National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Assessing health & environmental risks of nanoparticles

Current state of affairs in policy, science and areas of application

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Colophon

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Publiekssamenvatting

Beoordelen van risico's voor mens en milieu van nanodeeltjes

Nanodeeltjes zijn ultrakleine deeltjes met bijzondere eigenschappen, waardoor ze ongekende mogelijkheden hebben. Ze kunnen materialen en voorwerpen extra sterk maken, zonnecellen beter laten werken of heel gericht medicijnen op die plek in het lichaam brengen waar het nodig is. Vanwege deze veelbelovende eigenschappen wordt veel in nanotechnologie geïnvesteerd en is deze technologie niet meer weg te denken uit onze samenleving. Nanodeeltjes hebben echter andere eigenschappen en gedragen zich anders dan de klassieke, grotere bouwstenen van stoffen. De huidige modellen en technieken die nodig zijn voor een goede risicobeoordeling van nanodeeltjes en -materialen zijn nog niet voldoende geschikt om te beoordelen in hoeverre ze schadelijk zijn voor mens en milieu. Er zijn aanwijzingen dat sommige nanodeeltjes schadelijke eigenschappen hebben, maar het is onbekend waarom dat juist bij die deeltjes het geval is. Bovendien geldt het zeker niet voor alle nanodeeltjes en -materialen.

Dit blijkt uit een overzicht van het RIVM van de wetenschappelijke kennis over risicobeoordeling van nanodeeltjes en -materialen en hun toepassingen. Hierin staat onder meer de huidige stand van zaken in de Europese regelgeving beschreven. Behalve in algemene inzichten wordt dat verder uitgewerkt voor een aantal specifieke deelgebieden: consumentenproducten, voeding, medische toepassingen, toepassingen in de arbeidssituatie, en milieu.

Om de producten die momenteel worden ontwikkeld toch te kunnen beoordelen, moet de risicobeoordeling voorlopig met beperkte kaders worden uitgevoerd. Het RIVM signaleert de noodzaak om daar nu pragmatischer mee om te gaan. Gezien het hoge tempo van de nieuwe ontwikkelingen blijft aandacht noodzakelijk voor de wijze waarop risicobeoordeling vorm moet krijgen en hoe daarin met de onzekerheid over mogelijke risico’s moet worden omgegaan. Nieuwe aanpakken zijn hierbij behulpzaam, zoals safe innovation, waarbij de veiligheid van een product onderdeel is van het innovatieproces.

Voor de lange termijn zijn een goed werkende systematiek en beoordelingskader nodig. Belangrijke ingrediënten hiervoor zijn: gegevens over het gedrag van nanodeeltjes en -materialen, en kennis om de eigenschappen daarvan te kunnen voorspellen. Extra aandacht is nodig voor de aankomende nieuwe generaties nanomaterialen, zoals zelf-organiserende materialen, omdat over deze deeltjes en materialen de ontwikkeling van kennis nog in de kinderschoenen staat.

Kernwoorden: nanotechnologie, nanodeeltjes, nanomaterialen, risico's, gezondheid, milieu, wetgeving, consumenten producten, medische toepassingen, voedsel, arbo

Abstract

Assessing health and environmental risks of nanoparticles

Nanoparticles are ultrafine particles with exceptional properties that give them unbounded possibilities. They can add extra strength to materials and objects, make solar cells work more efficiently, and direct medicines straight to the place where the human body needs them. These highly promising properties are the reason why so much is being invested in nanotechnology and why it has become part and parcel of modern society. However, nanoparticles possess different properties and behave differently to the classical, larger building blocks of substances. The existing models and techniques used to assess the risks of nanoparticles and nanomaterials are not yet sufficiently tuned to determine how harmful they are to people and the environment. There are indications that some nanoparticles exhibit harmful properties, but exactly why this is true of these particular particles is unknown, and it certainly does not apply to all nanoparticles and nanomaterials.

These are the main conclusions of an overview produced by the Dutch National Institute for Public Health and the Environment (RIVM) of the scientific knowledge of risk assessments of nanoparticles and nanomaterials and their applications. The information in the report includes a description of the current European regulatory regime. General insights have been amplified for some distinct fields such as consumer products, food, medical applications, workplace applications and the environment.

The risks attached to products currently under development have to provisionally be examined within certain confines to be able to make an assessment of them. RIVM has flagged the need to adopt a more pragmatic approach. The rapid pace of new developments makes it necessary to continue devoting attention to how risk assessments must be designed and to how to deal with the uncertainty surrounding potential risks. New approaches like ‘safe innovation’, that make product safety part of the innovation process, are helpful.

An effective system and assessment framework is necessary for the long haul. Key components are data about the behaviour of nanoparticles and nanomaterials and knowledge of how to predict their properties. Increased attention needs to be directed towards the new generations of nanomaterials that are on the horizon, such as self-organising materials, because the development of knowledge of these particles and materials is still in its infancy.

Keywords: nanotechnology, nanoparticles, nanomaterials, risks, health, legislation, environment, consumer products, medical applications, food, worker safety

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1 Assessing health and environmental risks of nanoparticles – an overview

1.1 'Nanotechnology in Perspective' revisited

In 2009, RIVM published the report "Nanotechnology in Perspective: Risks to Man and its Environment" (Van Zijverden and Sips, 2009). At that moment, nanotoxicology was an emerging scientific field and it was considered necessary to elucidate potential ambiguities regarding the safety of nanomaterials. It now appears that this was far too demanding. Nanotoxicology was then in its infancy, exploring what distinguishes nanomaterials from molecular compounds in behaviour in test settings in both the human body and in the environment.

In 2014, it can now be concluded that huge global investments have been made by public authorities and industries alike, both in developing nanotoxicology and gaining insights into the safety of nanomaterials. Although questions about the safety of specific nanomaterials or nano-applications still cannot be answered in full, substantial progress has been made. The exploratory phase of what nanotoxicology should address has evolved towards the phase of making nanotoxicology testing fit for regulatory purposes. This phase requires a pragmatic approach in order to concisely cover all nanomaterials on the market and under development, as well as developing robust testing procedures. In our opinion, this cannot be addressed by adapting present testing to nanomaterials; it also will require some smart approaches which address reducing uncertainty regarding safety with an eye for (economic) feasibility within the innovation process. Some consider this as safe-by-design, but in our opinion this concept can too easily be interpreted as balancing risk or hazard and functionality.

More is needed. An exchange of questions and needs between innovators and regulators is required in order to make safety testing an adaptive concept, and to efficiently deal with all kinds of new nanomaterials that are still to come. Regulators will have to go back to the drawing board and question which information is pivotal for their considerations to be able to arrive at conclusions about safety. Innovators should fuel regulators with technical information to improve their insights in the specific issues that may come along with innovations (or not), and vice versa. Of course innovative approaches to support this interaction will be needed, as new courses have to be set out to tackle the questions about the safe use of nanomaterials. Otherwise, we will remain explorers, increasingly lagging behind innovations.

Scope of the report

This report describes and assesses the current state of affairs with regards to the development and use of nanomaterials/nanoparticles, including our ability to assess possible human and environmental toxicological risks.

In 2009, RIVM published the report 'Nanotechnology in Perspective: Risk to Man and the Environment (Van Zijverden and Sips, 2009). In 2015, the follow-up of this report was published (Westra, 2015). We can conclude that the conclusions of the 2009 report are still valid. We have noted a strong development in our understanding of nano-relevant phenomena, both regarding general science as well as toxicology. In addition, we see that nanotechnology is increasingly developing into the situation in which it is becoming considered as a relatively standard development platform.

In the update-report (Westra, 2015), we provide a follow-up to the 2009 report and focus on the current state of affairs of the possible human and environmental toxicological risks in relation to developments in the field of (engineered) nanomaterials. We do this by providing insights into the present state of knowledge with respect to these risks, including our scientific knowledge and ability to assess them.

Nanomaterials

In essence we focus on those materials that fall within the scope of the (recommendation for) EU-definition. However, toxicological behaviour is not determined by a legal definition. Some descriptions therefore adopt a more general perspective with the aim of underlining and conveying general principles and concepts.

In the chapters to follow we first of all provide an overview of the current state of the art in the field of legislation. Following this we focus on the current state of affairs in risk assessment and toxicology. Furthermore we provide an general overview of the developments in consumer products, agrofood and nanomedicine. Here we focus on aspects like use and occurrence, exposure, hazard, risk assessment, risk management and legislation. We provide a similar overview from the perspective of occupational health and the environment.

In this overarching summary of the update report, we present the most important findings from the report. In this summary we provide a general introduction to nanomaterials and nanoparticles (section 1.2), give a description of the economic development of nanotechnology (1.3), present the current state of affairs with respect to the use and risks of nanomaterials/nanoparticles (1.5), assess the current state of affairs of our ability to assess the risks of nanomaterials (1.5), and conclude with the essential agenda items for the future (1.6).

1.2 General introduction

The world around us consists of building blocks of matter in a variety of size-ranges: from small molecules to larger molecules like proteins and DNA, to aggregates and even more complex structures (see Figure 1.1). Part of these building blocks is in the size-range of nanometres and, as such, a normal and everyday constituent of matter. However, scientific, engineering and technological development has brought us to the point that we can actually physically handle materials on a scale of 1 to several hundreds of nanometres. Thus, we can now actually design, build and construct materials using these ultra-small pieces of

particulate matter. This is a remarkable achievement in itself, but also one that opens up an array of possibilities, which we are now pursuing on a global scale. Nanotechnology allows us to devise and develop new materials with new, interesting, and useful properties.

These materials can, for example, exhibit new electronic, magnetic, and material behaviour that we can put to use in a range of applications. From a scientific point of view, these interesting new properties are not so much the result of the fact that nanoparticles are 'small', but they result from the fact that a particle consisting of a relatively limited number of molecules behaves and interacts differently with its surroundings for fundamental physical reasons.

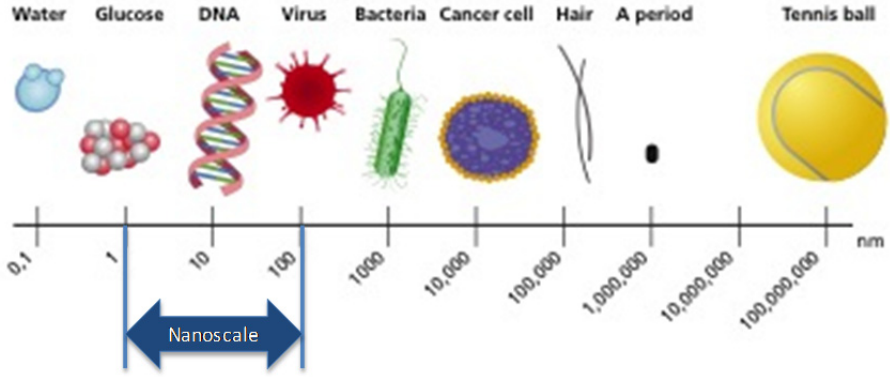

Figure 1.1 Size ranges of different materials; nanoparticles are in the size range of one to one hundred of nanometers (adapted from http://nano.cancer.gov/learn/understanding)

The technology is often viewed as an enabling platform-technology, i.e. a series of enabling technologies that can be used to improve current products and processes. It has a vast array of applications in various fields including healthcare, the environment, natural resources, construction, food systems, electronics, and services. Examples of different and emerging types of materials containing nanoparticles include simple granular-like particles from metal and metal oxides, but also carbon-based materials like carbon-nanotubes, and nanowires.

Applications

Materials containing nanoparticles are applied – and are being developed to be applied - in everyday materials for example as a component of polymer-based materials to reduce weight and enhance strength (e.g. tennis rackets, automobile bumpers), in cosmetic products to improve functionality and to add anti-bacterial activity (e.g. sunscreens, lotions, make-up), use in the food industry (e.g. in additives, packaging to enhance strength and barrier function), in the surface treatment of fabrics (e.g. improving resistance against wrinkling, staining, and bacterial growth), as a coating on windows, lenses and displays (e.g. making them surface water repellent, anti-reflective or self-cleaning). Other uses can be found in medicine for specialized targeted medication and functional improvement of medical devices (e.g. imaging devices), in sustainable energy applications (e.g. solar panels, production of catalysts), and in electronics and information technology applications (e.g. faster transistors, improved memory devices, and improved display devices); see *Figure 1.2*

In short, nanotechnology and engineered nanomaterials provide us with new material concepts and characteristics that have a multitude of applications in all materials and products as we currently know them.

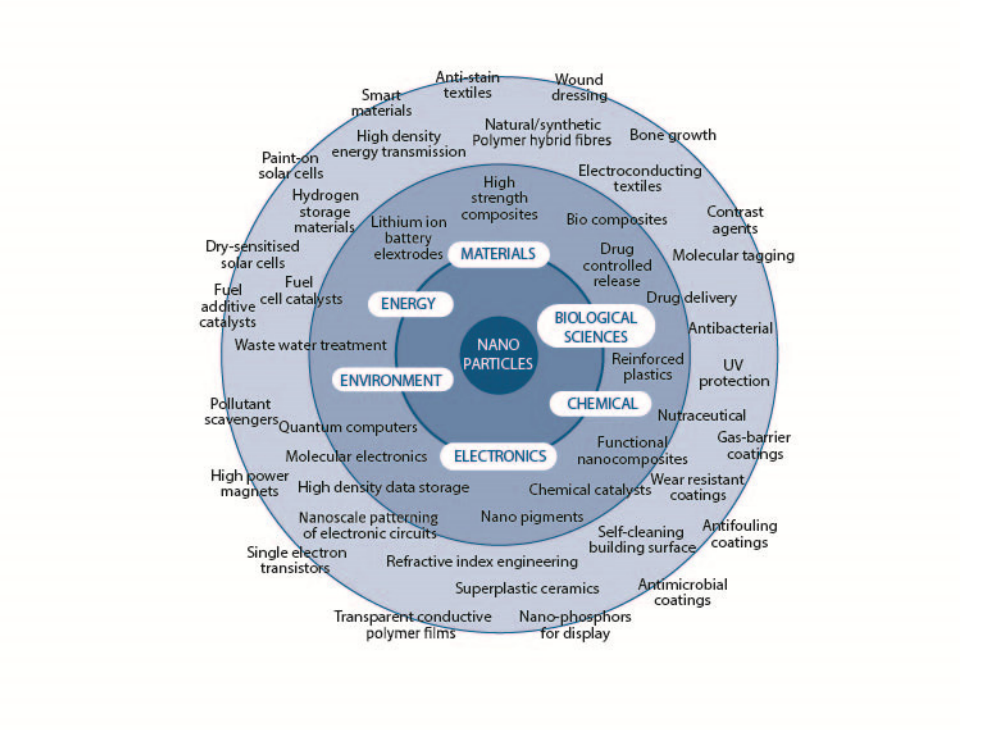

Figure 1.2 Overview of areas of application of nanomaterials (taken from: (McDermott et al., 2014))

Interaction with biological systems

Nanomaterials exhibit novel properties for fundamental physical reasons, and these can be put to good use. However, these properties and their underlying physical and chemical nature also enable novel and

new interactions with biological systems. New nanomaterials are comparable in size to biological machinery and may interact with biomolecules, cells, organs and organisms in a new and unexpected way. Therefore exposure of humans and the environment to nanomaterials may result in adverse effects; case studies show a range of possible negative impacts, and there is now a blossoming science to better understand and describe these toxicological phenomena. We stress that if the dimensions of a particle are on the nano-scale, this by no means implies that the particle is 'toxic'; it does mean that if we want to assess its possible adverse properties, we have to take its chemical composition, size, shape, and subsequent behaviour into account.

