'uncertain' category. It is therefore necessary for all the parties concerned to reach agreement about this at the start of the risk handling chain. Once that decision has been taken, the IRGC diagram (table 2) indicates which risk management instruments are most suitable. These are, for example, the ALARA* principle, in which the emission or exposure is kept as low as reasonably possible, and the BACT** principle, in which an attempt is made to use the best available control technology. In the case of synthetic, not readily degradable

* As Low As Reasonably Achievable
** Best Available Control Technology

nanoparticles, the Committee believes this means it is advisable to avoid exposure in the workplace and environmental emissions or, in any case, to minimise them. It still has to be determined whether the current procedures and techniques for protecting people in the workplace from excessive exposure and for removing substances from the waste flow are adequate for nanoparticles. The emission of free nanoparticles during the product's entire lifecycle also needs to be determined and limited. The Commission believes it is advisable to postpone the use of synthetic, free nanoparticles in the environment, for soil remediation operations for instance, until it is clear that the benefits outweigh the risks. If products (medicines, medical devices, cosmetics, crop-protection agents, biocides, etc.) contain synthetic, free nanoparticles, the risks these particles pose to human health and the environment should be considered separately in the (compulsory) safety assessment. Here too, the use of nanoparticles is only permitted if it is clear that the benefits outweigh the risks. These measures can also act as an incentive for the development of safe nanoparticles.

In keeping with the British Royal Society and the Royal Academy of Engineering[10] the Committee recommends that synthetic, free nanoparticles should be treated as new substances, even if the chemical composition is not new. After all, the nano-dimensions could give a substance novel properties. This means that the toxicity of nanoparticles could differ qualitatively and quantitatively from the toxicity of the same material in the form of larger particles. By way of supplement to the new European REACH* regulations that are currently being developed for chemical substances – that require registration and toxicological assessment, if the annual production or import of a substance exceeds 1000 kg – the Committee also recommends that separate regulations should be drafted for free nanoparticles stipulating a lower production and import threshold or none at all.

Modification of current toxicity tests

The Committee also believes that an accompanying policy is required for generating scientific data and insights concerning the precise nature and extent of the toxicological risks that nanomaterials present. Current insights are still inadequate. There is an urgent need for extra funding for research and the need for international coordination is even greater[24]. Better cooperation is also needed between particle toxicologists and pharmacologists who develop medicines on

* REACH stands for Registration, Evaluation, and Authorisation of Chemicals; see http://europa.eu.int/comm/environment/chemicals/reach.htm

the basis of nanoparticles[46]. It is doubtful whether the present methods for screening and evaluating the risks of substances and for managing exposure levels are adequate for nanomaterials[327]. The predominant opinion among toxicologists is that, although the conventional (eco)toxicity tests currently used for chemical substances (including medicines, biocides and crop-protection agents) provide a useful starting point for evaluating the potential hazards of nanoparticles, they need to be modified and that supplementary tests are required to do justice to the unique properties of the particles concerned[46,215,216]. An extremely important requirement is the physico-chemical characterisation of the nanomaterials which are used to conduct toxicity tests. This concerns characteristics such as particle size, particle size distribution, agglomeration status, shape, crystal structure, chemical composition, surface area, surface chemistry, surface charge and porosity[222,284,328]. These are not part of the standard measurements at the moment. It would also be advisable to characterise the administered dose against appropriate physical metrics in all toxicity tests. The three principle physical metrics are mass, surface area and the number of particles. Because it is unclear at the moment which measurement metric is the most relevant, it is important for all three to be measured or inferable in every study[215,222]. The present regulations do not require this[216]. Moreover, it would be advisable to arrange for the exposure route, exposure levels and particle properties used in the tests to correspond as closely as possible with the actual practice[222,328]. To this end, methods and equipment should be made available for routinely measuring nanoparticles (and their properties) in different media, i.e. in the body as well as the environment[216]. At least until sufficient information is available to answer the question of how the toxicity of nanoparticles differs from that of larger particles[328], it is recommended that both control particles of known toxicity and microparticles of the same chemical composition as the nanomaterial should be included in the tests[215,222]. In addition, more attention needs to be paid to the distribution of nanoparticles throughout the body (biokinetics) and to the possibility of nanoparticles exacerbating an already poor state of health. Finally, it is especially important for studies to be conducted of the nanoparticles' mechanisms of interaction with the body at the subcellular and molecular level. The key question in this concerns which unique physico-chemical properties of nanoparticles translate into unique modes of action[215,328].

Screening strategy

A start was recently made on a screening strategy for identifying the hazards that synthetic nanomaterials pose[215,222]. It includes physico-chemical characterisation of the material and *in vitro* and *in vivo* toxicity tests. The *in vitro* tests are important in this for clarifying working mechanisms and for the initial, quick toxicological characterisation of new materials during their development process. Many usable measurement and test methods and techniques are available in principle, in addition to which new ones are required. It is essential for them to be made suitable for routine use and for them to form part of the (statutory) directives.

The proposals are a start. Further refinement will be possible, as more experience is acquired in the research. Given the large number of different nanomaterials and applications being developed, it is important to determine which should be tested first. Priority should be given to the materials that are closest to being marketed and those that will be produced in large volumes as free nanoparticles, and therefore present the greatest likelihood of human exposure or environmental pollution[215]. The final goal is to move the risk problem presented by the toxicity of nanomaterials from the 'uncertain' category to the 'simple' category, so that only a small level of scientific uncertainty remains and a routine approach is sufficient.

7.5 International cooperation and regulations

Many fields affected by nanotechnologies are already covered by extensive legislation and regulations to protect humans and the environment and to prevent undesirable social developments. This includes legislation on existing and new chemical substances, crop-protection agents, biocides, veterinary medicines, medicines, medical devices and cosmetics, as well as legislation on population screening, consumer products, food, the environment, working conditions, privacy and insurance. The Committee believes it will be constantly necessary to ensure that the applicable legislation and regulations in all of these fields is sufficient, in relation to nanotechnological developments. In connection with this, the European Commission's action plan mentioned above encourages member states to review their legislation[329]. Warnings about shortcomings may come from the sectors themselves but also from the aforementioned monitoring committee. However, for economic reasons and in connection with providing efficient protection a lot of legislation exists at the international level, particularly at the level of the European Union. This legislation could only be amended through interna-

tional consultations. Apart from this legal aspect, national differences in the acceptance of new technologies could lead to tension. An example of this is the difference between the basic attitudes of Europe and the United States towards genetically modified food. Conflicts could also arise if some countries would like to embrace nanotechnologies for human enhancement, in sport for example (compare with the use of doping) or for military purposes, if others do not wish to do so. Consequently, risk governance concerned with nanotechnologies cannot be limited to the national level but has to take place at the international level, too. This should not only involve states but also the business community and relevant international organisations[321].

Numerous international organisations (UNEP, UNIDO, UNESCO, ISO, IUPAC, CAS, OECD, ILO, WHO)* are currently working on nomenclature, test procedures and legislation for nanomaterials. There is an urgent need for the work to be internationally coordinated[24]. The Committee therefore recommends the Netherlands to actively contribute to that coordination in the OECD's new working group Health and Environmental Safety Implications of Nanomaterials.

The European Group on Ethics (EGE) recently formulated an opinion on the ethical aspects of ICT implants in the human body[330]. The EGE called for, amongst other things, a statutory ban on ICT implants that enable remote control of the will of people, or for enhancement with a view to dominating others, to change identity, memory, self-perception or the perception of others. The EGE also pointed out that there are currently no regulations on non-medical applications. It also recommends that medical implants should be regulated in the same way as drugs when the medical goal is the same. In addition to the latter point, the Committee points out that various nanotechnologies are increasingly blurring the boundaries between medicines and medical devices, and therefore necessitate amendments to the relevant international legislation[331].

Some bodies are calling for completely new, separate regulations to ensure that nanotechnologies are developed along the right lines[332] but, along with others[333], the Committee believes that the use of existing regulations would be a better policy option. The applications are far too diverse for separate regulations. Many matters are also already completely or partially covered by existing laws. Entirely new legislation would therefore lead to duplication and over-regulation. That would create unnecessary delays in innovation and would only offer spuri-

* UNEP: United Nations Environment Programme; UNIDO: United Nations Industrial Development Organization; UNESCO: United Nations Educational, Scientific and Cultural Organization; ISO: International Organization for Standardization; IUPAC: International Union of Pure and Applied Chemistry; CAS: Chemical Abstracts Service; OECD: Organisation for Economic Co-operation and Development; ILO: International Labour Organization; WHO: World Health Organization)

ous protection. Moreover, in the Committee's opinion, many of the stated ethical and legal problems are not characteristic of nanotechnologies. The problems do not arise from the use of nanotechnologies but from goals that people are aiming or could aim to achieve, and the problems are therefore related to the nature of the applications. Nanotechnologies are only a means, even if they do have a highly facilitating effect. The need for supplementary or amended regulations does not therefore arise from the involvement of nanotechnologies but from the fact that applications can now become a reality, even if they are undesirable or their desirability is a point of discussion.

7.6 Involving the public

It is especially necessary to inform the general population properly about risk problems that are characterised by their ambiguity, to listen sincerely to the public's wishes, aspirations and fears concerning new scientific/technological developments and to involve the public in decision-making about the technologies[334]. In its recent action plan for nanosciences and nanotechnologies, the European Commission therefore called on member states to enter into dialogue with the public[329]. Numerous instruments are available for this, such as citizens' panels and juries, consensus conferences, ombudspersons, citizens' advisory committees, etc.[335-341]. A 'Nano Jury' held in the United Kingdom last year provided an opportunity to gain experience in this area. In 2004, the Rathenau Institute in the Netherlands drew up the first draft agenda for a national public discussion of nanotechnologies[1]. In 2005 and 2006, the institute will get public dialogue underway by focusing on a number of specific nanotechnology applications[342].

There is a crying need among all the parties concerned to learn the lessons from the major difficulties that accompanied the introduction of genetically modified food, at least in Europe[343,344]. The PABE research revealed that problems had been caused by misconceptions about public opinion[344,345]. The general public only has a limited knowledge of science and technology. However, concerns about biotechnology are often not a result of a lack of knowledge or incorrect information. Consequently, scientific education would not remove the concerns[346]. There are even indications that greater knowledge increases scepticism and polarisation. Many people believe that scientists cannot have a comprehensive view of all the long-term consequences of their own work for ecosystems, human health and social relations. The benefits that are experienced certainly play a role in acceptance – compare the 'red' medical biotechnology with the 'green' agricultural biotechnology – but do not dominate it. The more important factors are free choice, transparency and information tailored to a per-

son's requirements. Many people realise the necessity of weighing the costs against the benefits but have the feeling that they are not told how this is done and that their opinion is not taken into account. This gives rise to the suspicion that economic interests weigh heavier in regulations and risk management than health and the environment. Associations with other 'health affairs', such as BSE, dioxins in animal feed or pesticide use are not the result of confusion about the biological processes concerned but of the realisation that institutions can fail and that there is a possibility of negligence, a lack of expertise and funding and even fraud in supervisory bodies. Citizens want producers and authorities to carry out realistic risk evaluations. Statements by experts who deny or play down the risks are more likely to be considered worrying or unreliable by many people. The argument that the new products are so important for developing countries is viewed as hypocritical because it is the wealthy western countries that are inundated with them. The PABE researchers concluded that consumers may be concerned about products, even if they do not openly admit it and buy the products anyway[344,345]. Deeply felt, unexpressed concerns accumulate and eventually affect public reactions to technological innovation. Instead of wondering how communication can be improved with a view to gain/regain trust, it is better to realise that those reactions are a response to the behaviour of the institutions concerned. Therefore, according to the PABE researchers, instead of setting out to make the public 'more rational', institutions – governments, research organisations and the business community – should be more attentive to their own behaviour. Einsiedel and Goldenberg reach a similar conclusion[343].

The Committee subscribes to this analysis and believes it applies equally well to the introduction of nanotechnologies into society. Institutions would like to enjoy the public's trust but they will also have to earn it. Besides expertise, decisiveness and integrity, the key words here are openness and accountability.

References

1 van Est R, Malsch I, Rip A. Om het kleine te waarderen... Een schets van nanotechnologie: publiek debat, toepassingsgebieden en maatschappelijke aandachtspunten. The Hague: Rathenau Instituut; 2004: Werkdocument 93.

2 Kampers F. Potentiële risico's van bio-nanotechnologie voor mens en milieu. Oriëntatierapport in opdracht van de COGEM. Wageningen: Wageningen UR; 2004.

3 Koeman JH, Dekker C, Nolte RJM, Reinhoudt DN, Rip A, Robillard GT *et al*. Hoe groot kan klein zijn? Enkele kanttekeningen bij onderzoek op nanometerschaal en mogelijke gevolgen van nanotechnologie. The Hague: KNAW, Werkgroep Nanotechnologie; 2004.

4 de Jong WH, Roszek B, Geertsma RE. Nanotechnology in medical applications: possible risks for human health. Bilthoven: RIVM; 2005: 265001002.

5 Roszek B, de Jong WH, Geertsma RE. Nanotechnology in medical applications: state-of-the-art in materials and devices. Bilthoven: RIVM; 2005: 265001001.

6 Baumgartner W, Jäckli B, Schmithüsen B, Weber F. Nanotechnologie in der Medizin. Bern: TA-Swiss; 11-2003: TA 47/2003.

7 Morrison M. Nanotechnology and its implications for the health of the EU citizen. Nanoforum; 2003.

8 Malsch I. Benefits, risks, ethical, legal and social aspects of nanotechnology. Second Edition. Nanoforum; 2005.

9 Wagner V, Wechsler D. Nanobiotechnologie II: Anwendungen in der Medizin und Pharmazie. Düsseldorf: Zukünftige Technologien Consulting, VDI Technologiezentrum GmbH; 2004.

10 Royal Society & Royal Academy of Engineering. Nanoscience and Nanotechnologies. Opportunities and uncertainties. London: Royal Society & Royal Academy of Engineering; 29-7-2004.

11 Goldman L, Coussens C. Implications of nanotechnology for environmental health research. Washington D.C.: Institute of Medicine, The National Academies Press; 2005.
12 ETC group. No small Matter! Nanotech Particles Penetrate Living Cells and Accumulate in Animal Organs. Ottawa: ETC group; 2002: Communiqué 76.
13 ETC group. The big down: from genomes to atoms. Winnipeg: ETC Group; 2003.
14 ETC group. No small Matter II: The Case for a Global Moratorium. Occasional Paper Series 2003; 7(1).
15 Arnall AH. Future Technologies, Today's Choices. Nanotechnology, Artificial Intelligence and Robotics; a technical, political and institutional map of emerging technologies. London: Greenpeace Environmental Trust; 2003.
16 Feynman RP. There's plenty of room at the bottom; an invitation to enter a new field of physics. Engineering & Science 1960; 23(22 Feb.).
17 Taniguchi N. On the basic concept of 'nanotechnology'. In: Proceedings of the international conference on production engineering. Tokyo, Part II. Tokyo: Japan Society of Precion Engineering; 1974: 18-23.
18 Toumey C. Apostolic succession. Does nanotechnology descend from Richard Feynman's 1959 talk? Engineering & Science 2005; 68(1/2): 16-23.
19 Kouwenhoven LP. De science en fiction van nanotechnologie. Inaugurele Rede. 16-6-2000. Delft Technische Universiteit Delft.
20 Binnig G, Rohrer H, Gerber Ch, Weibel E. Surface studies by scanning tunneling microscopy. Phys Rev Lett 1982; 49: 57-61.
21 Eigler DM, Schweizer EK. Positioning single atoms with a scanning tunneling microscope. Nature 1990; 344: 524-526.
22 Roco MC. Nanotechnology: convergence with modern biology and medicine. Curr Opin Biotechnol 2003; 14(3): 337-346.
23 Ellen GJ, Enzing C, Luiten H, Willems M. Nanotechnologie en de kansen voor het milieu. Delft: TNO Bouw en Ondergrond; 2005: I&R 2005-17.
24 Service RF. Nanotechnology. Calls rise for more research on toxicology of nanomaterials. Science 2005; 310(5754): 1609.
25 Tweede Kamer. Wetenschapsbudget 2004. vergaderjaar 2003-2004, 29338 1. The Hague: Sdu Uitgevers, 26-11-2003.
26 Iijima S. Helical microtubules of graphitic carbon. Nature 1991; 345: 56-58.
27 Tenne R, Rao CN. Inorganic nanotubes. Philos Transact A Math Phys Eng Sci 2004; 362(1823): 2099-2125.
28 Vasita R, Katti DS. Nanofibers and their applications in tissue engineering. Int J Nanomedicine 2006; 1(1): 15-30.
29 Gogotsi Y, Nikitin A, Ye H, Zhou W, Fischer JE, Yi B *et al*. Nanoporous carbide-derived carbon with tunable pore size. Nat Mater 2003; 2(9): 591-594.

30 Swan EE, Popat KC, Grimes CA, Desai TA. Fabrication and evaluation of nanoporous alumina membranes for osteoblast culture. J Biomed Mater Res A 2005; 72A(3): 288-295.
31 Kohli P, Martin CR. Smart nanotubes for biotechnology. Curr Pharm Biotechnol 2005; 6(1): 35-47.
32 Kroto HW, Heath JR, O'brein SC, Curl RF, Smalley RF. C60: Buckminsterfullerene. Nature 1985; 318(6042): 162-163.
33 Krätschmer W, Lamb LD, Fostiropoulos K, Huffman DR. Solid C60: a new form of carbon. Nature 1990; 347: 354-358.
34 Holister P, Vas CR, Harper T. Fullerenes. Technology white papers nr. 7. London: Cientifica Ltd; 2003.
35 Svenson S, Tomalia DA. Dendrimers in biomedical applications--reflections on the field. Adv Drug Deliv Rev 2005; 57(15): 2106-2129.
36 Alivisatos P. The use of nanocrystals in biological detection. Nat Biotechnol 2004; 22(1): 47-52.
37 Drexler KE. Engines of Creation. The coming era of Nanotechnology. New York: Anchor Books; 1986.
38 Crichton M. Prey. London: HarperCollins; 2002.
39 Mnyusiwalla A, Daar AS, Singer PA. 'Mind the gap': science and ethics in nanotechnology. Nanotechnology 2003; 14: 9-13.
40 Public puts faith in nanotech despite little knowledge. Nature 2004; 430: 392.
41 Hanssen L, van Est R. De dubbele boodschap van nanotechnologie. Een onderzoek naar opkomende publiekspercepties. The Hague: Rathenau Instituut; 2004.
42 Zandonella C. Cell nanotechnology: The tiny toolkit. Nature 2003; 423(6935): 10-12.
43 Klarreich E. Biologists join the dots. Nature 2001; 413(6855): 450-452.
44 Emerich DF, Thanos CG. Nanotechnology and medicine. Expert Opin Biol Ther 2003; 3(4): 655-663.
45 Lamerichs R, Schäffter T, Hämisch Y, Powers J. Molecular imaging: the road to better healthcare. Medicamundi 2003; 47(1): 2-9.
46 European Science Foundation. Nanomedicine - An ESF - European Medical Research Councils (EMRC) forward look report. Strasbourg: European Science Foundation; 2005.
47 Health Council of the Netherlands. Neonatale screening. The Hague: Health Council of the Netherlands; 2005: 2005/11.
48 Hauptman A, Sharan Y. Envisioned developments in nanobiotechnology - Nano2Life expert survey report. Tel-Aviv: Interdisciplinary Center for Technology Analysis and Forecasting, Tel-Aviv University; 2005.
49 Health Council of the Netherlands. Farmacogenetica: signalement. The Hague: Health Council of the Netherlands; 2000: 2000/19.
50 't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M *et al*. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002; 415(6871): 530-536.
51 van de Vijver MJ, He YD, Van't Veer LJ, Dai H, Hart AA, Voskuil DW *et al*. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002; 347(25): 1999-2009.