Evidently, nanotechnology and nanomaterials hold great promise and bring with them potential economic and societal benefits. It is important that these developments are not hampered by limited and undeveloped knowledge of the possible adverse effects and associated risks. It is therefore essential to strike the right balance between economic and societal gain and the possible negative impacts of the new technology.

1.3 Nanotechnology: indicators for development

Summary

From a policy perspective, nanotechnology is positioned as essential for future economic and societal development; an innovative enabling technology with applications throughout the whole of product space. Stimulation policies and programmes around the world focus on further development of the science and engineering aspects as well as subsequent valorisation and utilisation. Increasingly large sums of public and private money are being invested to drive the technology forward. Indicators like the number of nano-related scientific publications and patents and the usage of nano-terminology in scientific publications all show a large, almost exponential increase. As yet, their economic impact is unclear, but economic assessment methods and data gathering are under development.

1.3.1 *Policy and funding*

Policy

The European Commission foresees a necessary change towards a low-carbon emission and knowledge-based economy, which are considered preconditions for ensuring welfare, prosperity and security. The Commission identified five Key Enabling Technologies (KET) that will drive this societal and economic change: nanotechnology, microelectronics and nanoelectronics (including semiconductors), photonics, advanced materials, and biotechnology. KETs are knowledge intensive and associated with high R&D intensity, rapid innovation cycles, high capital expenditure and highly skilled employment. Being at the forefront of these developments is seen as essential for Europe's future development. KETS therefore play a determining role in EU programmes like Horizon 2020 and the Seventh Framework programme (EC, 2009a) (EC, 2009b).

This resulted in an EU action plan for the nanosciences and nanotechnology with a focus on research, industrial innovation, infrastructures, education, societal aspects, risk assessment, regulation and international cooperation and dialogue (EC, 2009c). Nanotechnology and materials are expected to have a high impact on the economy, innovation, science and society. The US is frontrunner in nanotechnology developments and actively strives to keep their leading position. The US recently published the National Nanotechnology Initiative Strategic Plan (NSTCCT, 2014). It aims to ensure that advancements in and applications of nanotechnology continue in this vital area of R&D, while addressing potential concerns about future and existing applications.

In many other countries, the potential of nanotechnology and nanomaterials was recognized at an early stage. In the Netherlands for example, the policy vision 'Van klein naar groots'[1] was published in 2006 (Dutch Government, 2006) underlining the importance of nanotechnology for the Dutch economy. Combined action in the Netherlands resulted in the NanoNextNL initiative[2], now comprising more than one hundred companies, universities, knowledge institutes, and university medical centres – aiming at research into micro-technology and nanotechnology, including technology assessment and risk assessment. It brings the worlds of academia and the business community together to allow for and create a dynamic and sustainable platform for research and innovation. Many other countries and regions around the world have similar programmes.

Funding

The prominent position of nanotechnology in worldwide stimulation and policy programmes is reflected in the available government-based funding. Cientifica (Cientifica, 2011) projects that worldwide government funding in 2015 will be close to 120 billion US dollars, a number that is still rising. Cientifica furthermore conjectures that, considering that business investments will be significantly larger, the total worldwide investment in 2015 might add up to a quarter of a trillion US dollars.

Economic impact

Countries that wish to promote the continued, economically sound development of nanotechnology will, however, need quantitative data on the economic impact of nanotechnology to guide further investment and policy decisions. However, few widely accepted economic impact assessments have been conducted, and there are many questions regarding the best methodologies to be used. Assessing the economic impact of nanotechnology was subject of a recent symposium of the OECD (OECD/NNI, 2013). Several methodologies for impact assessment were discussed. An important conclusion was that the technology is sufficiently mature to justify the collection of data to support the performance of economic impact assessments. OECD is furthermore working on a statistical framework for nanotechnology to track the development, use and impact of the technology (OECD, 2014).

[1] 'From small to great'
[2] http://www.nanonextnl.nl/

1.3.2 *Patents and publications*

The number of scientific publications and patents also reflects the nanotechnology focus in research and development in the past decades (Chen et al., 2013) (McDermott et al., 2014). An analysis of US-based patents, publications and (US-based) science funding compared two decades: 1991-2000 and 2001-2010 and found a 4.3-fold increase in the number of nano-related patents and a 4.9 fold increase in the number of nano-related publications (see Figure 1.3). Furthermore, the growth rate for 2011 and 2012 appeared to be even higher. The top ranking patent topics are related to the electronics industry (semiconductors, transistors), but topics like 'coating processes' (rank 4), 'drug' (rank 6), 'chemistry' (rank 8) and 'synthetic resins' (rank 11) all show significant growth rates as well. Publications show a wide range of subjects – carbon nanotube being the top ranking key word.

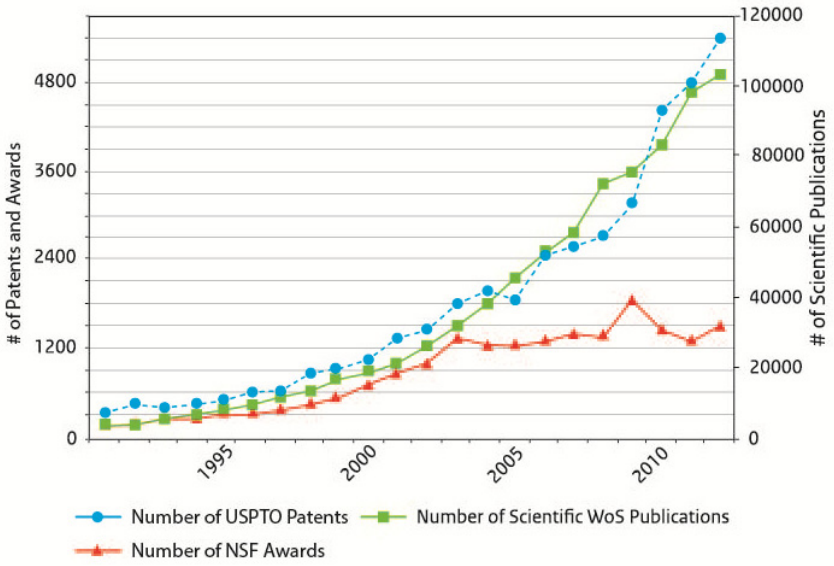

Figure 1.3 Development of nano-related patents, and publications from 1991 to 2012 (taken from (Chen et al., 2013). USPTO=United States Patent and Trademark Office; NSF=National Science Foundation (USA); WoS=Web of Science

Interestingly, the graphitic carbon-based nanotechnology innovation generally tracked that of nanotechnology innovation. However, in recent years, graphitic carbon-based nanotechnology innovation has experienced stronger growth compared to overall nanotechnology innovation. This recent strong growth appears to be fuelled by the recent isolation of and interest in graphene (McDermott et al., 2014).

Another interesting indicator of the continuous development in the field of nanotechnology is the use of the prefix 'nano' in science-based terminology. In two decades, the use of the prefix 'nano' in scientific publications increased from 10% (1990) to 80% (2010); the diversity of

nano-associated terms in scientific publications also increased enormously. Several explanations are considered – e.g. 'nano' as a popular catchphrase – but the use of this terminology in more than 800,000 scientific publications is evidently indicative of the focus of the scientific community (Arora et al., 2014).

1.4 Materials containing nanoparticles: uses and uncertainty about risks

Summary

In summary, considering their use and exposure, we find that the potential range of applications is virtually unlimited, since nanoparticles add specific functionalities like strength or electrical properties. Currently we only have a very limited idea of which products on the market actually contain engineered nanomaterials and nanoparticles, how much of these materials are or have the potential to be released, and in which particular form or modality. With respect to hazard, much progress has been made in understanding and explaining the (eco)toxicological mechanisms and the adaptation of the toxicological 'toolbox'. On the other hand, our scientific knowledge does not yet suffice for us to be able to develop, for instance, predictive models. More importantly, the pace at which new classes of nanomaterials with novel characteristics like self-organising properties are being developed is currently outrunning the pace of general scientific development and understanding.

1.4.1 *Occurrence and exposure*

Table 1.1 gives an overview of the different potential uses of nanomaterials in consumer products, agrofood and nanomedicine applications

Table 1.1 Generalized overview of the potential use of nanomaterials in several use categories. More detailed information is provided in chapters 4 to 8.

Use category	**Nanosized material**	**Product type**	**Functionality**
Consumer products (see chapter 4)	Particles (e.g. TiO2, Ag, ZnO, SiO2, carbon black) Carbonanotubes	Divers (e.g. cosmetics, personal care products, textiles)	Color pigments, antibacterial activity strength, durability,
Agrofood Direct use (see chapter 5)	Inorganic solid particles (SiO_2; TiO_2)[1]	Divers (powdery foodstuff; candy)	Anti caking agent, food colouring
Agrofood Direct use (see chapter 5)	Encapsulated active ingredients	Regular foodstuff (divers)	Improved stability of foodstuff; improved shelf life; improved control of

Use category	Nanosized material	Product type	Functionality
			bioactive ingredient, etc.
Agrofood Indirect use (see chapter 5)	Encapsulated active ingredients	Animal feed, fertilizers, pesticides, animal medicine, animal hygiene	- improved control of active substance - reduction of active substance
Agrofood Indirect use (see chapter 5)	Particulates (SiO2, silver, clays, starch, polymers)	Animal feed, packaging, various equipment	Anti-caking, improved packaging (e.g. strength, barrier function) anti-bacterial activity
Nanomedicine (see chapter 6)	Encapsulated active ingredients	Therapeutics (medication)	Improved control of active ingredient Targeting of active ingredient Reduction amount active ingredient
Nanomedicine (see chapter 6)	Particulates (various)	Cements, filling materials (e.g. for bone; dentistry); instruments, medical appliances	Improved strength, improved biocompatibility, anti bacterial activity

1: TiO2 usually is not deliberately added as a nanoparticle. However, some 10-30 % of the added material consists of particles <100 nm

Nanomaterials are developed and used to add a specific functionality to a product or an article. These functionalities are diverse e.g. improving the strength of a material, adding anti-bacterial activity, or improving control of an active ingredient in foodstuff or medication. As a consequence the (potential) application in products and foodstuffs is virtually unlimited. Table 1 can therefore best be interpreted as a general indication of the types of potential uses and materials.

At present, our actual knowledge of which product nanomaterials and/or nanoparticulates are actually used is very limited. Generally, product composition is regarded as confidential business information and belongs to the realm of the manufacturer. For the consumer products

and agrofood segments, public knowledge on the use and occurrence of nanomaterials is therefore limited.

This is also true for human exposure to nanomaterials. Since manufacturers do usually not disclose the presence of nanomaterials, information is limited and much of the current public knowledge is based on measurements. This means that the nanomaterial content of the material itself as well as the quantities released and and concentrations humans are exposed to, are determined experimentally. The current focus is still on exposure to a number of specific widely used particulates (metals, metaloxides, SiO_2, carbon, carbon nanotubes). Measuring nano-particulate matter poses a problem, and measurement techniques still need further development, as well as requiring skill and expertise.

From an occupational perspective, we currently have a general idea of the most important industries and branches that produce and/or use nanomaterials. However, at the moment, there are still no comprehensive insights into the actual fields that produce and use nanomaterials. Information on the size of the exposed worker population and exposure levels are usually, at best, only indicative and general.

From an environmental perspective, this situation is comparable and only generalized insights into potential emission sources are available. Nanomaterials employed for single use (e.g. in cosmetics or crop protection products) are expected to lead to larger emissions to (per unit product) and exposure levels in the environment, relative to other types of use.

1.4.2 *Hazard and risk assessment*

Hazard

The hazard potential is strongly dependent on the type of particle and its environment. Here again, we stress that the prefix 'nano' is by no means synonymous with 'toxic'. It does mean that if we want to assess its possible adverse properties we have to take both its particle aspect and size into account. The quest in addressing toxicological behaviour is to determine the various size-dependent, particle-specific properties and try to correlate these to the observed toxicological behaviour. This process is currently ongoing, with among others, the aim to predict possible adverse effects based on these characteristics.

SCENIHR[3] provided an overview of a number of important toxicological findings for non-soluble (water) nano-sized particulate matter (SCENIHR, 2009). In summary, inhalation exposure to nano-sized particulate matter may result in local lung inflammation, possibly resulting in subsequent responses such as allergy and genotoxic effects. Additional concerns are related to the internal exposure, as some particles may enter the bloodstream and accumulate in organs like the liver and spleen. In *in vitro* cell systems, particulate matter is able to

[3] Scientific Committee of Emerging and Newly Identified Risks

enter subcellular compartments opening up a possible route for direct and indirect genotoxic effects. Specific types of nano-fibres may exhibit asbestos like responses including chronic inflammation.

The current toxicological effort focuses on a number of relatively simple particulates (metals, metal-oxides, SiO2, carbon, CNT), mainly on the basis of their high and widespread current production and use, and thus their exposure potential. It is important to recognize that many of the substances that are the focus of current nano-toxicological studies are relatively 'simple' materials (often termed 'first-generation' nanomaterials). Increasingly complex and sophisticated nanomaterials are being developed at this moment; new generations of nanomaterials exhibit specifically designed bio-interactions or have a self-assembling nature.

Nano-encapsulates, developed to be used in food and feed products and already used for medical purposes, are an important novel class of nano-particulates. The current thinking is that in food products, the nano-structures quickly degrade back into their constituents in the human intestinal tract. There is however some concern about more stable forms of encapsulates that may result in, for example, increased bioavailability of ingredients.

In parallel with the growing interest in nanoparticles, information on their effects on humans and the environment is rapidly increasing. Most of the available information concerns the aquatic environment. Virtually no information exists on the hazards of nanoparticles in soils and sediments. The diversity of impact data makes it impossible to form a consistent opinion on the hazards of specific nanomaterials. Increasing attention is being paid to the hazards of transformation products which are formed after the introduction of a nanomaterial into the environment.