52 Valk PJ, Verhaak RG, Beijen MA, Erpelinck CA, Barjesteh van Waalwijk van Doorn-Khosrovani, Boer JM *et al*. Prognostically useful gene-expression profiles in acute myeloid leukemia. N Engl J Med 2004; 350(16): 1617-1628.

53 Lowenberg B, Delwel HR, Valk PJ. [The diagnosis of acute myeloid leukaemia enhanced by using DNA microarrays]. Ned Tijdschr Geneeskd 2005; 149(12): 623-625.

54 Roepman P, Wessels LF, Kettelarij N, Kemmeren P, Miles AJ, Lijnzaad P *et al*. An expression profile for diagnosis of lymph node metastases from primary head and neck squamous cell carcinomas. Nat Genet 2005.

55 Han M, Gao X, Su JZ, Nie S. Quantum-dot-tagged microbeads for multiplexed optical coding of biomolecules. Nat Biotechnol 2001; 19(7): 631-635.

56 Xu H, Sha MY, Wong EY, Uphoff J, Xu Y, Treadway JA *et al*. Multiplexed SNP genotyping using the Qbead system: a quantum dot-encoded microsphere-based assay. Nucleic Acids Res 2003; 31(8): e43.

57 LaVan DA, Lynn DM, Langer R. Moving smaller in drug discovery and delivery. Nat Rev Drug Discov 2002; 1(1): 77-84.

58 Howorka S, Cheley S, Bayley H. Sequence-specific detection of individual DNA strands using engineered nanopores. Nat Biotechnol 2001; 19(7): 636-639.

59 Wu G, Datar RH, Hansen KM, Thundat T, Cote RJ, Majumdar A. Bioassay of prostate-specific antigen (PSA) using microcantilevers. Nat Biotechnol 2001; 19(9): 856-860.

60 Majumdar A. Bioassays based on molecular nanomechanics. Dis Markers 2002; 18(4): 167-174.

61 Patolsky F, Zheng G, Hayden O, Lakadamyali M, Zhuang X, Lieber CM. Electrical detection of single viruses. Proc Natl Acad Sci U S A 2004; 101(39): 14017-14022.

62 Larkin M. Nanowires show potential as virus detectors. Lancet Infect Dis 2004; 4(11): 656.

63 Chen RJ, Bangsaruntip S, Drouvalakis KA, Kam NW, Shim M, Li Y *et al*. Noncovalent functionalization of carbon nanotubes for highly specific electronic biosensors. Proc Natl Acad Sci U S A 2003; 100(9): 4984-4989.

64 Deisingh AK, Thompson M. Biosensors for the detection of bacteria. Can J Microbiol 2004; 50(2): 69-77.

65 Gardeniers JG, van den Berg A. Lab-on-a-chip systems for biomedical and environmental monitoring. Anal Bioanal Chem 2004; 378(7): 1700-1703.

66 Vrouwe EX, Luttge R, van den Berg A. Direct measurement of lithium in whole blood using microchip capillary electrophoresis with integrated conductivity detection. Electrophoresis 2004; 25(10-11): 1660-1667.

67 Buck SM, Koo YE, Park E, Xu H, Philbert MA, Brasuel MA *et al*. Optochemical nanosensor PEBBLEs: photonic explorers for bioanalysis with biologically localized embedding. Curr Opin Chem Biol 2004; 8(5): 540-546.

68 Sumner JP, Aylott JW, Monson E, Kopelman R. A fluorescent PEBBLE nanosensor for intracellular free zinc. Analyst 2002; 127(1): 11-16.

69 Lanza GM, Lamerichs R, Caruthers S, Wickline SA. Molecular Imaging in MR with targeted paramagnetic nanoparticles. Medicamundi 2003; 47(1): 34-39.
70 Li KC, Pandit SD, Guccione S, Bednarski MD. Molecular imaging applications in nanomedicine. Biomed Microdevices 2004; 6(2): 113-116.
71 Sahoo SK, Labhasetwar V. Nanotech approaches to drug delivery and imaging. Drug Discov Today 2003; 8(24): 1112-1120.
72 Wickline SA, Lanza GM. Nanotechnology for molecular imaging and targeted therapy. Circulation 2003; 107(8): 1092-1095.
73 Dayton PA, Ferrara KW. Targeted imaging using ultrasound. J Magn Reson Imaging 2002; 16(4): 362-377.
74 Morawski AM, Winter PM, Crowder KC, Caruthers SD, Fuhrhop RW, Scott MJ *et al*. Targeted nanoparticles for quantitative imaging of sparse molecular epitopes with MRI. Magn Reson Med 2004; 51(3): 480-486.
75 Jordan A. [Nanotechnology and consequences for surgical oncology]. Kongressbd Dtsch Ges Chir Kongr 2002; 119: 821-828.
76 Torabi M, Aquino SL, Harisinghani MG. Current concepts in lymph node imaging. J Nucl Med 2004; 45(9): 1509-1518.
77 Bulte JW, Douglas T, Witwer B, Zhang SC, Strable E, Lewis BK *et al*. Magnetodendrimers allow endosomal magnetic labeling and in vivo tracking of stem cells. Nat Biotechnol 2001; 19(12): 1141-1147.
78 Stiriba SE, Frey H, Haag R. Dendritische Polymere für medizinische Anwendungen: auf dem Weg zum Einsatz in Diagnostik und Therapie. Angewandte Chemie 2002; 114(8): 1385-1390.
79 Kobayashi H, Brechbiel MW. Dendrimer-based nanosized MRI contrast agents. Curr Pharm Biotechnol 2004; 5(6): 539-549.
80 Kobayashi H, Brechbiel MW. Nano-sized MRI contrast agents with dendrimer cores. Adv Drug Deliv Rev 2005; 57(15): 2271-2286.
81 Parak WJ, Pellegrino T, Plank C. Labelling of cells with quantum dots. Nanotechnology 2005; 16: R9-R25.
82 Jovin TM. Quantum dots finally come of age. Nat Biotechnol 2003; 21(1): 32-33.
83 Lidke DS, Arndt-Jovin DJ. Imaging takes a quantum leap. Physiology (Bethesda) 2004; 19: 322-325.
84 Michalet X, Pinaud FF, Bentolila LA, Tsay JM, Doose S, Li JJ *et al*. Quantum dots for live cells, in vivo imaging, and diagnostics. Science 2005; 307(5709): 538-544.
85 Wu X, Liu H, Liu J, Haley KN, Treadway JA, Larson JP *et al*. Immunofluorescent labeling of cancer marker Her2 and other cellular targets with semiconductor quantum dots. Nat Biotechnol 2003; 21(1): 41-46.
86 Dubertret B, Skourides P, Norris DJ, Noireaux V, Brivanlou AH, Libchaber A. In vivo imaging of quantum dots encapsulated in phospholipid micelles. Science 2002; 298(5599): 1759-1762.

87 Larson DR, Zipfel WR, Williams RM, Clark SW, Bruchez MP, Wise FW *et al*. Water-soluble quantum dots for multiphoton fluorescence imaging in vivo. Science 2003; 300(5624): 1434-1436.
88 Kim S, Lim YT, Soltesz EG, De Grand AM, Lee J, Nakayama A *et al*. Near-infrared fluorescent type II quantum dots for sentinel lymph node mapping. Nat Biotechnol 2004; 22(1): 93-97.
89 Uren RF. Cancer surgery joins the dots. Nat Biotechnol 2004; 22(1): 38-39.
90 Allen TM, Cullis PR. Drug delivery systems: entering the mainstream. Science 2004; 303(5665): 1818-1822.
91 Langer R. Drug delivery and targeting. Nature 1998; 392(6679 Suppl): 5-10.
92 Kim CK, Lim SJ. Recent progress in drug delivery systems for anticancer agents. Arch Pharm Res 2002; 25(3): 229-239.
93 Crommelin DJ, Storm G, Jiskoot W, Stenekes R, Mastrobattista E, Hennink WE. Nanotechnological approaches for the delivery of macromolecules. J Control Release 2003; 87(1-3): 81-88.
94 Muller RH, Keck CM. Challenges and solutions for the delivery of biotech drugs--a review of drug nanocrystal technology and lipid nanoparticles. J Biotechnol 2004; 113(1-3): 151-170.
95 Gabizon AA. Stealth liposomes and tumor targeting: one step further in the quest for the magic bullet. Clin Cancer Res 2001; 7(2): 223-225.
96 Owens DE, III, Peppas NA. Opsonization, biodistribution, and pharmacokinetics of polymeric nanoparticles. Int J Pharm 2006; 307(1): 93-102.
97 Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Res 1986; 46(12 Pt 1): 6387-6392.
98 Moghimi SM, Hunter AC, Murray JC. Long-circulating and target-specific nanoparticles: theory to practice. Pharmacol Rev 2001; 53(2): 283-318.
99 Kreuter J, Shamenkov D, Petrov V, Ramge P, Cychutek K, Koch-Brandt C *et al*. Apolipoprotein-mediated transport of nanoparticle-bound drugs across the blood-brain barrier. J Drug Target 2002; 10(4): 317-325.
100 Muller RH, Keck CM. Drug delivery to the brain--realization by novel drug carriers. J Nanosci Nanotechnol 2004; 4(5): 471-483.
101 Harrington KJ, Mohammadtaghi S, Uster PS, Glass D, Peters AM, Vile RG *et al*. Effective targeting of solid tumors in patients with locally advanced cancers by radiolabeled pegylated liposomes. Clin Cancer Res 2001; 7(2): 243-254.
102 Quintana A, Raczka E, Piehler L, Lee I, Myc A, Majoros I *et al*. Design and function of a dendrimer-based therapeutic nanodevice targeted to tumor cells through the folate receptor. Pharm Res 2002; 19(9): 1310-1316.
103 Hong MS, Lim SJ, Oh YK, Kim CK. pH-sensitive, serum-stable and long-circulating liposomes as a new drug delivery system. J Pharm Pharmacol 2002; 54(1): 51-58.
104 Lubbe AS, Bergemann C, Riess H, Schriever F, Reichardt P, Possinger K *et al*. Clinical experiences with magnetic drug targeting: a phase I study with 4'-epidoxorubicin in 14 patients with advanced solid tumors. Cancer Res 1996; 56(20): 4686-4693.