Risk assessment

In essence the basic philosophy and methodology needed to perform an RA for nanoparticles is the same as for conventional non-nanomaterials: comparing the level of exposure with the (non-)toxic effect level. However, the instruments in the 'RA-toolbox' need to be adapted for nanoparticles because of their specific properties. Adapting old and developing new instruments, assessing usefulness and applicability of datasets, developing, implementing and harmonising procedures and methods is time consuming and requires considerable effort. In a semi-coordinated fashion, many projects covering these topics aim to deliver RA instruments between now (2014) and 2020. This means that further understanding of mechanisms, the development of the methods and tools and drafting of standards are well underway.

Additionally, existing knowledge focuses on finding more generalized assessment methods like grouping, read-across and nanoparticle

(Q)SAR[4]. Although still in its infancy, these developments are essential in order to assess the continuously and rapidly growing number of (increasingly complex) nanomaterials that are being developed and potentially applied.

The number of authoritative nanoparticle substance specific risk assessments performed by acknowledged specialists and that are of sufficient rigour is very limited. This is a consequence of both the lack of data on (the behaviour and effects of) the specific nanoparticle and the current lack of scientific and harmonized methods and tools. These assessments are limited to relatively simple nanomaterials:

- The SCCS[5] assessed a number of cosmetic ingredients; judgment was passed mainly on the basis of the low levels of dermal uptake and therefore the limited internal exposure. Use of spray applications resulting in possible inhalation exposure was not recommended.
- SCENIHR reviewed the available information for nano-silver and could not rule out adverse effects
- For a number of nanomaterials, a more detailed risk assessment is foreseen: SiO_2, currently under scrutiny because of it accumulating potential in humans combined with its widespread use, will be evaluated by SCCS and is undergoing a substance evaluation within REACH. Nano-silver and TiO_2 are also subject to a REACH evaluation in which (environmental) nano-aspects are also included.
- EFSA[6] is in the process of re-evaluating the possible risk as a result of the established food additives. This evaluation process will include nano-forms of the additives and is scheduled to be finished in 2020.

The greatest challenges for medicinal products, as identified by Ehmann (Ehmann et al., 2013b), are associated with the novel, "next generation" nanomedicinal products, e.g. based on dendrimers, and the generic versions of first generation products, e.g. based on liposomes or iron oxide nanoparticles, which are termed "nanosimilars".

Occupational risk assessments are (in the EU) primarily the responsibility of the employer. Derivation of occupational exposure limits is hampered by the lack of toxicological data. Also, many challenges in measurement techniques need to be overcome. Here, more pragmatic approaches (reference values, control banding) have been developed in order to aid in the assessment and subsequent control or nano-particle based risks.

Environmental risk assessment for metallic particles (nanozinc) shows that the gap between effect levels and exposure levels is relatively large, so that as yet, no risk for organisms in EU waters is anticipated. A similar approach for nano-silver does not exclude the occurrence of adverse effects on the environment.

[4] (Quantitative) structure activity relationship
[5] Scientific Committee on Consumer Safety
[6] European Food Safety Authority

1.4.3 *Legislation*

In general, the European Commission concludes that the current EU-legislative framework to a large extent covers potential risks in relation to nanomaterials (EC, 2008a). On the other hand, organisations like the RIVM demonstrated that within the various frameworks like REACH and OSH, legislative gaps still do exist (Bleeker et al., 2013). Thus, current legislation may have to be modified in the light of new information becoming available, for example regarding thresholds used in some legislation.

At a European level, several activities can be seen:

- A recommendation on the definition of nanomaterials was published. This forms the basis for the definition in several newly formulated EU-legislations
- Adaptation of the REACH regulation to include the generation of data and subsequent assessment of the risks. This is seen as essential as it regulates the generation of the necessary data to enable assessments of risks (consumer, occupational, and environment). The political process of adaptation of the regulation proceeds slowly.
- A number of product regulations now include a labelling obligation (regulations for cosmetics, food and biocides). Labelling for medical devices is foreseen, but still under discussion at the political level.

It is also recognized that although adaptation of REACH to include nanomaterials is an important step forward, data gaps still remain. REACH for instance poses a threshold of 1 ton/year, resulting in a limited availability of (legally required) data for substances with lower production volumes, as is typically the case for (individual) nanomaterials. In addition, REACH only adds limited data relevant for exposure, especially below the 10 ton/year production volume threshold.

Finally, there is a need (internationally) for reliable insights into the application of nanomaterials in consumer products. Owing to the lack of progress in the EU arena, a number of Member States have developed national initiatives for the registration of consumer products containing nanomaterials; each of these initiatives has its own assumptions and content. Ideally, the separate systems will be harmonized over time to achieve a coherent EU registration system, a process expected to become more complex as more national initiatives continue to crystalize. The possibilities for a European approach are now under the scrutiny of the Commission.

1.5 Current state of affairs

1.5.1 *Introduction*

Nanotechnology, and nanomaterials as a subset, has a great deal to offer to improve the quality of life (see Section 1.2). On the other hand, as for any emerging technology or development, there are potential downsides. We need to find ways to assess and deal with the uncertainties of these risks across time. In section 1.5.2, we provide an

assessment of the state of the art of our ability to make a statement on the potential risks of nanomaterials.

Over the past 5 to 10 years the toxicological-oriented research effort has been strongly focused on gathering empirical knowledge about toxicity, its mechanism, and the validity of (test) methods. This exploratory research has addressed questions like: what makes nanomaterials different from conventional molecular substances; how can we understand and describe this; and are the ways and methods with which we determine certain effects still applicable for nanoparticles and materials? As a result, we can now more firmly address the questions which parameters and toxicological endpoints should be determined, and in which way this can be achieved. A second important step in progress is the application this newfound toxicological knowledge in a regulatory context.

1.5.2 *Hazard and exposure*

Hazard

From the hazard perspective, an elementary but important observation is that nanomaterials and nanoparticles are in the size range of our biological machinery. Nanomaterials are a class of compounds that is toxicologically 'new', that is it may interact with biota in a way which we now only partly understand. At present, the simpler and better researched nanomaterials are relatively well understood. Our scientific understanding and ability to explain and describe the observed phenomena is growing, but is still relatively limited.

Presently, important positive developments are:

- The elementary (eco)toxicological understanding and risk assessment tools for the relatively simple nanomaterials are projected to be available around 2020;
- There is a growing awareness that particle toxicology (as to be applied in safety evaluation of nanomaterials) is fundamentally different from the classical toxicology of (soluble) substances;
- There is a considerable and continuous interdisciplinary effort to develop the necessary knowledge and generate all necessary information and data from a risk assessment point of view;
- Scientific understanding is growing significantly, but has not reached the point that we can provide general descriptive models; more empirical data and mechanistic understanding are necessary to support this process;
- In the occupational field, pragmatic approaches have been developed to temporarily deal with the present uncertainties in the determination of the hazard;
- The REACH regulation is in the process of being adapted to include the generation of data and subsequent assessment of nanomaterials.

On the other hand we see:

- A continuous development of new and novel nanomaterials to be used in a multitude of products. Potential risks still needs to be assessed on the basis of incomplete data and incomplete understanding of the relevant underlying (toxicological) phenomena;

- That generalized methods to deal with more than one substance at a time and to allow for grouping, read across or computer-based predictions are still in their infancy. A substantial amount of empirical data is needed to support this development;
- That nanomaterials may show complex dynamical behaviour, which fundamentally complicates the process of scientific understanding;
- That our toxicologically based and microbiologically based knowledge of more advanced materials – e.g. coated particulate matter, bioactive nanomaterials, self-organising particles – is very limited and not progressing at a pace that keeps up with the technological developments;
- That new fields of research with an impact on our current knowledge of toxicology and hazards are still emerging (bionanotechnology – nanotechnology using biological materials – is an example);
- That adaptation of regulatory frameworks (for example REACH, food related regulation) is a slow political process, and leaves data-gaps e.g. for materials below 1 ton/year production volume. As a consequence, regulation is likely to increasingly lag behind the development of new and innovative materials and products that hit the market;

Occurrence and exposure

From the occurrence and exposure perspective, the assessment of the state of the art is somewhat similar to that of the hazard side.

On the one hand we see:

- Increasing knowledge of the presence of nanomaterials in (consumer) products based on obligatory labelling information (cosmetics and biocides);
- Increasing knowledge of amounts, number of particles and concentrations in consumer products based on experimental measurements;
- Several pragmatic approaches in exposure determination and risk management being developed in the occupational field;
- Development of the fundamentals of (fate) models allowing for a description of release, distribution and exposure; data to validate the models are however still scarce;
- REACH regulations, when adapted, will provide some of data on exposure and on risk reduction measures, albeit at a fairly limited level;
- Progress in the development of the analytical tools and methods for measuring nano-characteristics in complex media needed to gain insights into the presence of and exposure to nanomaterials.

On the other hand:

- There is still a serious lack of information on the use and presence of nanomaterials in (consumer) products;
- For a number of product categories, there is no regulatory incentive or otherwise for manufacturers to make data available about the presence of nanomaterials in their product;
- Experimental measuring techniques still require highly skilled personnel and bring high costs, and thus are not universally

available; different techniques are often required to measure different characteristics;
- There is a continuous development of novel nanomaterials which are either already being used or are planned to be used in a variety of (consumer) products;
- The speed at which new products with nanomaterials are expected to hit the market and the sheer number of them exceeds the pace at which our knowledge on their risks is developing;
- Adaptation of regulatory frameworks (e.g. REACH) is slow and leaves data gaps, especially for substances below a production volume of 1 ton/year.

1.6 Four needs for follow up

Leading on from the previous section the following gaps are clear:

First of all there is a serious need for data – i.e. nanomaterial and nanoparticle specific data (physical-chemical, (eco)toxicology, exposure) but also data on the use of nanomaterials/particles in products and the release of these materials/particles from products.

Secondly there is a need for knowledge; we need to improve our current scientific understanding of nano-toxicological behaviour and make the step towards generalisation and abstraction.

Thirdly, we need to broaden our scope; we currently focus on relatively simple nano-materials, but we need to monitor and assess new developments of novel nanomaterials (e.g. bioactive and self-assembling materials) and new, emerging technologies. This includes, for example, the development of new generations of nano-materials (the so-called 3rd and 4th generation materials).

Fourthly, we need to find ways - scientific, regulatory and societal – to deal with the difference in pace between nanomaterial innovations and our scientific and regulatory capacity to assess the uncertainties and risks and ways of dealing with these potential risks and uncertainties.

1.6.1 *Contextual considerations*

Evidently, there still is significant work to be done to resolve the many unanswered scientific-regulatory questions. Regulatory questions are awaiting sound scientific evidence but the lack of clarity about the nature of the required evidence as well as the scientific hurdles to be taken make this a potentially tedious process. In the next section, we offer a number of considerations that provide useful context for subsequent steps to be taken.

Need for data

Adaptation of the REACH annexes with regards to the information requirements for nanomaterials is essential for the provision of scientific data. These data are also needed and used in other legislative frameworks e.g. occupational health and consumer protection. Additionally, it adds to the bulk of empirical data that are necessary to improve our general scientific understanding of nanoparticle behaviour.

Additionally, more and serious efforts in making better use of the multitude of (scattered) data on nanomaterials that is generated may

help to increase output. The many data generated in the numerous European and global projects could for example be shared and combined at a more structural level. On top of that, developing novel ways to exploit these data may add to the results, including new ways of managing and coordinating the data(sources). Although much discussion on this issue is ongoing, it still seems an elegant and important route to make more efficient use of existing data.

Improved insights into the products that contain nanoparticles will help to increase transparency. Currently regulatory labelling incentives for cosmetics and biocides, and provisionally for food and medical appliances, provide basic insights into the use of nanomaterials in the product space. Another (potential) source of information could be provided by a consumer product registry, as currently under discussion in the EU. This process of designing and setting-up a European wide comprehensive product registry will provide a major challenge as the political context is complex and the technical realization will by no means be straightforward.

Knowledge development

Getting to grips with nanoparticle (eco)toxicology and adapting and redesigning existing instruments for risk assessments is still a major challenge. This is true for both human health aspects and environmental aspects. The amount of research being performed in this field is extensive, and a better coordinated approach and research agenda may be beneficial for optimising output and results.

As part of this effort, the step towards scientific understanding and development of models and tools for more generalised approaches (grouping, read-across, QSARs) is essential to be able to deal with the growing number of nanomaterials. These concepts and developments are by no means easily established, and many fundamental steps need to be taken; for example for grouping: there is still a need for a well-defined, harmonised and generally accepted view on the criteria for grouping. International processes which are currently initiated on e.g. OECD-level provide essential support for achieving much needed progress on this topic.

Furthermore, additional approaches may be considered to be able to deal with limited resources and speed of development. Present examples concern driven approaches, in which the applied testing strategy is determined on the basis of indicators of concern and so-called intelligent testing strategies. But more multidisciplinary approaches and cross-fertilisation with other disciplines are also worthwhile exploring. In the research focus, the question that needs to be addressed is how to deal with assessing the potential risk of pristine nanoparticles versus the potential risk for humankind and the environment during and after use of the product containing these nanoparticles.

In parallel, life cycle approaches and approaches like ‘safe innovation’ are gaining ground in various areas of research, like in the EU’s H2020

programme. Safe innovation is a preventive conceptual method within the context of risk reduction. Safe innovation is the integration of hazard identification and risk assessment methods early in the design process of nanomaterials to eliminate or minimise the safety and health risks in the different stages of the lifecycle of nanomaterials. At an operational level, physical-chemical characteristics are an important cornerstone of safe innovation approaches. They are important determinants of the functionality as well as the hazard of a material. These 'precautionary' approaches help to identify possible risks and adverse effects at an early – preferably premarket - stage of product development, when economic impact is still limited.

Broaden the scope

Novel higher generation nanomaterials are currently being developed. These developments need to be monitored closely as they venture into the unknown from a toxicological and (micro-)biological point of view. In parallel, the scientific fundamentals of the interaction of these materials with biota need to be explored and a baseline assessment of potential hazardous impact needs to be made.

Aspects of risk governance

We have now been discussing the safety of nanomaterials and the uncertainties in their determination for at least a decade.. Despite all our efforts, speeding up the progress in coming to conclusive answers about health risks seems to be inevitable as increasing numbers of materials containing nanoparticles enter the market.

The current situation is that nanomaterials and materials containing nanoparticles are on the market, the instruments needed to assess the risk are in development but not yet sufficiently matured, and the number of products expected to hit the market will most likely show a large increase. On the one hand this means that the scientific-regulatory community needs to develop a fully functional toolbox that helps the risk assessors assess the risks; a process that is currently ongoing. On the other hand, instruments to deal with and assess the current situation are also required. Therefore, the regulatory-scientific community is exploring options for finding alternative testing strategies which assess the level of concern and base the subsequent (testing) strategy on this concern. Developments like this will provide policy-makers with additional tools and policy options for decision-making and prioritisation.

Another interesting development can be seen in the field of occupational exposure. Here, 'reference values' are derived that, for all practical purposes, act as exposure limits. These values are derived through scientific reasoning, using the knowledge available at that moment. Similar, more pragmatic reasoning in which false negatives are accepted, i.e. we accept the fact in that some cases protection cannot be 100%, might be worthwhile considering as an interim solution. We stress that this is not an appeal to set aside the current (legal) principles for protecting humans and the environment, but a pragmatic and

realistic assessment of the current situation, and an instrument to help prioritise efforts.

Several initiatives might support new ways of efficiently addressing nanomaterial safety in such a way that they do not hamper the innovation potential. On the one hand, initiatives addressing safety can be distinguished, for example safe innovation or responsible research and innovation. On the other hand, there are also initiatives aiming to better tune regulatory approaches to innovations; initiatives like adaptive governance or flexible regulations. In the regulatory-scientific context, both innovation and risk assessment processes may benefit from increased cooperation and data-sharing. Joint efforts by risk-assessors and industry scientists may help to identify possible undesired effects at an early stage, thus allowing for improved pre-market screening of nanomaterials.

In this context there is a need to find ways in which information on composition and underlying data that are fundamental to nanomaterial behaviour and dynamics become available to risk assessors. From a scientific-regulatory perspective, sharing and having access to the multitude of data is essential for making sufficient progress, a process which, up to now, has been hampered by aspects like confidential business information.

Additionally, we observe that the emphasis of the scientific nano-safety community is on safety, whereas for fundamental scientists and the scientific business community, innovation is more leading. Joining and combining those viewpoints, focussing on mutual understanding of the underlying concepts will help to make a shift towards approaches based on a shared frame of reference.

In short, from a scientific-regulatory perspective, an arrangement in which government, society in general, the regulatory-based scientific community, and the business community cooperatively work to find ways of dealing with fundamentally new and innovative developments in both materials and risks, would add a firm foundation of increased data and mutual understanding. The challenge is to find an approach that is attuned to how society deals with these new developments, using regulation or otherwise, as well as to the need for innovation and development by the business community. For the regulatory-scientific community, cooperation and sharing during the innovation process seem to form an important exploratory route forward, as they may provide approaches for policy-makers that support regulatory decision-making at the pre-market stage.

2 Policy and legislation

2.1 Introduction

Legislation on managing risks is often based on the precautionary notion that substances and products can only be placed on the market if health, safety and environmental risks are sufficiently controlled (e.g. EC, 2001b, 2003a, b), or in general that, while uncertainty about these risks is diminished, precautionary measures are taken to prevent exposure and hazards (EC, 2000a). The rapid development of nanomaterials in combination with their potentially different behaviour has raised concerns that these materials may introduce new hazards during occupational, consumer, patient and/or environmental exposure. In addition to new hazards, regulation of nanomaterials may be further complicated by the fact that nanomaterials can change during their life cycle. A material may not necessarily be considered a nanomaterial in all stages of its life cycle.

The European Commission concluded that although legislation covers potential environmental, health and safety risks in relation to nanomaterials (EC, 2008a), nanomaterials are not specifically mentioned and legislation may need to be adapted.

In this chapter we summarize the developments in adapting legislation. We focus on European legislation, but in section 2.4.5 we briefly describe some developments outside the EU as well.

2.2 European definition of nanomaterials

In 2011, the EC has published a recommendation on a definition for nanomaterials. Currently discussions are taking place in several regulatory frameworks to incorporate this definition. The EC recommendation is a good starting point for further discussions. The implementation of the definition in the regulation on biocidal products shows the potential of the recommendation. However, discussions within specific frameworks (e.g. in food and cosmetics) show issues on limitation of the definition, not in the least the difficulties to ensure the essential harmonisation of the definition over the different frameworks.

The first step in adapting legislation for nanomaterials is the formulation of a definition to distinguish nanomaterials from non-nanomaterials. To this end, the European Commission (EC) published a recommendation in October 2011 (see box below). This recommendation clearly is a first step, as it is currently not legally binding and further discussions are still necessary to come to a definitive and broadly accepted definition. In its recommendation the EC clearly states that the definition is not intended to classify nanomaterials as intrinsically hazardous (EU, 2011a). In subsequent discussions on (implementation of) a definition, it also appears essential to solely focus on identifying nanomaterials. Determining hazard and risk (and the necessary requirements to do so) is seen as a second step in the adaptation of the individual regulatory frameworks.

Some of the discussions have already started (see below). To feed into these discussions, RIVM summarised their view on interpretation and implications of the recommendation in 2012 (Bleeker et al., 2012), and recently JRC published their first report in preparation of the December 2014 review of the definition (Rauscher et al., 2014).

'Recommendation on the definition of nanomaterial' (EU, 2011a)**:**

'Nanomaterial' means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm–100 nm.

In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %.

By derogation from [the previous paragraphs], fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials.

For the purposes of [the above], 'particle', 'agglomerate' and 'aggregate' are defined as follows:

- *'particle' means a minute piece of matter with defined physical boundaries;*
- *'agglomerate' means a collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components;*
- *'aggregate' means a particle comprising of strongly bound or fused particles.*

Where technically feasible and requested in specific legislation, compliance with the definition [above] may be determined on the basis of the specific surface area by volume. A material should be considered as falling under the definition [above] where the specific surface area by volume of the material is greater than 60 m^2/cm^3. However, a material which, based on its number size distribution, is a nanomaterial should be considered as complying with the definition [above] even if the material has a specific surface area lower than 60 m^2/cm^3.

The Commission solely aims to identify substances within a specific size range and does not aim to classify nanomaterials as intrinsically hazardous (EU, 2011a).

Currently only three European regulations incorporate a definition of a nanomaterial to enable specific provisions for nanomaterials: cosmetics (EC, 2009e), food labelling (EU, 2011c), and on biocidal products (EU, 2012). These are summarized in Table 2.1.

Table 2.1 shows that different regulations define nanomaterials differently. The publication of the recommendation renewed the definition discussion, supporting the process of harmonization in the definitions, although some differences are likely to remain (e.g. limitation to "intentionally manufactured" in EU/1363/2013).

If different definitions continue to exist within the various regulatory frameworks, a material defined as a nanomaterial in one framework, could be considered a non-nanomaterial in another legal framework. This will lead to unequal treatment of producers and/or importers (non-level playing field) and decreased transparency for workers and consumers, as well as regulators and risk assessors.

The usefulness of a single legally binding definition is evident. The scope of such a single definition should be limited to the identification of nanomaterials. All elements of the subsequent hazard or risk assessment of nanomaterials (and the necessary requirements) need to be addressed in the specific legislation (Bleeker et al., 2013).

Table 2.1: Definitions for nanomaterials in legislation.

Legislation	**Definition**[1]
Regulation on Cosmetics (EC/1223/2009)[2]	*"nanomaterial" means an **insoluble or biopersistent and intentionally manufactured** material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm*
Regulation on food labelling (EU/1169/2011)	*'engineered nanomaterial' means any **intentionally produced** material that has one or more dimensions of the order of 100 nm or less or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain **properties that are characteristic of the nanoscale**.* *Properties that are characteristic of the nanoscale include:* *(i) those related to the large specific surface area of the materials considered; and/or* *(ii) specific physicochemical properties that are different from those of the non-nanoform of the same material*
Regulation on Biocidal products (EU/528/2012)	*'nanomaterial' means a **natural or manufactured** active substance or non-active substance containing particles[3], in an unbound state or as an aggregate[3] or as an agglomerate[3] and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1-100 nm* *Fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below 1 nm shall be considered as nanomaterials.*
Regulation on food labelling (under consideration) EU/1363/2013[4]	*"engineered nanomaterial" means any **intentionally manufactured**[3] material, containing particles[3], in an unbound state or as an aggregate[3] or as an agglomerate[3] and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm to 100 nm.* *By way of derogation:* *(a) **food additives** covered by the definition set out in the first paragraph shall not be considered as engineered nanomaterials, if […];* *(b) fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm shall be considered as engineered nanomaterials.*

[1] Main differences between the definitions are indicated in **bold** text.

[2] The publication of the recommendation (EU, 2011a) has re-opened discussions on this definition, and it will be revised.

[3] Additional definitions are included for these terms of the specific definition.

[4] This definition was intended to replace the definition in EU/1169/2011, but it has been rejected by the European Parliament on March 12, 2014[7].

Data requirements for risk assessment generally differ for different legislations, underlining the need to define these requirements separately in each type of legislation, as is common practice for non-nanomaterials. The specific way to generate the required data, e.g. a tiered approach, could easily be described in guidance (e.g. EFSA guidance; Antunović et al., 2011), which implies that inclusion of e.g. 'solubility' in the definition of a nanomaterial is not necessary.

2.3 Standardisation of methods

In 2006 the Dutch government already recognised the need for standardisation to come to an adequate legislation that ensures a level playing field for all parties (Dutch Government, 2006).

Standardisation is best achieved in an international context with an important role for the International Organization for Standardization (ISO; www.iso.org). ISO Technical Committee 229 focuses on standardisation in the area of nanotechnology. TC 229 develops standards for (1) terminology and nomenclature, (2) metrology and instrumentation, including specifications for reference materials, (3) test methodologies, (4) modelling and simulations, and (5) science-based health, safety, and environmental practices. So far, this resulted in 42 published standards (mainly Technical Specifications and Technical Reports) and another 24 in progress[8]. This started with standards on terminology in 2008, but now includes standards for all of the five categories indicated. The standards in progress mainly focus on characterisation (often limited to – small groups of – specific nanomaterials), but also further work on terminology is in progress, indicating that additional projects for TC 229 are likely to commence.

Another important international body in standardisation is the Organisation for Economic Cooperation and Development (OECD). Within its Chemicals Committee, OECD has developed guidelines for the testing of chemicals for assessing the potential effects of chemicals on human health and the environment[9]. These are accepted internationally as standard methods for safety testing. In 2006 OECD's Working Party on Manufactured Nanomaterials (WPMN) was established to assess the potential implications of manufactured nanomaterials for human health and environmental safety. Among other projects, the WPMN is carefully evaluating any concrete proposals for the 'nano-specific' development or revision of test guidelines and/or guidance documents. A preliminary review of OECD test guidelines (OECD, 2009) has shown that most

[7] http://www.europarl.europa.eu/sides/getDoc.do?type=TA&reference=P7-TA-2014-0218&language=EN&ring=B7-2014-0185; visited on August 4, 2014.

[8] www.iso.org/iso/home/standards_development/list_of_iso_technical_committees.htm; visited on July 7, 2014.

[9] Available at www.oecd-ilibrary.org/content/package/chem_guide_pkg-en.

guidelines are suitable for nanomaterials but that, in some cases, modification will be needed for their applicability to manufactured nanomaterials. Currently, projects have started to develop new or adapt existing several OECD test guidelines and guidance documents, e.g. on inhalation toxicology and environmental endpoints. In addition, more general guidance has been developed, e.g. on sample preparation and dosimetry (OECD, 2012). Furthermore, other test guidelines have been identified that need adaption and/or development, but work on those has not yet started.

2.4 Legislation

In the EU the basic viewpoint is that nanomaterial related risks are in essence covered by the current legislative frameworks. However, some regulatory elements need some specific adaptation to include nanomaterials. Especially the adaptation of the REACH regulation is considered as vital as it provides the basic and essential data needed for risk assessment. The progress is however subject to a complex political process and proceeds slowly.

2.4.1 *Introduction*

In 2008 the European Commission (EC) published its first document on Regulatory Aspects of Nanomaterials (EC, 2008a). In this document the EC stated that

> *"Overall, it can be concluded that current legislation covers to a large extent risks in relation to nanomaterials and that risks can be dealt with under the current legislative framework. However, current legislation may have to be modified in the light of new information becoming available, for example as regards thresholds used in some legislation."*

In 2012 the Commission published the Second Regulatory Review on Nanomaterials as a follow-up of the 2008 document (EC, 2012b). In this document, the 2008 statement was repeated and necessary modifications were further substantiated, including the addition that adaptation of the REACH annexes is a prerequisite.

Since 2008 legislation on cosmetic products (EC, 2009e), food information for consumers (EU, 2011c) and biocides (EU, 2012) were adapted, partly to include a definition for nanomaterials (see section 2.1), but also to include specific requirements for nanomaterials. Such requirements vary from e.g. a labelling requirement (e.g. in the FIC-regulation; EU, 2011c) to a separate risk assessment for nanomaterials (EU, 2012).

Regarding environmental legislation, the EC underlines in its "Second Regulatory Review" (EC, 2012b) the importance of the REACH regulation (EC, 2006) in the risk assessment of nanomaterials and recognizes the need for adaptation thereof. In addition, the EC foresees adaptation of worker and medical devices legislations (EC, 2012b). Each of these will be addressed below.

Currently, a few types of legislation start to incorporate elements to ensure safe use of nanomaterials (see examples in Table 2.2). Apart from incorporation of a definition, which appears to be happening now (albeit slowly), many of these legislations rely on a separate assessment of nanomaterials. This raises the question what such an assessment should include. Furthermore, currently risk assessment of nanomaterials is severely hampered by a lack of data. Since the REACH Regulation is the main driver in generating data, adaptation of this legislation is of utmost importance to enable sufficiently sound risk assessments and ensure safe use of nanomaterials.

Table 2.2: State of the art of European regulatory frameworks that deal or potentially have to deal with nanomaterials.