105 Alexiou C, Jurgons R, Schmid RJ, Bergemann C, Henke J, Erhardt W *et al*. Magnetic drug targeting--biodistribution of the magnetic carrier and the chemotherapeutic agent mitoxantrone after locoregional cancer treatment. J Drug Target 2003; 11(3): 139-149.

106 Saiyed Z, Telang S, Ramchand C. Application of magnetic techniques in the field of drug discovery and biomedicine. Biomagn Res Technol 2003; 1(1): 2.

107 Radt B, Smith TA, Caruso F. Optically addressable nanostructured capsules. Advanced Materials 2004; 16(23-24): 2184-2189.

108 Nelson JL, Roeder BL, Carmen JC, Roloff F, Pitt WG. Ultrasonically activated chemotherapeutic drug delivery in a rat model. Cancer Res 2002; 62(24): 7280-7283.

109 Kong G, Braun RD, Dewhirst MW. Characterization of the effect of hyperthermia on nanoparticle extravasation from tumor vasculature. Cancer Res 2001; 61(7): 3027-3032.

110 Meyer DE, Shin BC, Kong GA, Dewhirst MW, Chilkoti A. Drug targeting using thermally responsive polymers and local hyperthermia. J Control Release 2001; 74(1-3): 213-224.

111 Meyer DE, Kong GA, Dewhirst MW, Zalutsky MR, Chilkoti A. Targeting a genetically engineered elastin-like polypeptide to solid tumors by local hyperthermia. Cancer Res 2001; 61(4): 1548-1554.

112 Hirsch LR, Stafford RJ, Bankson JA, Sershen SR, Rivera B, Price RE *et al*. Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance. Proc Natl Acad Sci U S A 2003; 100(23): 13549-13554.

113 O'Neal DP, Hirsch LR, Halas NJ, Payne JD, West JL. Photo-thermal tumor ablation in mice using near infrared-absorbing nanoparticles. Cancer Lett 2004; 209(2): 171-176.

114 Johannsen M, Thiesen B, Jordan A, Taymoorian K, Gneveckow U, Waldofner N *et al*. Magnetic fluid hyperthermia (MFH)reduces prostate cancer growth in the orthotopic Dunning R3327 rat model. Prostate 2005; 64(3): 283-292.

115 Kam NW, O'connell M, Wisdom JA, Dai H. Carbon nanotubes as multifunctional biological transporters and near-infrared agents for selective cancer cell destruction. Proc Natl Acad Sci U S A 2005.

116 Park GE, Webster TJ. A review of nanotechnology for the development of better orthopedic implants. J Biomed Nanotechnol 2005; 1(1): 18-29.

117 Catledge SA, Fries MD, Vohra YK, Lacefield WR, Lemons JE, Woodard S *et al*. Nanostructured ceramics for biomedical implants. J Nanosci Nanotechnol 2002; 2(3-4): 293-312.

118 Webster TJ, Siegel RW, Bizios R. Osteoblast adhesion on nanophase ceramics. Biomaterials 1999; 20(13): 1221-1227.

119 Webster TJ, Ejiofor JU. Increased osteoblast adhesion on nanophase metals: Ti, Ti6Al4V, and CoCrMo. Biomaterials 2004; 25(19): 4731-4739.

120 Webster TJ, Hellenmeyer EL, Price RL. Increased osteoblast functions on theta + delta nanofiber alumina. Biomaterials 2005; 26(9): 953-960.

121 Woo KM, Chen VJ, Ma PX. Nano-fibrous scaffolding architecture selectively enhances protein adsorption contributing to cell attachment. J Biomed Mater Res A 2003; 67A(2): 531-537.

122 Price RL, Haberstroh KM, Webster TJ. Enhanced functions of osteoblasts on nanostructured surfaces of carbon and alumina. Med Biol Eng Comput 2003; 41(3): 372-375.
123 Salata OV. Applications of nanoparticles in biology and medicine. J Nanobiotechnology 2004; 2(1): 3-8.
124 Heidenau F, Mittelmeier W, Detsch R, Haenle M, Stenzel F, Ziegler G *et al*. A novel antibacterial titania coating: Metal ion toxicity and in vitro surface colonization. J Mater Sci Mater Med 2005; 16(10): 883-888.
125 Price RL, Waid MC, Haberstroh KM, Webster TJ. Selective bone cell adhesion on formulations containing carbon nanofibers. Biomaterials 2003; 24(11): 1877-1887.
126 Kay S, Thapa A, Haberstroh KM, Webster TJ. Nanostructured polymer/nanophase ceramic composites enhance osteoblast and chondrocyte adhesion. Tissue Eng 2002; 8(5): 753-761.
127 Zhao B, Hu H, Mandal SK, Haddon RC. A Bone Mimic Based on the Self-Assembly of Hydroxyapatite on Chemically Functionalized Single-Walled Carbon Nanotubes. Chem Mater 2005; 17(12): 3235-3241.
128 Ellis-Behnke RG, Liang Y-X, You S-W, Tay DCK, Zhang S, So K-F *et al*. Nano neuro knitting: peptide nanofiber scaffold for brain repair and axon regeneration with functional return of vision. Proc Natl Acad Sci U S A 2006; 103(13): 5054-5059.
129 Santini JT, Jr., Cima MJ, Langer R. A controlled-release microchip. Nature 1999; 397(6717): 335-338.
130 Santini JT, Jr., Richards AC, Scheidt RA, Cima MJ, Langer RS. Microchip technology in drug delivery. Ann Med 2000; 32(6): 377-379.
131 Zrenner E. Will retinal implants restore vision? Science 2002; 295(5557): 1022-1025.
132 Nicolelis MA. Actions from thoughts. Nature 2001; 409(6818): 403-407.
133 Nicolelis MA. Brain-machine interfaces to restore motor function and probe neural circuits. Nat Rev Neurosci 2003; 4(5): 417-422.
134 Nicolelis MA, Chapin JK. Controlling robots with the mind. Sci Am 2002; 287(4): 46-53.
135 Serruya MD, Hatsopoulos NG, Paninski L, Fellows MR, Donoghue JP. Instant neural control of a movement signal. Nature 2002; 416(6877): 141-142.
136 Donoghue JP. Connecting cortex to machines: recent advances in brain interfaces. Nat Neurosci 2002; 5 Suppl: 1085-1088.
137 Schwartz AB. Cortical neural prosthetics. Annu Rev Neurosci 2004; 27: 487-507.
138 Kennedy PR, Bakay RA, Moore MM, Adams K, Goldwaithe J. Direct control of a computer from the human central nervous system. IEEE Trans Rehabil Eng 2000; 8(2): 198-202.
139 Nicolelis MA. The amazing adventures of robotrat. Trends Cogn Sci 2002; 6(11): 449-450.
140 Talwar SK, Xu S, Hawley ES, Weiss SA, Moxon KA, Chapin JK. Rat navigation guided by remote control. Nature 2002; 417(6884): 37-38.
141 Stieglitz T. Considerations on surface and structural biocompatibility as prerequisite for long-term stability of neural prostheses. J Nanosci Nanotechnol 2004; 4(5): 496-503.

142 Moxon KA, Kalkhoran NM, Markert M, Sambito MA, McKenzie JL, Webster JT. Nanostructured surface modification of ceramic-based microelectrodes to enhance biocompatibility for a direct brain-machine interface. IEEE Trans Biomed Eng 2004; 51(6): 881-889.

143 Lansdown AB. Silver. I: Its antibacterial properties and mechanism of action. J Wound Care 2002; 11(4): 125-130.

144 Baker C, Pradhan A, Pakstis L, Pochan DJ, Shah SI. Synthesis and antibacterial properties of silver nanoparticles. J Nanosci Nanotechnol 2005; 5(2): 244-249.

145 Furno F, Morley KS, Wong B, Sharp BL, Arnold PL, Howdle SM *et al*. Silver nanoparticles and polymeric medical devices: a new approach to prevention of infection? J Antimicrob Chemother 2004; 54(6): 1019-1024.

146 Samuel U, Guggenbichler JP. Prevention of catheter-related infections: the potential of a new nano-silver impregnated catheter. Int J Antimicrob Agents 2004; 23 Suppl 1: S75-S78.

147 Alt V, Bechert T, Steinrucke P, Wagener M, Seidel P, Dingeldein E *et al*. [Nanoparticulate silver. A new antimicrobial substance for bone cement]. Orthopade 2004; 33(8): 885-892.

148 Alt V, Bechert T, Steinrucke P, Wagener M, Seidel P, Dingeldein E *et al*. An in vitro assessment of the antibacterial properties and cytotoxicity of nanoparticulate silver bone cement. Biomaterials 2004; 25(18): 4383-4391.