Legislation	**Definition**[a]	**Label**[b]	**Specific provisions**	**Further discussion/development anticipated on**[c]**:**
Biocides[d]	Yes	Yes	Separate assessment	Guidance
PPP[e]	No	No	None	Guidance
Cosmetics[f]	Yesg	Yes	Separate assessment	Guidance[h]
Food				
Information to consumers[i]	Yesg	Yes	None	None
Contact materials[j]	Nok	No	Separate assessment	Guidancel
Novel foods/feeds[m]	Yesn	Yes	Separate assessment	Guidancel
Additives[o]	No	No	Separate assessment	Re-evaluation of authorised food additives; guidancel
Medicinal products	Nop	No	Noneq	Guidance
Medical devices[r]	Yes	Yes	Placed in highest risk class (class III)	Guidance
REACH[s]	No	No	None	Adaptation of legislation and guidance
CLP[t]	No	No	None	Adaptation of legislation and guidance
OHS[u]	No	No	None	Guidance and OEL[sv]

a. In case the specific legislation includes a definition of 'nanomaterial', this is indicated by 'Yes'.

b. In case the specific legislation (will) require(s) that the use of nanomaterials is indicated on the label, this is indicated by 'Yes'.

c. Issues to be considered in these discussions/developments are further elaborated on in section 6.1 and more detailed in Bleeker et al. (2012).

d. Biocides Regulation (Regulation (EU) No 528/2012; EU, 2012).

e. Plant protection products (Regulation (EC) No 1107/2009; EC, 2009d).

f. Cosmetics Regulation (EC No 1223/2009; EC, 2009e).

g. These definitions are currently under discussion, due to the publication of the Recommendation (see section 2.2)

h. The Scientific Committee on Consumer Safety (SCCS) has developed a guidance document (SCCS, 2012a).

i. Regulation (EU) No 1169/2011 (EU, 2011c).

j. Regulation (EC) No 10/2011 (EU, 2011b).

k. Nanoforms are mentioned but the term is not defined.

l. The European Food Safety Authority (EFSA) has adopted a guidance document clarifying the data to be provided when submitting an application dossier for a nanomaterial to be incorporated in food and feed (Antunović et al., 2011).

m. This refers to the new draft Regulation on novel foods.

n. No definition is included as such, but reference is made to the one in Regulation (EU) No 1169/2011.

o. Regulation (EC) No 1331/2008 (EC, 2008c) and related Regulations.

p. The legislation does not include a definition, but the European Medicines Agency does describe nanotechnology on its website as the use of tiny structures - less than 1,000 nanometres across - that are designed to have specific properties.

q. The Commission takes the view that current legislation on medicinal products allows an appropriate risk/benefit analysis and risk management of nanomaterials (EC, 2012b).

r. This refers to the Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (EC, 2012d). Negotiations on this proposal are not yet finalised.

s. Registration, Evaluation, Authorisation and Restriction of Chemicals (EC, 2006).

t. Classification, Labelling and Packaging (EC, 2008b).

u. Occupational Health and Safety (i.a. EEC, 1989; EC, 1998, 2004, 2006, 2008b). A final assessment on a review of occupational health and safety legislation will be made by 2014 (EC, 2012b).

v. Occupational Exposure Limits.

2.4.2 *REACH*

RIVM (Bleeker et al., 2013) recently discussed which elements in the REACH Regulation (EC, 2006) need to be adapted to enable a separate assessment of nanomaterials. Similar issues are likely to play a role in other legislations where hazard assessment of nanomaterials is required. The report concludes that the main challenges lie in a proper identification and characterisation of the (nano)material, because this enables finding correlations between physicochemical characteristics and potential hazards. Such correlations are essential to enable a hazard assessment that is based on a limited set of toxicological tests (and thus minimising the use of animal testing). Furthermore, it is highly unlikely that each individual nanomaterial (varying in size, shape, coating, etc.) can be tested individually.

As summarised by Bleeker et al. (2013), basic information on (nano)materials should include information related to the identification and characterisation of nanomaterials in various life cycle stages (particle size distribution; specific surface area), and thus on substance identity (characterisation; appearance/morphology; aggregation and agglomeration; spectral data; crystalline structure/atomic structure; surface reactivity; surface charge; catalytic properties).

For risk assessment purposes further information is necessary, including:

- Information on fate and (toxico)kinetics, including dissolution kinetics, dispersibility/dispersion stability, and dustiness, both in test systems and in humans and the environment;
- Ecotoxicological information, including sediment and terrestrial toxicity testing, as well as acute and particularly chronic testing;
- Toxicological information, including extra genotoxicity tests, a focus on the inhalation route, and adaptation of repeated dose testing regulations;
- Information on exposure, risk characterisation and risk management, including exposure and release information, identification and characterisation of nanomaterials in various life cycle stages, and nanospecific risk management measures.

As indicated above, the EC also points at the REACH Regulation to enable generation of data that may be useful in other legislations (e.g. Water Framework Directive (EC, 2000b) and other legislation in place to protect the environment).
For the REACH regulation, such further requirements for identification and risk assessment need to be incorporated in the legal text (i.e. in the Annexes). The topic in question is subject to complex political discussions that tend to slow down the desired progress. Generally for other legislations development of guidance documents appears sufficient (e.g. on biocides;EU, 2012).

2.4.3 *Worker legislation*

The framework directive for occupational safety and health (EEC, 1989) and the daughter Chemical Agents Directive (CAD; EC, 1998) set an obligation on employers to ensure safe use of chemicals as well as to establish rules for dealing with the risks in the workplace. Nanomaterials are not specifically mentioned in these directives, but implicitly included. In addition, REACH (EC, 2006) provides the legal instrument for generating the information needed on the hazards, exposure of workers and safety assessment for the majority of chemicals (including nanomaterials) and ensures communication through the supply chain. In this respect, adaptation of REACH will be beneficial to worker protection as well.

Nevertheless, RIVM concluded that adaptation of REACH will still leave gaps in legislation (Bleeker et al., 2013), most notably where substances (including nanomaterials) fall outside the scope of REACH. To improve knowledge on nanomaterials on the work floor, further adaptation of existing legislation therefore appears necessary, specifically the inclusion of a definition, but also requirements for additional information (e.g. in assessing the risk of plant protection products).

In worker legislation, CAD appears the most appropriate directive for adaptation to improve the safe use of nanomaterials. First, the inclusion of a definition is needed to enable a specific adaptation for nanomaterials of the obligation for a risk inventory and evaluation. Additionally, the introduction of a register of workers' exposure and health surveillance could be considered, although discussion on the pros

and cons of such a registry (at EU level) appears necessary. Finally, the development of nanospecific health-based occupational exposure limits (OELs) by companies or authorities will also contribute to worker protection.

Regarding a register of workers' exposure, the Dutch organisations of employers and employees recently joined forces in a pilot study regarding the pros and cons of exposure registration for working with synthetic nanomaterials. The pilot is co-financed by the Netherlands Ministry of Social Affairs and Employment and will run from April 2014 until the end of 2015.

2.4.4 *Medicinal products and medical devices*

The regulatory system for medicinal products is based on the provisions of Directive 2001/83/EC (EC, 2001a) that details the EU marketing authorisation system. This directive is supplemented with 13 Directives, 21 Commission Regulations and several legal reference documents. The current regulatory framework has no specific provisions for nanomaterials.

In its Second Regulatory Review (EC, 2012b), "the Commission takes the view that current legislation on medicinal products allows an appropriate risk/benefit analysis and risk management of nanomaterials."

Legislation on medicinal products requires careful risk assessment and risk management on a case-by-case basis before products can be brought to the market. Even though the specific risks of nanomedicine products are not as yet fully known, they are to be thoroughly evaluated in registration dossiers. The availability of alternatives and the clinical benefits of the products will also be taken into account in this process.

Also for medical devices, the current regulatory framework contains no specific provisions for nanomaterials. Here, however, the EC published a proposal for a Regulation of the European Parliament and of the Council on medical devices (September 2012; EC, 2012d). In this proposal the definition from the recommendation (EU, 2011a) is used, but without the option to lower the number size distribution threshold of 50 % in specific cases (see box in section 2.2). If needed, the Commission may adapt this definition by delegated act. The proposal indicates that nanomaterials should fall in the highest risk class (class III), and that the use of nanomaterials should be indicated on the label, "unless the nanomaterial is encapsulated or bound in such a manner that it cannot be released into the patient's or user's body when the device is used within its intended purpose" (EC, 2012d). Negotiations on this proposal are not yet finalised.

2.4.5 *Developments in legislation outside the EU*

In many countries outside the EU, chemical legislation is based on safety assessment of chemicals by a governmental body before a specific chemical can be placed on the market. This has consequences for the way nanomaterials are handled and consequently for the way the legislation needs to be adapted.

As examples of such an approach, developments in Australia, the US and Canada are briefly outlined below.

In Australia, NICNAS[10] uses a working definition for an industrial nanomaterial that is restricted to those materials that are produced for their properties at the nanoscale (1-100 nm)[11]. Nanomaterials are regulated as 'conventional' chemicals under the *Industrial Chemicals Notification and Assessment Act 1989*, which distinguishes 'new' and 'existing' chemicals, and nanomaterials are similarly divided over these groups. Currently, discussions are ongoing about options for reforming the chemicals regulation and the role of NICNAS[12].
Similarly, in Canada and the US adaptation of the legislation has been limited, as the existing legislation (Canadian New Substances Notification Regulations[13] and the Canadian Environmental Protection Act[14]; US Toxic Substances Control Act[15]) appears to be generally sufficient. Nevertheless, definitions for nanomaterials were drafted that incorporate a size range (1-100 nm) and "nanospecific properties" and it was recognized that standardised methods are necessary for the assessment of nanomaterials (Sinervo et al., 2008).

The US and Canada seek further cooperation in regulatory issues, including those related to nanomaterials (formalised in the Regulatory Cooperation Council[16]). While they recognise that each country has its own domestic legislation, cooperation is sought to ensure similar regulatory approaches to nanomaterials. These include a similar approach to distinguish nanomaterials that raise concern and those that do not raise concern. Furthermore, a uniform approach will be sought for a definition, characteristics and test methods in risk assessment of nanomaterials.

2.4.6 *Legislation in the Netherlands*

Currently, there is no specific legislation in the Netherlands regarding nanomaterials. In general, legislation on safe use of substances and products in the Netherlands is an implementation of EU legislation (e.g. REACH, CAD). Also for nanomaterials, the Dutch government aims at adaptation of EU legislation. To this end, the Netherlands are actively involved in discussions on this topic on the EU level. So far, two policy conferences were organised in The Hague, which resulted in concrete suggestions for adaptation of legislation and letters to the EC for taking action on adaptation of legislation.

In addition, the Netherlands initiated the NANoREG project[17]. This EU FP7 project aims to deliver the answers needed by regulators and

[10] NICNAS: National Industrial Chemicals Notification and Assessment Scheme. It falls under the Department of Health of the Australian Government (www.nicnas.gov.au).
[11] www.nicnas.gov.au/communications/issues/nanomaterials-nanotechnology/nicnas-working-definition-for-industrial-nanomaterial
[12] www.health.gov.au/internet/main/publishing.nsf/Content/ohp-nicnas-draft-regulation-impact-statement.htm
[13] www.ec.gc.ca/subsnouvelles-newsubs/default.asp?lang=En&n=FD117B60-1
[14] www.ec.gc.ca/lcpe-cepa
[15] www.epa.gov/lawsregs/laws/tsca.html
[16] www.actionplan.gc.ca/page/rcc-ccr/about-regulatory-cooperation-council
[17] www.nanoreg.eu

legislators on environmental, health and safety issues by linking them to a scientific evaluation of data and test methods.

3 Risk assessment and toxicology

3.1 Introduction

Developing Risk Assessment (RA) methodologies for nanoparticles is one of the essential strategies to support policy development and decision making. In essence the basic philosophy and methodology needed to perform an RA for nanoparticles is the same as for conventional non-nanomaterials. In such an assessment the exposure to a substance is compared to the level at which a toxic effect occurs. This ratio then provides insight into the question whether or not an effect (on health, or the environment) is to be expected at that level of exposure. Performing an actual risk assessment for a chemical substance is, however, much less straightforward then it seems. It makes use of a complicated methodology, and a highly specialized 'toolbox', including specific test guidelines, modeling tools and different approaches to handle uncertainty and lacking information within the available data set, which require in-depth knowledge to use.

For nanoparticles the basic RA philosophy still stands, but needs to be scrutinized in detail for its applicability at the operational level. That is, the instruments in the standard RA-toolbox for conventional chemicals are not by definition suited for nanoparticles. For example, the way specific, standard toxicity tests are being carried out for conventional chemicals is not always directly applicable to nanoparticles. Thus, the instruments in the toolbox need to be assessed for their validity for use on nanoparticles and if necessary adapted to make them suited[18]. This partial incompatibility of the RA-toolbox for nanoparticles is both fundamental and operational in nature. For conventional chemicals, the toxicological behavior is related to the number of molecules exposed to. For (non-soluble) nanoparticles however the toxicity is determined by the size (surface area) of the particle as well. On the operational level nanoparticles may just behave differently (e.g. due to their physical-chemical characteristics) from conventional chemicals or their larger "bulk" counterparts.

Currently a huge effort is undertaken – worldwide including at the EU and OECD level – to evolve the current knowledge base for nanoparticles. A range of subjects is being studied in detail e.g. toxicity mechanisms, physio-chemical behavior, and the distribution within the environment and human body (kinetics).

3.2 Risk assessment

In summary, in recent years considerable funding and effort has been invested in toxicological research of nanoparticles – resulting in important additions to the necessary empirical data, scientific insight in toxicological mechanisms, and an understanding of the knowledge gaps. However, much additional, coordinated work is still necessary to develop

[18] See OECD website: http://www.oecd.org/science/nanosafety/

more generalized methods and to prepare for the new generations of nanoparticles and – materials.

From a risk assessment perspective the first necessary big step forward has been taken: many essential knowledge gaps have been identified, both scientifically and from a regulatory-toxicology point of view. These 'need-to-know', fundamental pieces of knowledge are now - in a serious and considerable effort - being researched and data are generated in numerous projects[19] around the world, many of which have an European origin. Many of these projects aim to deliver between now (2014) and 2018. This means that further understanding of toxicological mechanisms, the development of the methods and tools and drafting of standards are well underway.

On the other hand, at this point in time (2014) the current scientific understanding and assessment methodology is not sufficiently developed to fully assess the current potential risks with regard to nanoparticles. This applies to both human as well as environmental risks. An individual, case-by-case assessment based on incomplete data and incomplete knowledge is still the only approach possible – keeping in mind that the knowledge base continually grows making these approaches more and more scientifically sound as time progresses.

Finally, the current research effort has another important yield. It provides the knowledge and insight that enables a more general, generic approach to assess the risks of nanomaterials. The knowledge currently developed supports and focuses on finding more generalized assessment methods like grouping, read-across and nanoparticle (Q)SARs. These are essential developments to be up to the task of assessing the continuously and rapidly growing amount of (more and more complex) nanomaterials.

3.2.1 *Recent developments*

As mentioned above, the chemical RA process in its simplest form requires two parameters to be determined: the (potential) amount of the substance exposure (exposure level) and the dose at which a toxic effect occurs (effect level). The several steps needed and nano-related questions are elaborated in *Figure 3.1*.

A number of fundamental questions still needs to be answered. A considerable research effort - worldwide but with an important emphasis in Europe –focuses directly or indirectly on these questions. Much scientific work is going on to elucidate a large number of aspects: among others the fundamentals of nano-particle toxicity and understanding the physical-chemical characteristics of nano-particles. In a recent report of the NanoReg project, a detailed gap-analysis with respect to regulatory toxicity testing is presented. *Table 3.1* summarises the findings of this gap analysis and some additional elements that were outside the scope of this gap analysis (e.g. exposure assessment).

[19] For an EU overview see e.g. http://www.nanosafetycluster.eu/www.nanosafetycluster.eu/home/european-nanosafety-cluster-compendium.html).