149 Dowsett C. An overview of Acticoat dressing in wound management. Br J Nurs 2003; 12(19 Suppl): S44-S49.

150 Lansdown AB. A guide to the properties and uses of silver dressings in wound care. Prof Nurse 2005; 20(5): 41-43.

151 Maness PC, Smolinski S, Blake DM, Huang Z, Wolfrum EJ, Jacoby WA. Bactericidal activity of photocatalytic TiO(2) reaction: toward an understanding of its killing mechanism. Appl Environ Microbiol 1999; 65(9): 4094-4098.

152 Kai Y, Komazawa Y, Miyajima A, Miyata N, Yamakoshi Y. [60]fullerene as a novel photoinduced antibiotic. Fullerenes, Nanotubes and Carbon Nanostructures 2003; 11(1): 79-87.

153 Radio-frequency identification: its potential in healthcare. Health Devices 2005; 34(5): 149-160.

154 Valenstein PN, Sirota RL. Identification errors in pathology and laboratory medicine. Clin Lab Med 2004; 24(4): 979-996.

155 Sandberg WS, Hakkinen M, Egan M, Curran PK, Fairbrother P, Choquette K *et al*. Automatic detection and notification of "wrong patient-wrong location" errors in the operating room. Surg Innov 2005; 12(3): 253-260.

156 Ahrens N, Pruss A, Kiesewetter H, Salama A. Failure of bedside ABO testing is still the most common cause of incorrect blood transfusion in the Barcode era. Transfus Apher Sci 2005; 33(1): 25-29.

157 Meyer HJ, Chansue N, Monticelli F. Implantation of radio frequency identification device (RFID) microchip in disaster victim identification (DVI). Forensic Sci Int 2006; 157(2-3): 168-171.

158 Chehab N, Enzing CM. Nanotechnologie. Quick Scan. The Hague: Nationale Raad voor Landbouwkundig Onderzoek; 1998: NRLO-rapport nr 98/37.

159 Moraru CI, Panchapakesan CP, Huang Q, Takhistov P, Liu S, Kokini JL. Nanotechnology: A New Frontier in Food Science. FoodTechnology 2003; 57(12): 24-29.
160 Scott N, Chen H. Science and engineering for agriculture and food systems. A report submitted to Cooperative State Research, Education and Extension Service. The United States Department of Agriculture. Washington, DC: National Planning Workshop November 18-19, 2002; 2003.
161 Enzing C. Startnotitie Nano in Agrofood, behorend bij Verslaglegging Rondetafelgesprek Nanotechnologie in de Agrofoodsector (Rathenau Instituut). Delft: TNO strategie, Technologie en Beleid; 2004.
162 Ross SA, Srinivas PR, Clifford AJ, Lee SC, Philbert MA, Hettich RL. New technologies for nutrition research. J Nutr 2004; 134(3): 681-685.
163 Down on the farm. The impact of nano-scale technologies on food and agriculture. Ottawa: ETC Group; 2004.
164 Chen H, Weiss J, Shahidi F. Nanotechnology in nutraceuticals and functional foods. FoodTechnology 2006; 60(3): 30-36.
165 Masciangioli T, Zhang WX. Environmental technologies at the nanoscale. Environ Sci Technol 2003; 37(5): 102A-108A.
166 Nationale Raad voor Landbouwkundig Onderzoek. Nanotechnologie. Speerpunten voor actie. The Hague: Nationale Raad voor Landbouwkundig Onderzoek; 1999: 99/7.
167 Grauwet TJMA, Cammue BPA, Thomma BPHJ. Recente ontwikkelingen in detectie en identificatie van plantenpathogenen: van microscopie naar moleculaire diagnostiek. Gewasbescherming 2004; 35(4): 201-207.
168 Le Roy Boehm AL, Zerrouk R, Fessi H. Poly epsilon-caprolactone nanoparticles containing a poorly soluble pesticide: formulation and stability study. J Microencapsul 2000; 17(2): 195-205.
169 Boehm AL, Martinon I, Zerrouk R, Rump E, Fessi H. Nanoprecipitation technique for the encapsulation of agrochemical active ingredients. J Microencapsul 2003; 20(4): 433-441.
170 Roadmap microsysteem- en nanotechnologie in food and nutrition. Amersfoort: MinacNed; 2004. Internet: http://www.minacned.nl/download/roadmap_food_nutrition.pdf.
171 Brody AL. “Nano, Nano” Food packaging technology. FoodTechnology 2003; 57(12): 52-54.
172 de Jong AR, van Veen JJF. Versheid, houdbaarheid en bederf. vmt 2005;(6): 18-19.
173 Zhang WX, Karn B. Nanoscale environmental science and technology: challenges and opportunities. Environ Sci Technol 2005; 39(5): 94A-95A.
174 Nanotechnology helps solve the world's energy problems. Nanoforum; 4-2004.
175 Mueller AH, Petruska MA, Achermann M, Werder DJ, Akhadov EA, Koleske DD *et al*. Multicolor Light-Emitting Diodes Based on Semiconductor Nanocrystals Encapsulated in GaN Charge Injection Layers. Nano Lett 2005; 5(6): 1039-1044.
176 Stockman M. From nano-optics to street lights. Nat Mater 2004; 3(7): 423-424.
177 Wang P, Zakeeruddin SM, Moser JE, Nazeeruddin MK, Sekiguchi T, Gratzel M. A stable quasi-solid-state dye-sensitized solar cell with an amphiphilic ruthenium sensitizer and polymer gel electrolyte. Nat Mater 2003; 2(6): 402-407.

178 Schaller RD, Klimov VI. High efficiency carrier multiplication in PbSe nanocrystals: implications for solar energy conversion. Phys Rev Lett 2004; 92(18): 186601.
179 Basic research needs for the hydrogen economy. Washington, DC: Office of Science, US Department of Energy; 2004: second printing.
180 Arico AS, Bruce P, Scrosati B, Tarascon JM, van Schalkwijk W. Nanostructured materials for advanced energy conversion and storage devices. Nat Mater 2005; 4(5): 366-377.
181 Zieziulewicz TJ, Unfricht DW, Hadjout N, Lynes MA, Lawrence DA. Shrinking the biologic world--nanobiotechnologies for toxicology. Toxicol Sci 2003; 74(2): 235-244.
182 Modi A, Koratkar N, Lass E, Wei B, Ajayan PM. Miniaturized gas ionization sensors using carbon nanotubes. Nature 2003; 424(6945): 171-174.
183 Novak JP, Snow ES, Houser EJ, Park D, Stepnowski JL, McGill RA. Nerve agent detection using networks of single-walled carbon nanotubes. Applied physics letters 2003; 83(19): 4026-4028.
184 Snow ES, Perkins FK, Houser EJ, Badescu SC, Reinecke TL. Chemical detection with a single-walled carbon nanotube capacitor. Science 2005; 307(5717): 1942-1945.
185 Cui Y, Wei Q, Park H, Lieber CM. Nanowire nanosensors for highly sensitive and selective detection of biological and chemical species. Science 2001; 293(5533): 1289-1292.
186 Friedrich MJ. Nanoscale biosensors show promise. JAMA 2005; 293(16): 1965.
187 Baraton M-I, Merhari L. Advances in air quality monitoring via nanotechnology. J Nanoparticle Research 2004; 6(1): 107-117.
188 Zhao X, Hilliard LR, Mechery SJ, Wang Y, Bagwe RP, Jin S *et al*. A rapid bioassay for single bacterial cell quantitation using bioconjugated nanoparticles. Proc Natl Acad Sci U S A 2004; 101(42): 15027-15032.
189 Choongho Y, Hao Q, Saha S, Shi L, Kong X, Wang ZL. Integration of metal oxide nanobelts with microsystems for nerve agent detection. Appl Phys Lett 2005; 86(6).
190 Alvarez M, Calle A, Tamayo J, Lechuga LM, Abad A, Montoya A. Development of nanomechanical biosensors for detection of the pesticide DDT. Biosens Bioelectron 2003; 18(5-6): 649-653.
191 Gupta A, Akin D. Detection of bacterial cells and antibodies using surface micromachined thin silicon cantilever resonators. J Vac Sci Technol B 2004; 22(6): 2785-2791.
192 Gupta A, Akin D, Bashir R. Single virus particle mass detection using microresonators with nanoscale thickness. Appl Phys Lett 2004; 84(11): 1976-1978.
193 Chang AC, Gillespie JB, Tabacco MB. Enhanced detection of live bacteria using a dendrimer thin film in an optical biosensor. Anal Chem 2001; 73(3): 467-470.
194 Ji J, Schanzle JA, Tabacco MB. Real-time detection of bacterial contamination in dynamic aqueous environments using optical sensors. Anal Chem 2004; 76(5): 1411-1418.
195 Suprun SC, Jr. Nerve agent attack: a dangerous threat to emergency responders & the public. JEMS 2003; 28(10): 60-71.
196 Health Council of the Netherlands. Bioterrorisme: vervolgadvies. The Hague: Health Council of the Netherlands; 2002: 2002/11.

197 Atlas RM. Bioterrorism and biodefence research: changing the focus of microbiology. Nat Rev Microbiol 2003; 1(1): 70-74.

198 Balshaw DM, Philbert M, Suk WA. Research Strategies for Safety Evaluation of Nanomaterials, Part III: Nanoscale Technologies for Assessing Risk and Improving Public Health. Toxicol Sci 2005; 88(2): 298-306.

199 Weis BK, Balshaw D, Barr JR, Brown D, Ellisman M, Lioy P *et al*. Personalized exposure assessment: promising approaches for human environmental health research. Environ Health Perspect 2005; 113(7): 840-848.

200 Vo-Dinh T, Kasili P. Fiber-optic nanosensors for single-cell monitoring. Anal Bioanal Chem 2005.

201 Zhang WX. Nanoscale iron particles for environmental remediation: An overview. Journal of Nanoparticle Research 2003; 5(3-4): 323-332.