With respect to the definition and the uses and application (see *Table 3.1*) we note the following. How to define nanomaterials is still under discussion in the EU arena, but progress is being made albeit slowly. However, different EU Regulations make use of different definitions, i.e. there is no harmonization yet on EU-level. Similarly, on a global level different definitions of nanoparticles are being used.

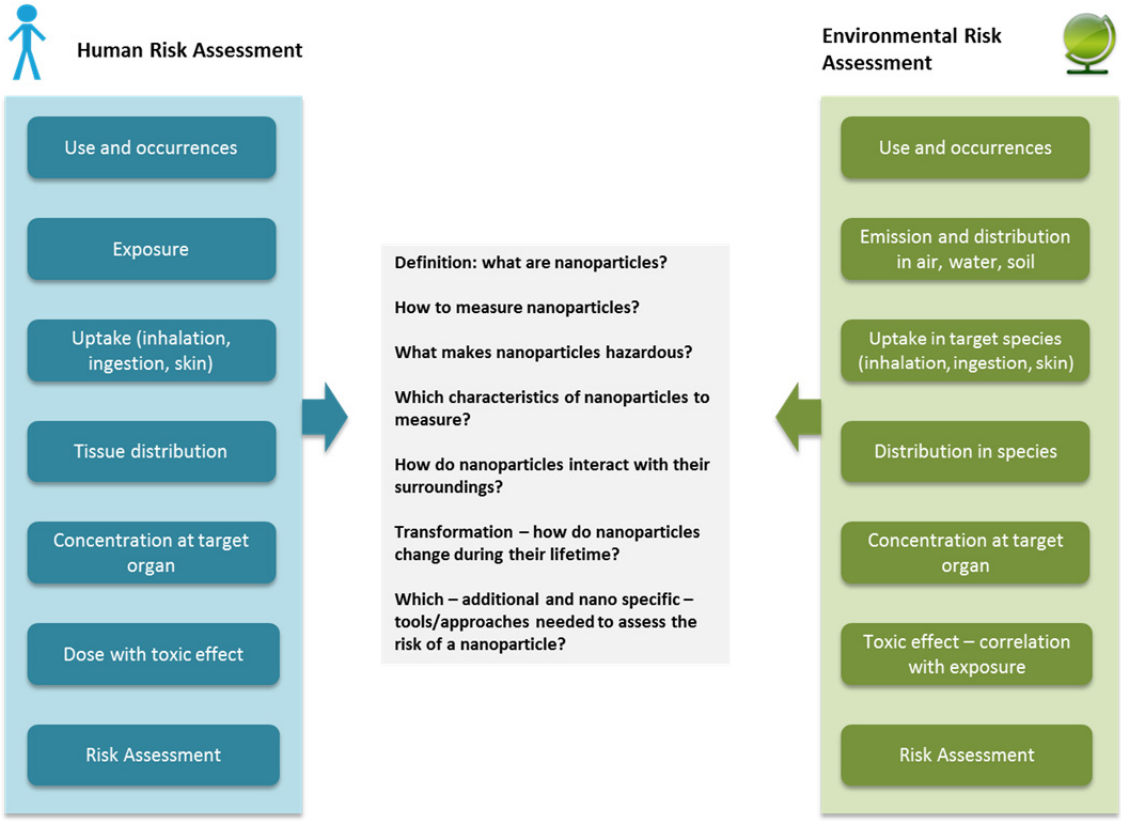

Figure 3.1 Elements of human and environmental risk assessment and the essential questions/knowledge gaps that currently are being filled.

It should also be recognized that a definition provides focus and defines the scope, but has only limited relevance for assessing toxicological effects. The information on use and application is limited, but crucial from the perspective of risk assessment. Discussions on databases and subsequent operationalization for e.g. consumer products are now ongoing on EU level. Similar discussions are presently carried out in many individual member states, including the actual operationalization (e.g. in France). The political process is however slow and improved insight in the market and products consequently proceeds at similar low pace.

With respect to the development of technical elements of the risk assessment methodology many projects are on-going to further research and generate the needed data, information, methods and tools. The expectation is that by the end of the decade (2020) the present risk assessment toolbox will be substantially adapted to cover nanomaterials (Savolainen et al., 2013).

Table 3.1 Overview of recent developments with respect to fundamental elements of risk assessment for nanoparticles

Risk Assessment element	Description	Current situation	Important developments[1]
Use and applications	▪ Use and application of nanoparticle containing materials	▪ Strong indications of increased number of applications ▪ Sketchy insight in type of nanomaterials applied in products ▪ Very limited knowledge of number of products, market share and extent of market penetration of nanoproducts, etc.	▪ EU and national policy discussions on the need for a product database ▪ EU legislation for specific product types requiring labelling (food, cosmetics, biocides)
Other sources	▪ Processes in which nanoparticles are formed leading to environmental emissions and worker exposure	▪ Relative importance has experimentally been shown in occupational health situation ▪ Experimentally shown in e.g. (waste) incineration processes ▪ Transformation dynamics is a topic of research	▪ Process generated nanoparticles identified by the Dutch social economic council as subject for further study (OSH perspective).
Nanoparticle definition	▪ Definition of nanomaterials including nanoparticles. Is essential from a regulatory, legal and scoping point of view	▪ The EU provided a recommendation on the definition; ▪ Three EU Regulations make explicit reference to nanoparticles (see Chapter 2); ▪ ISO provides a technical and scientific definition for nanoparticles which contains similar elements.	▪ The definition of nanoparticle in the food labelling regulation and in the cosmetics regulation are currently under revision.
Identification of nano-specific properties and risks	▪ Nanoparticles give rise to specific risks as a result of the nano-sized nature of the particle. The characteristics and properties of the nanoparticles that determine the release, exposure, behaviour and toxicological effects in the environment, environmental species and humans need to be established.	▪ A basic understanding of the most important properties and mechanisms has been established. ▪ The relative importance of these properties and mechanisms is not clear and therefore predictive modelling is not feasible yet. ▪ Knowledge gaps have largely been identified ▪ Roadmaps and ensuing projects are drafted/being developed and executed	▪ A number of EU-based/funded projects is currently in execution which (partly) address these questions. ▪ *MARINA, NanoReg, ITS NANO, MODERN, MODENTOX, NANOTRANS_KINETICS, NANOPUZZLES* ▪ *NanoMILE, SUN,GUIDEnano*
Methods and techniques on how to characterize and measure nanoparticles	▪ Methods on how to characterize specific nano properties need to be established ▪ Methods and techniques on how to characterize and measure exposure to nanoparticles need to be developed ▪ Methods and techniques need to be harmonized and	▪ A multitude of methods but with a limited scope of application for a number of nano-particle characteristics and a number of matrices is presently available.	▪ A number of EU-based/funded projects is currently in execution which (partly) address these questions. ▪ *NANoReg, NANOVALID, MARINA, NANODEVICE, NANODETECTOR, NANOPOLYTOX, INSTANT, NANOLYSE, NANOSTAIR, SMART-NANO*

Risk Assessment element	Description	Current situation	Important developments[1]
	standardized to enable unambiguous use in a regulatory context		▪ The OECD facilitates and coordinates international harmonization.
Knowledge of transformation processes	▪ Interactions with the surroundings and external processes result in the creation, transformation or destruction of nanoparticles. ▪ E.g. nanoparticles may be released from a matrix, or disappear by a process of dissolution.	▪ Currently limited knowledge of the transformation processes and its underlying mechanisms is available. ▪ There is a limited availability of standardized methods for determining the characteristics of these processes.	▪ A number of EU-based/funded projects is currently in execution which (partly) address these questions. ▪ *NANoReg, NANOVALID, NANOFATE, NANOPOLYTON, NANOSUSTAIN, OECD WPMN (other FP 7 projects)*
Dose metrics	▪ Which measure of the dose gives the best correlation between exposure to a nanoparticle and the observed toxicological effect.	▪ There is a reasonably well developed insight into which properties are possible candidates for determining the dose metrics. However, the most appropriate metrics for each type of nanomaterial within each specific route of exposure and each toxicological endpoint is not known.	A number of EU-based/funded project s are currently in execution which (partly) address these questions. ▪ *NANoReg (Dose metrics)*
Standardized methods for toxicity testing	▪ Standardized methods for sample preparation ▪ Standardized methods for characterization toxicity studies	▪ Standard methods for sample preparation available for several situations ▪ Standard methods for characterisation available for some properties and matrices	▪ NANOVALID, NANoREG, Other FP 7 projects (Standards sample prep.) ▪ NANoREG, NANOVALID, MARINA, NANODEVICE, NANOPOLYTOX, INSTANT, NANOLYSE (standard methods for characterisation)
Fate and distribution	What are the mechanisms and characteristics that determine how a nanoparticle is distributed in organisms and the environment	▪ Developed understanding of the properties and mechanisms that are important for understanding kinetics and accumulation ▪ Knowledge is increasing (e.g. some metal nanoparticles tend to accumulate and persist)	A number of EU-based/funded projects is currently in execution which (partly) address these questions. NANOMILE, NANOTRANSKINETICS, NANoREG, MODNATOX, MembranceNanoPart, NANOGENOTOX, Other FP 7 projects
Development of predictive methods	Developing models, methods and approaches to extrapolate and predict nanoparticle behaviour and toxicity	▪ Limited understanding of the basic underlying mechanisms	A number of EU-based/funded projects is currently in execution which (partly) address these questions. NANoREG, OECD, MARINA, MODERN, NANOTRANSKINETICS, MODNANOTOX.

3.3 Substance specific Risk Assessments

In summary, only a limited amount of risk assessments for nanoparticles is available, and only for the relatively 'common' nanoparticles.

The actual number of substance specific risk assessments for nanoparticles that were performed is very limited. This is a consequence of both the lack of data on (the behavior of) the specific nanoparticle and the current lack of scientific understanding and lack and harmonized methods and tools. Table 3.2 provides an overview of a number of authoritative EU risk assessments (i.e. risk assessments of sufficient rigor by recognized specialists) – those already performed and those foreseen.

Table 3.2: Overview of substance specific risk assessments in the EU

Nanoparticle	**Scope of RA**	**Performed by**	**General Result/remarks**
ZnO	Use as UV filter in sunscreens	SCCS	Considered safe for use when inhalation exposure is excluded*
TiO_2	Use as UV-filter in sunscreens	SCCS	Considered safe for use when inhalation exposure is excluded*
ETH-50	Use as UV-filter in sunscreens	SCCS	Considered safe for use when inhalation exposure is excluded*
MBBT	Use as UV-filter in Sunscreens	SCCS	No opinion – insufficient data**
Carbon Black	Use as a colorant in cosmetics	SCCS	Considered safe for use when inhalation exposure is excluded*
Ag	Nanosilver: safety, health and environmental effects and role in antimicrobial resistance	SCENIHR	Additional effects of wide-spread use cannot be ruled out (human and environment)
Foreseen RA			
SiO_2 (different nano forms)	Use in leave-on and rinse-off cosmetics products	SCCS	Mandate for opinion; Opinion to be expected in end of 2014 early 2015
Food additives	Food applications	EFSA	Re-evaluation of food additives, specifically on nano forms (2020).
SiO_2	Substance	Substance	Substance evaluation

Nanoparticle	Scope of RA	Performed by	General Result/remarks
(several nano forms)	characterization / nanoparticles, toxicity of different forms of the substance	evaluation in REACH	focuses a.o. on nano forms of the material (2014)
Ag	Nanoparticles/ Ecotoxicity of different forms of the substance; Environmental fate	Substance evaluation in REACH	Substance evaluation focuses a.o. on nano forms of the material (2014)
TiO_2	Nanoparticles/ Ecotoxicity of different forms of the substance; Environmental fate	Substance evaluation in REACH	Substance evaluation focuses a.o. on nano forms of the material (2014)

*The opinions of the SCCS are valid only for the specific ingredient definition and specific conditions of use discussed in the individual opinions of the SCCS.

**No appropriate data on genotoxicity of nano form of MBBT were provided, therefore no conclusion on the safety of this substance was drawn. However regarding systemic effects there seems no concern for the dermal application of nano-sized MBBT

The conclusions arrived at by the SCCS is essentially based on the assessment that no or very limited uptake of nano-particles takes place through the intact skin. The SCCS specifically adds in their opinions that reassessment is necessary in case the nano-particle is coated or adsorption enhancers are present in the cosmetics formulation.

The SCENIHR provided a comprehensive overview of the current state of affairs regarding nano-silver (SCENIHR, 2014a). Much of the present scientific information on silver is actually on the ionic form of silver and not so much on the nano-particle form. Human and environmental effects now seem to be linked predominantly to silver ions, but also for the silver case there is a lack of data for the nanoparticle form to make a solid assessment. Nano-silver will now (2014) be evaluated under the REACH substance evaluation process, opening up the possibility to obtain more data from industry to enable a more complete assessment.

Synthetic amorphous silicates (SAS) are widely used in foodstuff and many other applications. The toxicological behaviour combined with the widespread use has resulted in reasons for concern. The substance is under scrutiny of the SCCS as well as under the REACH substance evaluation.

From an occupational health point of view risk assessment itself belongs to the realm of the employer. Some proposals have been made for exposure limits (e.g. for CNT, fullerenes, silver and TiO_2) (Broekhuizen et al., 2012), but the lack of data hampers the derivation of an health-based limit value. Other pragmatic tools to facilitate the risk assessment process e.g. based on fundamental aspects of particle and fiber behavior have been developed (see chapter on Occupational health).

Initial environmental risk assessment for metallic particles[20] indicatively shows for nano zinc particles that effect levels and exposure levels are relatively far apart that for as yet no risk for EU waters is anticipated. A similar indicative approach for nano silver does not exclude the occurrence of adverse effects on the environment.

3.4 Hazard

In summary, nano-toxicology is an emerging science which essentially has to incorporate – besides the chemical identity – aspects as size and shape to enable a more complete understanding of toxicological behavior of nanoparticles. This process is further complicated by (possible) complex dynamic behavior of the particle depending on its specific surroundings. Reviews show that specific hazards have been identified for both human and environmental exposure.

Nanotoxicology
The field of nanotoxicology is rapidly developing and is by now recognized as an important specialism. The history dates back to the risks associated with ultrafine particles in air pollution. Several recent publications provide an overview of the state of affairs and the scientific challenges faced (Aitken et al., 2009; Oberdörster, 2009; SCENIHR, 2009; Maynard et al., 2011; Johnston et al., 2013).

Essentially, nanotoxicology focuses on the possible adverse effects induced by non-soluble particulates in the nanometre size range on biological systems. This field of research revolves around the notion that not only the chemical composition is essential for a description of its toxicological behaviour, but also its size and its shape. By now it seems well established that non-soluble particulate matter in the smaller size ranges fundamentally differs in characteristics and properties from particles in the micrometre range or larger (Oberdörster, 2009; Maynard et al., 2011) but also differs in characteristics from its molecular constituents.