202 Diallo MS, Christie S, Swaminathan P, Johnson JH, Jr., Goddard WA, III. Dendrimer enhanced ultrafiltration. 1. Recovery of Cu(II) from aqueous solutions using PAMAM dendrimers with ethylene diamine core and terminal NH2 groups. Environ Sci Technol 2005; 39(5): 1366-1377.

203 Van der Bruggen B, Vandecasteele C. Removal of pollutants from surface water and groundwater by nanofiltration: overview of possible applications in the drinking water industry. Environ Pollut 2003; 122(3): 435-445.

204 ETC group. Green Goo: nanobiotechnology comes alive! Winnipeg: ETC Group; 2003: Communiqué 77.

205 Anastasio C, Martin ST. 8 Atmospheric nanoparticles. In: Banfield JF, Navrotsky A, editors. Nanoparticles and the environment. Washington DC: Mineralogical Society of America; 2001: 293-349.

206 Banfield JF, Zhang H. 1 Nanoparticles in the environment. In: Banfield JF, Navrotsky A, editors. Nanoparticles and the environment. Washington DC: Mineralogical Society of America; 2001: 1-58.

207 Rancourt DG. 7 Magnetism of earth, planetary, and environmental nanomaterials. In: Banfield JF, Navrotsky A, editors. Nanoparticles and the environment. Washington DC: Mineralogical Society of America; 2001: 217-292.

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

209 Ebelt S, Brauer M, Cyrys J, Tuch T, Kreyling WG, Wichmann HE *et al*. Air quality in postunification Erfurt, East Germany: associating changes in pollutant concentrations with changes in emissions. Environ Health Perspect 2001; 109(4): 325-333.

210 Dockery DW, Pope CA, III, Xu X, Spengler JD, Ware JH, Fay ME *et al*. An association between air pollution and mortality in six US cities. N Engl J Med 1993; 329(24): 1753-1759.

211 Borm PJ. Particle toxicology: from coal mining to nanotechnology. Inhal Toxicol 2002; 14(3): 311-324.

212 Borm PJA, Kreyling W. Toxicological Hazards of Inhaled Nanoparticles - Potential Implications for Drug Delivery. Journal of Nanoscience and Nanotechnology 2004; 4(5): 521-531.

213 Hoet PH, Bruske-Hohlfeld I, Salata OV. Nanoparticles - known and unknown health risks. J Nanobiotechnology 2004; 2(1): 12.

214 Reijnders L. Cleaner nanotechnology and hazard reduction of manufactured nanoparticles. J Cleaner Production 2006; 14(2): 124-133.

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

216 Scientific Committee on Emerging and Newly Identified Health Risks. Opinion on the appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies. Brussels: European Commission; 9-2005: SCENIHR/ 002/05.

217 Colvin VL. The potential environmental impact of engineered nanomaterials. Nat Biotechnol 2003; 21(10): 1166-1170.

218 Lomer MC, Thompson RP, Powell JJ. Fine and ultrafine particles of the diet: influence on the mucosal immune response and association with Crohn's disease. Proc Nutr Soc 2002; 61(1): 123-130.

219 Lomer MC, Hutchinson C, Volkert S, Greenfield SM, Catterall A, Thompson RP *et al*. Dietary sources of inorganic microparticles and their intake in healthy subjects and patients with Crohn's disease. Br J Nutr 2004; 92(6): 947-955.

220 Colbert DT, Smalley RE. 1 Past, Present and Future of Fullerene Nanotubes: Buckytubes. In: Osawa E, editor. Perspectives of Fullerene Nanotechnology. Dordrecht: Kluwer Academic Publishers; 2002: 3-10.

221 Maynard AD, Baron PA, Foley M, Shvedova AA, Kisin ER, Castranova V. Exposure to carbon nanotube material: aerosol release during the handling of unrefined single-walled carbon nanotube material. J Toxicol Environ Health A 2004; 67(1): 87-107.

222 Oberdorster G, Maynard A, Donaldson K, Castranova V, Fitzpatrick J, Ausman K *et al*. Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy. Part Fibre Toxicol 2005; 2: 8.

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

224 Jani P, Halbert GW, Langridge J, Florence AT. Nanoparticle uptake by the rat gastrointestinal mucosa: quantitation and particle size dependency. J Pharm Pharmacol 1990; 42(12): 821-826.

225 Florence AT, Hillery AM, Hussain N, Jani PU. Factors affecting the oral uptake and translocation of polystyrene nanoparticles: histological and analytical evidence. J Drug Target 1995; 3(1): 65-70.

226 Bockmann J, Lahl H, Eckert T, Unterhalt B. [Blood titanium levels before and after oral administration titanium dioxide]. Pharmazie 2000; 55(2): 140-143.

227 Kreyling WG, Semmler M, Erbe F, Mayer P, Takenaka S, Schulz H *et al*. Translocation of ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low. J Toxicol Environ Health A 2002; 65(20): 1513-1530.

228 Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products intended for consumers concerning titanium dioxide Colipa No S75. Adopted 24 October 2000. Brussels: SCCNFP; 2000.

229 Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products intended for consumers concerning zinc oxide Colipa No S76. Adopted 24-25 June 2003. Brussels: SCCNFP; 2003.

230 Sagman U. Application and commercial prospects of fullerenes in medicine and biology. In: Osawa E, editor. Perspectives of Fullerene Nanotechnology. Dordrecht: Kluwer Academic Publishers; 2002: 145-154.

231 Yamago S, Tokuyama H, Nakamura E, Kikuchi K, Kananishi S, Sueki K *et al*. In vivo biological behavior of a water-miscible fullerene: 14C labeling, absorption, distribution, excretion and acute toxicity. Chem Biol 1995; 2(6): 385-389.

232 Wang H, Wang J, Deng X, Sun H, Shi Z, Gu Z *et al*. Biodistribution of carbon single-wall carbon nanotubes in mice. J Nanosci Nanotechnol 2004; 4(8): 1019-1024.

233 Ferin J, Oberdorster G, Penney DP. Pulmonary retention of ultrafine and fine particles in rats. Am J Respir Cell Mol Biol 1992; 6(5): 535-542.

234 Borm PJ, Schins RP, Albrecht C. Inhaled particles and lung cancer, part B: paradigms and risk assessment. Int J Cancer 2004; 110(1): 3-14.

235 Dick CA, Brown DM, Donaldson K, Stone V. The role of free radicals in the toxic and inflammatory effects of four different ultrafine particle types. Inhal Toxicol 2003; 15(1): 39-52.

236 Maynard AD, Kuempel ED. Airborne Nanostructured Particles and Occupational Health. J Nanoparticle Research 2005; 7(6): 587-614.

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

238 Lam CW, James JT, McCluskey R, Hunter RL. Pulmonary toxicity of single-wall carbon nanotubes in mice 7 and 90 days after intratracheal instillation. Toxicol Sci 2004; 77(1): 126-134.

239 Warheit DB, Laurence BR, Reed KL, Roach DH, Reynolds GA, Webb TR. Comparative pulmonary toxicity assessment of single-wall carbon nanotubes in rats. Toxicol Sci 2004; 77(1): 117-125.

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

241 Donaldson K, Aitken R, Tran L, Stone V, Duffin R, Forrest G *et al*. Carbon Nanotubes: a Review of Their Properties in Relation to Pulmonary Toxicology and Workplace Safety. Toxicol Sci 2006 (accepted for publication).

242 Shvedova AA, Kisin ER, Mercer R, Murray AR, Johnson VJ, Potapovich AI *et al*. Unusual inflammatory and fibrogenic pulmonary responses to single-walled carbon nanotubes in mice. Am J Physiol Lung Cell Mol Physiol 2005; 289(5): L698-L708.

243 Dreher KL. Health and environmental impact of nanotechnology: toxicological assessment of manufactured nanoparticles. Toxicol Sci 2004; 77(1): 3-5.

244 Donaldson K, Stone V, Borm PJ, Jimenez LA, Gilmour PS, Schins RP *et al*. Oxidative stress and calcium signaling in the adverse effects of environmental particles (PM10). Free Radic Biol Med 2003; 34(11): 1369-1382.

245 Shvedova AA, Castranova V, Kisin ER, Schwegler-Berry D, Murray AR, Gandelsman VZ *et al*. Exposure to carbon nanotube material: assessment of nanotube cytotoxicity using human keratinocyte cells. J Toxicol Environ Health A 2003; 66(20): 1909-1926.

246 Monteiro-Riviere NA, Nemanich RJ, Inman AO, Wang YY, Riviere JE. Multi-walled carbon nanotube interactions with human epidermal keratinocytes. Toxicol Lett 2005; 155(3): 377-384.

247 Sayes CM, Liang F, Hudson JL, Mendez J, Guo W, Beach JM *et al*. Functionalization density dependence of single-walled carbon nanotubes cytotoxicity in vitro. Toxicol Lett 2006; 161(2): 135-142.

248 Sayes CM, Fortner JD, Guo W, Lyon D, Boyd AM, Ausman KD *et al*. The differential cytotoxicity of water-soluble fullerenes. Nano Letters 2004; 4(10): 1881-1887.

249 Sayes CM, Gobin AM, Ausman KD, Mendez J, West JL, Colvin VL. Nano-C60 cytotoxicity is due to lipid peroxidation. Biomaterials 2005; 26(36): 7587-7595.

250 Zhao X, Striolo A, Cummings PT. C60 binds to and deforms nucleotides. Biophys J 2005; 89(6): 3856-3862.

251 Jia G, Wang H, Yan L, Wang X, Pei R, Yan T *et al*. Cytotoxicity of carbon nanomaterials: single-wall nanotube, multi-wall nanotube, and fullerene. Environ Sci Technol 2005; 39(5): 1378-1383.

252 Duncan R, Izzo L. Dendrimer biocompatibility and toxicity. Adv Drug Deliv Rev 2005; 57(15): 2215-2237.

253 Derfus AM, Chan WCW, Bhatia SN. Probing the Cytotoxicity of Semiconductor Quantum Dots. Nano Letters 2004; 4(1): 11-18.

254 Shiohara A, Hoshino A, Hanaki K, Suzuki K, Yamamoto K. On the cyto-toxicity caused by quantum dots. Microbiol Immunol 2004; 48(9): 669-675.

255 Lovric J, Bazzi HS, Cuie Y, Fortin GR, Winnik FM, Maysinger D. Differences in subcellular distribution and toxicity of green and red emitting CdTe quantum dots. J Mol Med 2005; 83(5): 377-385.

256 Lovric J, Cho SJ, Winnik FM, Maysinger D. Unmodified cadmium telluride quantum dots induce reactive oxygen species formation leading to multiple organelle damage and cell death. Chem Biol 2005; 12(11): 1227-1234.

257 Green M, Howman E. Semiconductor quantum dots and free radical induced DNA nicking. Chem Commun (Camb) 2005;(1): 121-123.

258 Hoshino A, Fujioka K, Oku T, Suga M, Sasaki Y, Ohta T *et al*. Physicochemical Properties and Cellular Toxicity of Nanocrystal Quantum Dots Depend on Their Surface Modification. Nano Letters 2004; 4(11): 2163-2169.

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

260 Health Council of the Netherlands. Asbest, toetsing van een ontwerp-basisdocument. The Hague: Health Council of the Netherlands; 1988: 1988/31.

261 Health Council of the Netherlands. Quartz: evaluation of the carcinogenicity and genotoxicity. Rijswijk: Health Council of the Netherlands; 1998: 1998/02WGD.

262 Health Council of the Netherlands. Deeltjesvormige luchtverontreiniging. The Hague: Health Council of the Netherlands; 1995: 1995/14.

263 Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. Lancet 2002; 360(9341): 1203-1209.

264 Seaton A, MacNee W, Donaldson K, Godden D. Particulate air pollution and acute health effects. Lancet 1995; 345(8943): 176-178.

265 Utell MJ, Frampton MW. Acute health effects of ambient air pollution: the ultrafine particle hypothesis. J Aerosol Med 2000; 13(4): 355-359.

266 Donaldson K, Stone V, Clouter A, Renwick L, MacNee W. Ultrafine particles. Occup Environ Med 2001; 58(3): 211-216.

267 Peters A, Wichmann HE, Tuch T, Heinrich J, Heyder J. Respiratory effects are associated with the number of ultrafine particles. Am J Respir Crit Care Med 1997; 155(4): 1376-1383.

268 Wichmann HE, Spix C, Tuch T, Wolke G, Peters A, Heinrich J *et al*. Daily mortality and fine and ultrafine particles in erfurt, germany part I: role of particle number and particle mass. Res Rep Health Eff Inst 2000;(98): 5-86.

269 Ibald-Mulli A, Wichmann HE, Kreyling W, Peters A. Epidemiological evidence on health effects of ultrafine particles. J Aerosol Med 2002; 15(2): 189-201.

270 Frampton MW, Utell MJ, Zareba W, Oberdorster G, Cox C, Huang LS *et al*. Effects of exposure to ultrafine carbon particles in healthy subjects and subjects with asthma. Res Rep Health Eff Inst 2004; (126): 1-47.

271 Beeson WL, Abbey DE, Knutsen SF. Long-term concentrations of ambient air pollutants and incident lung cancer in California adults: results from the AHSMOG study.Adventist Health Study on Smog. Environ Health Perspect 1998; 106(12): 813-823.

272 Abbey DE, Nishino N, McDonnell WF, Burchette RJ, Knutsen SF, Lawrence BW *et al*. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am J Respir Crit Care Med 1999; 159(2): 373-382.

273 Pope CA, III, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K *et al*. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 2002; 287(9): 1132-1141.

274 Nemmar A, Hamoir J, Nemery B, Gustin P. Evaluation of particle translocation across the alveolo-capillary barrier in isolated perfused rabbit lung model. Toxicology 2005; 208(1): 105-113.

275 Thomas K, Sayre P. Research Strategies for Safety Evaluation of Nanomaterials, Part I: Evaluating the Human Health Implications of Exposure to Nanoscale Materials. Toxicol Sci 2005; 87(2): 316-321.

276 Chang CC, Chiu HF, Wu YS, Li YC, Tsai ML, Shen CK *et al*. The induction of vascular endothelial growth factor by ultrafine carbon black contributes to the increase of alveolar-capillary permeability. Environ Health Perspect 2005; 113(4): 454-460.

277 Meiring JJ, Borm PJ, Bagate K, Semmler M, Seitz J, Takenaka S *et al*. The influence of hydrogen peroxide and histamine on lung permeability and translocation of iridium nanoparticles in the isolated perfused rat lung. Part Fibre Toxicol 2005; 2: 3.

278 Heckel K, Kiefmann R, Dorger M, Stoeckelhuber M, Goetz AE. Colloidal gold particles as a new in vivo marker of early acute lung injury. Am J Physiol Lung Cell Mol Physiol 2004; 287(4): L867-L878.

279 Suwa T, Hogg JC, Quinlan KB, Ohgami A, Vincent R, Van Eeden SF. Particulate air pollution induces progression of atherosclerosis. J Am Coll Cardiol 2002; 39(6): 935-942.

280 Chen LC, Nadziejko C. Effects of subchronic exposures to concentrated ambient particles (CAPs) in mice. V. CAPs exacerbate aortic plaque development in hyperlipidemic mice. Inhal Toxicol 2005; 17(4-5): 217-224.

281 Lomer MC, Grainger SL, Ede R, Catterall AP, Greenfield SM, Cowan RE *et al*. Lack of efficacy of a reduced microparticle diet in a multi-centred trial of patients with active Crohn's disease. Eur J Gastroenterol Hepatol 2005; 17(3): 377-384.

282 Dunford R, Salinaro A, Cai L, Serpone N, Horikoshi S, Hidaka H *et al*. Chemical oxidation and DNA damage catalysed by inorganic sunscreen ingredients. FEBS Lett 1997; 418(1-2): 87-90.

283 Brezova V, Gabcova S, Dvoranova D, Stasko A. Reactive oxygen species produced upon photoexcitation of sunscreens containing titanium dioxide (an EPR study). J Photochem Photobiol B 2005; 79(2): 121-134.

284 Tsuji JS, Maynard AD, Howard PC, James JT, Lam CW, Warheit DB *et al*. Research strategies for safety evaluation of nanomaterials, part IV: risk assessment of nanoparticles. Toxicol Sci 2006; 89(1): 42-50.

285 Ingham E, Fisher J. Biological reactions to wear debris in total joint replacement. Proc Inst Mech Eng [H] 2000; 214(1): 21-37.

286 DeHeer DH, Engels JA, DeVries AS, Knapp RH, Beebe JD. In situ complement activation by polyethylene wear debris. J Biomed Mater Res 2001; 54(1): 12-19.

287 Urban RM, Jacobs JJ, Tomlinson MJ, Gavrilovic J, Black J, Peoc'h M. Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement. J Bone Joint Surg Am 2000; 82(4): 457-476.

288 Urban RM, Tomlinson MJ, Hall DJ, Jacobs JJ. Accumulation in liver and spleen of metal particles generated at nonbearing surfaces in hip arthroplasty. J Arthroplasty 2004; 19(8 Suppl 3): 94-101.

289 Buxton DB, Lee SC, Wickline SA, Ferrari M. Recommendations of the National Heart, Lung, and Blood Institute Nanotechnology Working Group. Circulation 2003; 108(22): 2737-2742.

290 Owen R, Depledge M. Nanotechnology and the environment: Risks and rewards. Mar Pollut Bull 2005; 50(6): 609-612.

291 Fortner JD, Lyon DY, Sayes CM, Boyd AM, Falkner JC, Hotze EM *et al*. C60 in water: nanocrystal formation and microbial response. Environ Sci Technol 2005; 39(11): 4307-4316.
292 Brant J, Lecoanet H, Wiesner MR. Aggregation and Deposition Characteristics of Fullerene Nanoparticles in Aqueous Systems. J Nanoparticle Research 2005; 7(4-5): 545-553.
293 Oberdorster E. Manufactured nanomaterials (fullerenes, C60) induce oxidative stress in the brain of juvenile largemouth bass. Environ Health Perspect 2004; 112(10): 1058-1062.
294 Lecoanet HF, Bottero JY, Wiesner MR. Laboratory assessment of the mobility of nanomaterials in porous media. Environ Sci Technol 2004; 38(19): 5164-5169.
295 Lecoanet HF, Wiesner MR. Velocity effects on fullerene and oxide nanoparticle deposition in porous media. Environ Sci Technol 2004; 38(16): 4377-4382.
296 Yang L, Watts DJ. Particle surface characteristics may play an important role in phytotoxicity of alumina nanoparticles. Toxicol Lett 2005; 158(2): 122-132.
297 Whatmore RW. An introduction to nanoscience and nanotechnology. In: Nanotechnology - Impact on health and regulation. Proceedings of a conference held in London, 27 October 2005. London: MHRA; 2005: 1-8, consulted 27-10-2005.
298 Salamanca-Buentello F, Persad DL, Court EB, Martin DK, Daar AS, Singer PA. Nanotechnology and the developing world. PLoS Med 2005; 2(5): e97.
299 Barker T, Lesnick M, Mealey T, Raimond R, Walker S, Rejeski D *et al*. Nanotechnology and the poor: opportunities and risks - Closing the gaps within and between sectors of society. Washington, DC: Meridian Institute; 1-2005.
300 Hassan MH. Nanotechnology. Small things and big changes in the developing world. Science 2005; 309(5731): 65-66.
301 Health Council of the Netherlands. Screening van pasgeborenen op aangeboren stofwisselingsziekten. In: Signalering ethiek en gezondheid 2003. The Hague: Health Council of the Netherlands: 2003/8; 2003: 51-71.
302 Field MJ, Grigsby J. Telemedicine and remote patient monitoring. JAMA 2002; 288(4): 423-425.
303 Celler BG, Lovell NH, Basilakis J. Using information technology to improve the management of chronic disease. Med J Aust 2003; 179(5): 242-246.
304 Meystre S. The current state of telemonitoring: a comment on the literature. Telemed J E Health 2005; 11(1): 63-69.
305 Health Council of the Netherlands. Geavanceerde thuiszorgtechnologie: morele vragen bij een ethisch ideaal. In: Signalering ethiek en gezondheid 2004. The Hague: Health Council of the Netherlands: 2004/12; 2004: 69-92.
306 Raad voor de Volksgezondheid en Zorg. Geavanceerde thuiszorgtechnologie: morele vragen bij een nieuwe zorgpraktijk. In: Signalering ethiek en gezondheid 2004. Zoetermeer: Raad voor de Volksgezondheid en Zorg; 2004: 101-125.
307 Raad voor de Volksgezondheid en Zorg. Zelftests. Zoetermeer: Raad voor de Volksgezondheid en Zorg; 3-1999.
308 Medical self-test kits. London: Parliamentary Office of Science and Technology; 2003: 194.