Additionally, it is not possible to identify a common threshold at which specific nanoscale characteristics become apparent. Auffan and co-workers (Auffan et al., 2009) indicated that for a subgroup of nanomaterials (inorganic nanoparticles) that the change in characteristics occurs at approximately 30 nm. For other nanomaterials quite different sizes are observed (SCENIHR, 2010). The specific threshold value can vary between several nanometres up to a few hundred nanometres, and sometimes no real threshold value can be

[20] www.nanofate.eu

determined, e.g. when a certain parameter changes on a continuous scale (SCENIHR, 2010; Hassinger and Sellers, 2012). Where a threshold can be identified, it often not only depends on the material itself, but also on the toxicological endpoint (Hassinger and Sellers, 2012).

The possible interaction with biological systems needs to be described and understood in terms of these new, nanoparticle characteristics. Thus, to understand and describe nano-toxicology, 'size' and 'shape' need to be incorporated as a points of reference into the methodology, description and toolbox. Considering that 'regular' toxicology takes only chemical composition of a substance as point of reference, the science behind nanotoxicology is considerably more complex.

This intrinsic complexity is illustrated by two important general observations. First of all there is a virtually limitless variety in composition, shape, size, surface property, solubility etc. Developing science and insight within this myriad of possibilities takes time and above all needs an empirical basis. Secondly, dynamic interactions with its surroundings affect the particle (surface) composition, its characteristics and its behaviour. For example, nanoparticles can agglomerate or form aggregates – thus forming new particulate entities with their own set of characteristics. Also, in e.g. biological fluids, biomolecules (e.g. proteins and lipids) can adsorb to the particle surface – effectively forming a new surface on the particle, which can have a profound influence on the interactions of that particle with its environment.

All in all, nanotoxicology is a fairly new field of expertise and although scientific progress is made at a steady pace, many fundamental questions remain as yet unanswered and are subject of continuing research. Much of the current work focuses on the scientific understanding of the observed interactions between nanoparticles and biological systems, which hopefully will provide the scientific basis for more comprehensive and generalized approaches.

As a consequence only a fairly limited number of particles have been subjected to detailed nanotoxicological investigations. The current focus is mainly on particles with a high exposure potential (high production volume and/or widespread use) and particles for which existing evidence of adverse effects exists. Based on these criteria the Organisation for Economic Co-operation and Development (OECD, 2010) identified a list of "representative NMs" whose safety should be assessed with highest priority, and the toxicity of these materials has been under investigation. The first results of this research programme start to become available. Currently these are mainly limited to physicochemical properties (e.g. (Singh et al., 2011; Rasmussen et al., 2013; Rasmussen et al., 2014; Singh et al., 2014), although some of the toxicological data are already available in the peer-reviewed literature (e.g. (Pietroiusti et al., 2011; Kim et al., 2013)).

It is important to recognize that many of the substances that are the focus of current nanotoxicological studies are relatively 'simple' materials. More and more complex and sophisticated nanomaterials are being developed at this moment. New generations of nanomaterials

which exhibit specifically designed bio-interactions of have a self-assembling nature.

Toxicological findings

The SCENIHR provided an important overview of the main toxicological findings in 2009, and showed that there are several reasons for concern.

- The highest risk, and thus concern, is considered to be associated with the presence or occurrence of *free* (non-bound) insoluble nanoparticles either in a (liquid) dispersion or airborne dusts.
- Inhalation of nanoparticles results an inflammatory response, that in turn can result in a range of responses including allergy and genotoxicity.
- For certain specific carbon nanotubes similar inflammatory responses as asbestos fibers were observed. SCENIHR concludes that for such specific nanomaterials a chronic inflammation might induce serious effects like mesothelioma.
- Nanoparticles can enter the blood circulation after inhalation or ingestion, but only in limited amounts (typically less than 1% (on a mass basis) from the respiratory tract or the gastro-intestinal tract). However, although minimal in percentage this may result in a systemic availability of a considerable number of nanoparticles. In addition, potential accumulation of persistent nanomaterials may occur after such low uptake.
- When the nanoparticles reach the blood circulation, the liver and the spleen are the two major organs for distribution. Circulation time increases drastically when the nanoparticles are hydrophilic and their surface is positively charged (e.g. after coatng with poly-ethylene-glycol, PEG).
- Recent findings (Geraets et al., 2014; van Kesteren et al., 2014; van der Zande et al., 2014) for silica and TiO_2 nanoparticles show that after oral exposure accumulation of these particles occurs in the liver and spleen.
- Analogous to the effects of exposure to air pollution, there are some suspicions of cardio vascular effects, but further evidence is needed.
- The fundamental mechanisms that drive genotoxic effects for non-nano particulate matter are observed for nanoparticles as well. Additionally the presences of nanoparticles in sub-cellar compartments opens up other routes and mechanisms for possible genotoxic effects.

Environment

- Ecotoxicological effects on environmental species have been demonstrated; aquatic species have been most studied;
- The common endpoints and descriptors used in ecotoxicology such as mortality, growth, feeding, and reproduction can also be used for the evaluation of ecotoxicity by nanomaterials;
- Some biomarkers similar to those used in the assessment of mammalian;
- toxicity, such as oxidative stress, genetic damage and gene expression, may provide some insight in toxic mechanisms of nanomaterials.

4 Nanomaterials in consumer products

4.1 Introduction

Nanomaterials in consumer products is the subject of increasing attention. The application range of nanotechnology is extremely wide. In this section, we focus on products to which nanomaterials are added. Nanomaterials in a product can give it added value, such as improved functionality. The product becomes stronger, lighter, has better resistance to ultraviolet (UV) rays, or is a more effective antibacterial agent. At the same time, these interesting and new features raise the issue of whether the use of nanomaterials entails new risks.

The extent to which use of these nanomaterials present a new risk to humans and the environment has not yet been properly determined. Various stakeholders have a growing need for an overview of the application of nanomaterials in consumer products. Such an overview does not currently exist. Inventories of non-food consumer products claiming to contain nanomaterials show that the number of products has grown over the last years (Figure 4.1.) These claims made for products have not been verified, and legal requirements covering cosmetics and biocides were introduced only very recently in the European Union. In this situation, estimating the risks for consumers when using products containing nanomaterials is extremely difficult.

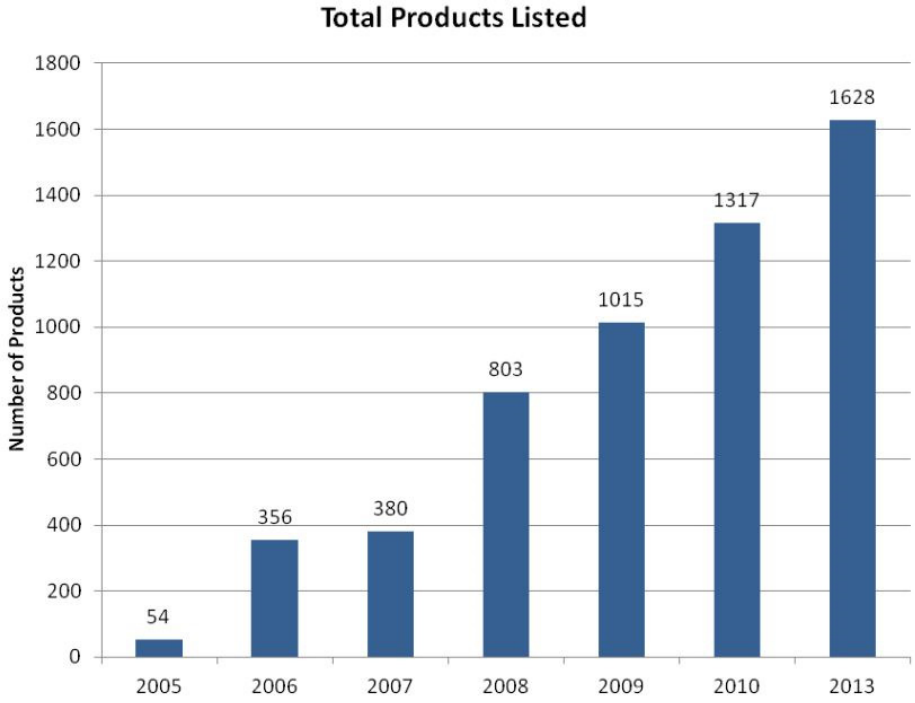

Figure 4.1 Increase in consumer products with a claim containing nanomaterials (Woodrow-Wilson, 2013). Number of products is defined as individual products available on the market.

4.2 Sources and exposure

4.2.1 *Sources*

In summary, nanomaterials are applied in a wide variety of consumer products e.g. personal care products, cosmetics and textiles. Nanoclaims on product labels or websites are difficult to interpret as they do not always reflect the actual presence of nanomaterials. To obtain a better insight into the use of nanomaterials in consumer products approaches such as measurements, verified product labeling or validated inventories on nanomaterials are essential. The current uncertainty about the use of nanomaterials hampers the process of risk assessment for consumer products. The recent obligatory labelling for nanomaterials in cosmetic products and biocides in the EU is an important step forward and may serve as a test case for nanomaterial related product information in consumer products.

Nanomaterials are increasingly applied in a wide variety of consumer products to add to or change the functionality of the product, e.g. increased anti-bacterial activity (in textiles and cosmetics), increased strength of the material (of tennis rackets or bikes), white pigment (in paints), increased UV filter function (in sunscreens, creams and paints) and anti-caking agent (in cosmetics and food).

Figure 4.2 Examples of consumer product categories potentially containing nanomaterials: sunscreen, personal care products and cosmetics, vehicles, sport goods and household products.

Consumer products categories potentially containing nanomaterials are "Appliances, Electronics and computers, Home furnishing and household products, Motor vehicles, Packages, Personal care products and cosmetics, Health, Sporting goods, Textiles, Toys and games, Cross-cutting and Miscellaneous" (Figure 4.2; (VWA, 2010; Wijnhoven et al., 2010; Woodrow-Wilson, 2013). Important product categories containing nanomaterials are personal care products, cosmetics and textiles (*Figure 4.3*; (Woodrow-Wilson, 2013)

Inventories of consumer products containing nanomaterials are available, but these overviews are mainly based on claims of manufacturers. No other, more reliable product databases are available at this moment. Product registration is only obligatory in France at this moment, and will be in Belgium and Denmark in the near future. The first evaluation of the French system (after one year) has revealed a

couple of difficulties with respect to the detail of information provided. The Cosmetics Regulation, which has a notification obligation for nanomaterials, has only recently been adapted (July 2013) within the EU. This operational period is too short for further analyses. Because there is still a lack of a reliable overview of the actual presence and application of nanomaterials in consumer products in general, more detailed information from the producer as well as additional measurements and characterization of nanomaterials in consumer products are essential to get a better and more complete picture.

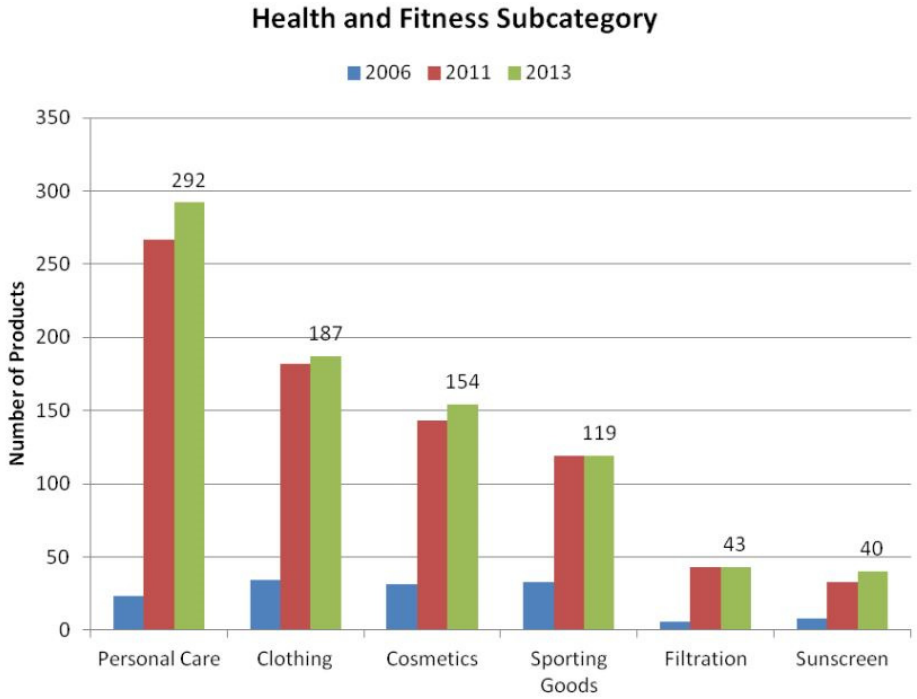

Figure 4.3 Important consumer product categories containing nanomaterials. Number of products is defined as individual products available on the market (Woodrow-Wilson, 2013).

4.2.2 *Measurements*

In summary, since concentrations of nanomaterials in consumer products are seldom disclosed by the manufacturer, experimental determination of nanomaterials in the product is essential, and having suitable analysis methods is therefore vital. Various measurement and analysis methods are available for the characterization of nanomaterials, dependent on the nanomaterial and the matrix in which the nanomaterials is present (solid, cream/ emulsion, gas, surface). Generally speaking the available analysis methods are expensive and need further development and validation. In addition, measurements in consumer products don't distinguish between engineerd nanomaterials and natural nanomaterials.

In recent years, an increasing number of measurements have been performed on nanomaterials in different consumer products (Benn et al., 2010; Chen B.T et al., 2010; Lorenz C et al., 2010; Lorenz et al., 2010; Nazarenko et al., 2011; Oomen et al., 2011; Peters, 2011a, b; Quadros

and Marr, 2011; Lorenz et al., 2012; Mihranyan A et al., 2012; von Götz et al., 2013). Various analysis methods are available, for nanomaterials present in solid, liquid and aerosol phase. Electron microscopy (EM) is a method that is frequently used; this is mainly suitable for nanomaterials in solid and liquid matrices (not for aerosols). However, EM is not quantitative, but only gives an impression on the shape and size of the nanomaterial. Nano tracking analysis (NTA), Field Flow Fractionation (FFF) en Single Particle ICPMS (SP-ICPMS) are more suitable for measurements in creams and liquids. Analysis of nanomaterials in spray applications are very relevant since an increasing number of consumer products are available in spray form. However, measurement of these aerosols is complex because spraying generates aerosols containing nanomaterias, which have to be separated during analysis. Advanced techniques to analyse nanomaterials in consumer products are expensive also because for a detailed analysis, a combination of techniques is needed.