309 Humphries SE, Ridker PM, Talmud PJ. Genetic testing for cardiovascular disease susceptibility: a useful clinical management tool or possible misinformation? Arterioscler Thromb Vasc Biol 2004; 24(4): 628-636.
310 Health Council of the Netherlands. Screening op type 2 diabetes. The Hague: Health Council of the Netherlands; 2004: 2004/16.
311 Sandberg A, Ingdahl W. Nanotechnology and health policy. Poster at Conference EuroNanoForum, Trieste (It.), 9-12 December 2003.
312 Moor JH. Should we let computers get under our skins? In: Cavalier RJ, editor. The impact of the internet on our moral lives. Albany: State University of New York Press; 2005: 121-138.
313 Roco MC, Bainbridge WS. Converging Technologies for Improving Human Performance. Nanotechnology, Biotechnology, Information Technology and Cognitive Science. Arlington, Virginia: 2002.
314 Nordmann A. Converging technologies - shaping the future of European societies. Brussels: European Commission, DG Research; 2004.
315 Health Council of the Netherlands. De maakbare mens. In: Signalering ethiek en gezondheid 2003. The Hague: Health Council of the Netherlands: 2003/8; 2003: 83-99.
316 Wolpe PR. Neurotechnology and brain-computer interfaces - Ethical and social implications. In: Johnson DG, Ahearne JF, Bird SJ, Wulf WA, editors. Emerging technologies and ethical issues in engineering - papers from a workshop October 14-15, 2003. Washington D.C.: National Academy of Engineering, The National Academies Press; 2004: 57-65.
317 Juengst ET. What does enhancement mean? In: Parens E, editor. Enhancing human traits: ethical and social implications. Washington, DC: Georgetown University Press; 1998: 29-47.
318 Altmann J. Military Uses of Nanotechnology: Perspectives and Concerns. Security Dialogue 2004; 35(1): 61-79.
319 Simonis F, Schilthuizen S. Nanotechnology - Innovation opportunities for tomorrow’s defence. Eindhoven: TNO Industrie en Techniek; 2006.
320 National Cancer Institute. Cancer Nanotechnology. Going Small for Big Advances. Bethesda: National Cancer Institute; 2004.
321 Renn O. White paper on risk governance - towards an integrative approach. Geneva: International Risk Governance Council; 2005.
322 Health Council of the Netherlands. Niet alle risico's zijn gelijk. The Hague: Health Council of the Netherlands; 1995: 1995/06.
323 Health Council of the Netherlands. Risico, meer dan een getal. The Hague: Health Council of the Netherlands; 1996: 1996/03.
324 van Bruggen M, Fast T. Beoordelingskader gezondheid en milieu. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu; 2003: 609026003.
325 Health Council of the Netherlands. Gezondheid en milieu: beoordelingskader beoordeeld. The Hague: Health Council of the Netherlands; 2004: 2004/03.

326 Roco MC, Litten E. Survey on nanotechnology governance. Volume A. The role of government. Geneva: International Risk Governance Council; 2005.
327 Mark D. Nanomaterials - a risk to health at work? First International Symposium on Occupational Health Implications of Nanomaterials. Palace Hotel, Buxton, UK, 12-14 October 2004. Buxton: Health and Safety Laboratory; 2004.
328 Holsapple MP, Farland WH, Landry TD, Monteiro-Riviere NA, Carter JM, Walker NJ *et al*. Research Strategies for Safety Evaluation of Nanomaterials: Part 2, Toxicological and Safety Evaluation of Nanomaterials: Current Challenges and Data Needs. Toxicol Sci 2005; 88(1): 12-17.
329 Nanowetenschappen en nanotechnologieën: een actieplan voor Europa 2005-2009. Brussels: European Commission; 7-6-2005: COM (2005) 243.
330 European Group on Ethics. Ethical aspects of ICT implants in the human body. Opinion of the European Group on Ethics in Science and New Technologies to the European Commission. Brussels: European Group on Ethics; 2005.
331 MHRA. Corporate plan 2004-05 to 2009-10. London: Medicines and Healthcare products Regulatory Agency; 2004.
332 Davies JC. Managing the effects of nanotechnology. Washington DC: Woodrow Wilson International Center for Scholars; 2006.
333 Directoraat-Generaal Gezondheid en Consumentenbescherming. Nanotechnologies: a Preliminary Risk Analysis on the Basis of a Workshop Organized in Brussels on 1-2 March by the Health and Consumer Protection Directorate General of the European Commission. Brussels: European Commission; 2004.
334 Clift R. Nanotechnology: an example of risk management and regulation in an emerging technology. In: Special session of the Joint Meeting: Potential implications of manufactured nanomaterials for human health and environmental safety. Paris: OECD; 2005.
335 Dienel PC. Contributing to social decision methodology: citizen reports on technological projects. In: Vlek C, Cvetkovich G, editors. Social decision methodology: citizen reports for technological projects. Dordrecht & Boston: Kluwer; 1989: 133-151.
336 Fiorino DJ. Citizen participation and environmental risk: a survey of institutional mechanisms. Sci Technol Human Values 1990; 15(2): 226-243.
337 Durant J, Joss S. Public participation in science. London: Science Museum; 1995.
338 Armour A. The citizen's jury model of public participation. In: Renn O, Webler T, Wiedermann P, editors. Fainess and competence in citizen participation. Evaluating new models for environmental discourse. Dordrecht & Boston: Kluwer; 1995: 175-188.
339 Applegate J. Beyond the usual suspects: the use of citizens advisory boards in environmental decisionmaking. Indiana Law Journal 1998; 73: 903.
340 Guston DH. Evaluating the first US consensus conference: the impact of the Citizen's Panel on telecommunications and the future of democracy. Sci Technol Human Values 1999; 24(4): 451-482.
341 Rowe G, Frewer LJ. Public participation methods: a framework for evaluation. Sci Technol Human Values 2000; 25(1): 3-29.

342 Rathenau Instituut. Werkprogramma 2005-2006. The Hague: Rathenau Instituut; 2005.
343 Einsiedel EF, Goldenburg L. Dwarfing the Social? Nanotechnology Lessons From the Biotechnology Front. Bulletin of Science, Technology & Society 2004; 24(1): 28-33.
344 Marris C. Public views on GMOs: deconstructing the myths. Stakeholders in the GMO debate often describe public opinion as irrational. But do they really understand the public? EMBO Rep 2001; 2(7): 545-548.
345 Marris C, Wynne B, Simmons P, Weldon S. Public perceptions of agricultural biotechnologies in Europe. Final report of the PABE research project. Lancaster UK: Lancaster University; 2001.
346 Wynne B. Unruly technology: practical rules, impractical discourses and public understanding. Social Studies of Science 1988; 18: 147-167.

Annexes

Annex **A**

The text of the Work Programme for 2004

9.14 Risks and benefits of nanotechnology for public health (772)

In many Western countries, including the Netherlands, considerable sums of money are being made available for the development of nanotechnology, which is based on the manipulation of processes at the molecular scale. Much is made of the benefits of nanotechnology but little attention is paid to the risks associated with the new technology*. The Health Council will provide an overview of the risks and benefits in its investigative advisory report.

* See, amongst others, Brumfield G. Nanotechnology: a little knowledge … [new feature]. Nature 2003; 424: 246-248.

(page 47 of the work programme)

Annex **B**

The Committee's composition

- Professor WE Bijker, *chairman*
  professor of technology and society studies; University of Maastricht
- Professor ID de Beaufort
  professor of medical ethics; Erasmus MC, Rotterdam
- Professor A van den Berg
  professor of biomedical and environmental sensor systems; University of Twente, Enschede
- Professor PJA Borm
  professor of inhalation toxicology; University of Düsseldorf; Lector Life Sciences, Hogeschool Zuyd, Heerlen
- Professor WJG Oyen
  professor of nuclear medicine; University Medical Centre St. Radboud Nijmegen
- Professor GT Robillard
  professor of enzymology; University of Groningen
- Doctor HFG van Dijk, *scientific secretary*
  Health Council, The Hague

Secretarial support: Ms TME Smith-Mets, Health Council, The Hague

CFJ Feenstra carried out preparatory work for the Committee.

The Health Council and interests

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

Annex C

Experts consulted

- Professor A Rip
  professor of the philosophy of science and technology: University of Twente
- Professor CAJ Vlek
  emeritus professor of environmental psychology and behavioural decision research: University of Groningen.