4.2.3 *Frequently applied nanomaterials in consumer products*
In summary, nanomaterials mostly frequently used – or at least considered as such – in consumer products are silver, titanium oxide, zinc oxide, silica and carbon black. Also carbon nanotubes (CNT) are used to generate stronger sporting goods like tennis rackets, bikes etc. These materials are by now relatively widely investigated, because a) of their widespread use, b) the relatively developed insight in use and behavior, and c) they are relatively easy to detect (metals). However, these materials are not necessarily the most important in consumer products or cause potential risk.

Table 4.1 Frequently applied nanomaterials in consumer products

Nanomaterial	**Type of application**	**Function**
Ag	Disinfecting sprays, textiles, cosmetics, food packaging, household products, paint	Antibacterial activity
TiO_2	Sunscreens, textiles, paint, paper, plastics	White pigment, UV-filter, antibacterial activity, antifouling water purification
ZnO	Sunscreens	White pigment, UV-filter
SiO_2	Cosmetics	Anti-caking agent
Carbon black	Cosmetics, tires	Colorant, UV absorber, reinforcing agent, filler
CNT	Sporting goods Shielding	Strength Electric conductivity

Ag: Nanosilver is applied in a large variety of consumer products because of its antibacterial activity (see Table 4.1 Frequently applied nanomaterials in consumer products). Also in products specifically

developed for children, like toys and textiles, nano-Ag is potentially present (Quadros M.E. et al., 2013). The amount of released nano-Ag from consumer products appears to be relatively small, resulting in a minor exposure to silver due to dissolotion of nano-Ag when compared to the total silver exposure. However, the widespread and increasing use of nano-Ag in consumer products leads to concern because of potential aggregated exposure after using several different products. In addition, there is a potential risk of bacterial resistance, but it is currently not possible to estimate whether or not the use of nano-Ag increases antimicrobial resistance (SCENIHR, 2014a).

TiO_2: Titanium dioxide is used on a large scale as white pigment in paint, paper, plastic, cosmetics and food (additive E171). A major application of the transparent nano-TiO_2 is in sunscreens. Compared to microsized TiO_2, nano-TiO_2 has a higher sun protection factor and is transparent when applied. Because of its UV absorbing properties, TiO_2 is also applied to textiles, as a pigment, as an anti-bacterial agent and as way of reducing shine. The amount of nano-TiO_2 washed out of textile depends on how a textile product is manufactured and processed. For example, an antibacterial surface coating results in the release of more TiO_2 than when the particles are worked into the fibres. For each wash, a small number of nanoparticles are released into the environment. The total release is one factor that determines the final impact on the environment.

Silica: Synthetic Amorphous Silica (SAS) is added as an anti-caking to several types of food (*see chapter 5*). Apart from food, nanosilica is also found in consumer products such as cosmetics. The SCCS recently received a mandate from the European Commission (EC) to draft an opinion on nanosilica in cosmetics which is expected at the end of 2014. A substance evaluation of nanosilica is currently performed.

Other: Also commonly used nanomaterials in consumer products are ZnO as UV filter in sunscreens and carbon black as colouring agent in cosmetics and tattoos. Carbon black (f.e. printing ink) and carbon nanotubes also have a wide range of applications.

4.2.4 *Relevant exposure routes for consumers*

In summary, consumers can come into contact with nanomaterials in consumer products via all known exposure routes. The greatest concern at the moment is about the effects following inhalation exposure to nanoparticles, such as from increasing use of spray products and powders. Less concern exists in the case of dermal application because of the apparent lack of penetration of nanoparticles through the skin. To assess the exposure, it is important to distinguish between the presence of NM in consumer products and the release of NM from these products. Realistic user scenarios are key tools in this context.

The general opinion regarding the intake of nanomaterials through the intact skin is that it is minor (Wijnhoven, 2012). However, there are clear indications of inhalation deposition of nanoparticles from exposure to spray products and cosmetic powders. In contrast to the primary nanoparticles, nanoparticles in powder products can form larger deposits

in more upper parts of the lungs due to their increase in size. Next to inhalation exposure, sniffing and swallowing (secondary ingestion) result in oral exposure, which is a significant factor in assessing the ultimate risk.

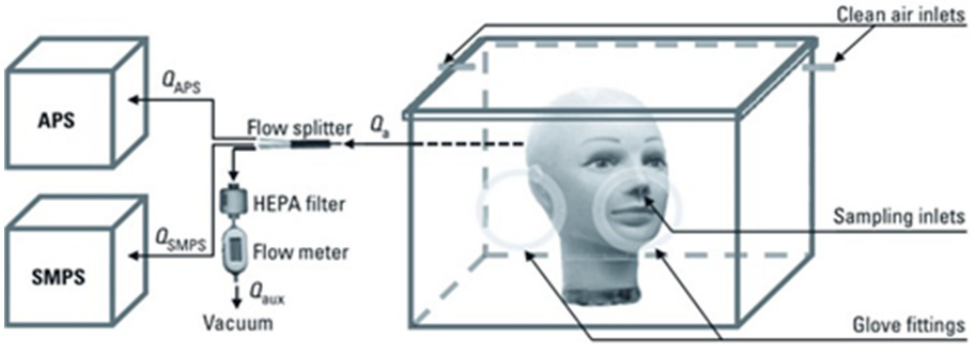

Figure 4.4 Experimental setup for simulated cosmetic powder application and measurement of the resulting aerosol (Nazarenko Y et al., 2012).

To form a reliable assessment of exposure after inhalation exposure, it is important to test the particles in a realistic user scenario (see for an example Figure 4.4 Experimental setup for simulated cosmetic powder application and measurement of the resulting aerosol). Nanomaterials released from a product may differ from the material originally used in a product.

4.3 Risk assessment

4.3.1 *SCCS[21] opinions of nanomaterials in cosmetics*

In summary, the SCCS (Scientific Committee on Consumer Safety) published opinions on a number of nano UV filters in cosmetics (1,3,5-Triazine, 2,4,6-tris[1,1'-biphenyl]-4-yl (ETH50), TiO_2, ZnO and 2,2'-Methylene-bis-(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol) (MBBT)) and an opinion on carbon black (nano form). The opinion on particles assessed thus far is primarily based on the apparent lack of penetration of nanomaterials by the skin. Dermal applications of products containing these particles are therefore considered safe. Determining the safety after inhalation exposure is less straightforward, as too little is known about the toxicity following inhalation of nanomaterials.

The Scientific Committee on Consumer Safety of the European Commission (SCCS) recently drew up opinions on five nanomaterials in cosmetics, specifically, the UV filters ETH50, ZnO, TiO_2, and MBBT (SCCS, 2012b, 2014a, c, d, e). The conclusions expressed in the opinions are based on study results provided by manufacturers. There is

[21] SCCS and SCENIHR are independent Scientific Committees advising the European Commission on issues regarding Cosmetics (SCCS) and Emerging and Newly Identified Health Risks (SCENIHR)

an apparent lack of penetration of nanomaterials through the skin. The conclusion is that dermal application of these ingredients in accordance with the assessment conditions set by the SCCS will present no greater risks than their application in non-nano form. It is therefore considered safe to keep or launch these UV filters in cream form on the market.

It is currently not possible to effectively assess the risk from exposure to nanomaterials via cosmetic spray applications, owing to insufficient suitable toxicity data on inhalation exposure. Accordingly, spray products containing these materials are not yet permitted. This can have major consequences for the industry, as an increasing number of sunscreens in spray form are appearing on the market. The data requirements for assessing an ingredient in nano form are described in a separate document (SCCS, 2014b) with the aim of simplifying assessments in the future. Moreover, according to the SCCS, the opinions must not be seen as blueprints for all subsequent assessments. Better test methods and test data might become available later, making it necessary to modify the current opinions.

Recently, the SCCS also received the mandate to write an opinion on nanosilica in cosmetics. This substance is one of the most commonly produced nanomaterials and is used in a very wide range of cosmetic products. Silica is the subject of interest in other legal frameworks as well. Within the REACH framework, the Netherlands began the substance evaluation of synthetic amorphous silica in 2012. The process is still ongoing, with a definitive decision planned for 2014.

4.3.2 *SCENIHR[22] opinion nano-Ag*

In summary, a SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks) study group for nano-Ag recently published an opinion containing an assessment of the material, including its use in consumer products. The opinion shows that even for a data-rich nanomaterial such as nano-Ag, it is difficult to estimate the risks for humans and the environment.

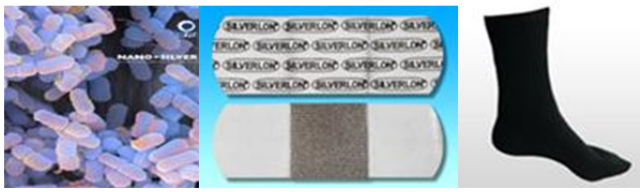

Figure 4.5 Nano-silver in yarns

The increase in the use of nanosilver in consumer products has led to concern. For that reason, the European Commission asked SCENIHR (Scientific Committee on Newly Identified Health Risks) to write an opinion on the risk of using nano-Ag, based on all the available data. SCENIHR provides evidence that exposure to nano-Ag can produce chronic health effects such as argyria (bluish-grey colouring of the skin).

[22] SCCS and SCENIHR are independent Scientific Committees advising the European Commission on issues regarding Cosmetics (SCCS) and Newly Identified Health Risks (SCENIHR)

Current human risk assessments are mainly based on the development of argyria. No specific exposure limits have been calculated for nano-Ag. The probability of bacterial resistance to the antimicrobial action of nano-Ag is also increasing, since the material is used in an ever-greater number of products. Despite the availability of considerable data, SCENIHR cannot make a firm statement on the risk that nanosilver poses to humans and the environment. SCENIHR concludes that additional long-term effects cannot be ruled out, and that there are too few data on the effect of nano-Ag on bacterial resistance mechanisms.

The probability of bacterial resistance and the limited need for the use of nanosilver in consumer products led Germany's Federal Institute for Risk Assessment (BfR) in June 2010 to recommend non-application of the material in such products for the time being so as to reduce the probability of resistance to nanosilver in medical products. Views are mixed in various countries on how to deal with uncertainty of this nature. A recommendation similar to the above has not been issued in the Netherlands.

Apart from the assessments from the scientific committees, the process of substance evaluation under REACH also covers nano-forms of substances. Substance evaluations may include a risk assessment of the use of a substance throughout the entire life cycle and consideration of all possible uses but may also focus on specific uses or hazards and thus a tighter focus. The National Institute for Public Health and the Environment (RIVM) is currently evaluating nanosilica and nano-Ag on behalf of the Dutch Competent Authority of REACH, whereas ECHA is responsible for the outcome.

4.4 Risk management/ risk communication/ consumer perception

In summary, there is currently no general legal obligation to register consumer products that contain nanomaterials (with the exception of cosmetics) or a separate registration under REACH. A lack of market insight causes difficulties for efficient risk management and risk communication. Consumer perception on the risk of the use of nanomaterials is low, with the average consumer feeling little involvement in the subject. Communication about nanomaterials is extremely important for maintaining the general population's trust in nanotechnology and for demonstrating that nanomaterials have benefits as well as drawbacks. In the future, it is important to engage the general population in the debate on nanotechnology.

Cosmetic products and biocides aside, the EU does not have a general legal obligation for registering the presence of nanomaterials in consumer products. A lack of insight into prevention and spreading makes both risk management and communication about risk difficult. An initial step was recently taken with the inclusion in the new EU Cosmetic Regulation (EC, 2009e) of a notification requirement for products containing nanomaterials. In addition, the product label must state which ingredients are present in nano form, so that consumers have freedom of choice. The EU's recently introduced Biocidal Product

Regulation (EU, 2012) also includes a labelling requirement for nanomaterials.

In general, consumers still feel hardly involved in the subject of nanomaterials and nanotechnology. Openness towards the general public seems vital for building and maintaining trust in nanoapplications, as well as for creating an understanding of the benefits and drawbacks of the technology. Clear information about available products containing nanomaterials supports the process (The Rathenau Instituut, the Netherlands www.rathenau.nl). The importance of this is underscored by research conducted by BASF in Germany. From the research, it appears that effective transfer of information from manufacturer to consumer takes place on three levels: (1) general information available on nanomaterials and nanotechnology, (2) intelligible information about specific products, and (3) supplementary information and links for consumers with greater interest in the subject. Expansion of this study to the EU scale is desirable.

The Rathenau Instituut stresses the importance of having the general population and NGOs share in the thinking on the future of nanotechnology and nanomaterials. In this context, it is sensible to separate the risk issue from the wider debate on nanotechnology. The preferred approach is to handle the risk issue through the formulation of clear policy, with NGOs being drawn into the process. The Rathenau Instituut also advocates providing transparency about nanomaterials in products and clearly communicating the uncertainties concerning health and environmental risks, as well as any government measures that address them.

The joint research centre (JRC) reviewed the on-going discussion on transparency and requests for more information regarding the use of nanomaterials in consumer products. They concluded that this can in principle be provided by labelling of products containing nanomateirals and by collecting information in a product register or inventory. While labelling provides information to the consumer at the time of purchase, product registers can give a better overview of the overall production and use of nanomaterials. This should be based on a (internationally) harmonised definition of nanomaterial. National regulations may lead to different information requirements and could create cross-border trade barriers (Aschberger et al., 2014).

4.5 Legislation and policy

4.5.1 *Legal frameworks*

Definition

Implementation of the EU's umbrella "recommendation on the definition of a nanomaterial" within the specific legal frameworks is proceeding slowly. There is a continuing debate over the precise formulation of the definition, as well as on how to deal with legislation incorporating its own definition for nanomaterials (for example, the EU Cosmetic Regulation). As a result the overall political process is perceived as slow and confusion is felt by both industry and the consumer.

REACH and CLP

For substances, including their nano forms, REACH and CLP are key frameworks. They focus on assessment of the risks and the conditions required for safe use (REACH), as well as the corresponding information intended for consumers (CLP). Within the scope of REACH, several initiatives are underway to better incorporate the definition, the information requirements and therefore the possibility to perform risk assessment of nanomaterials in the legislation. A more detailed explanation of this is provided in chapter 2.

Cosmetic and Biocide Regulations
Consumer products are regulated by many types of specific product legislation, two being worthy of mentioning here. Other product-specific legislation (for example, the Commodities Act and the Regulation applying to toys) do not currently have any nano-specific provisions.

The Cosmetics Regulation includes its own definition of nanomaterials and requirements for the notification of products containing nanomaterials, together with a labelling requirement applying to ingredients consisting of nanomaterials.
The Biocidal Product Regulation governs the approval and use of biocides, including rules for articles treated with biocides. As definition of "nanomaterial", the one included in the EC recommendation has been adopted. Moreover, approval of the active substance does not automatically apply to its nano form. Separate information requirements are set for nanomaterials (active as well as inert forms). Biocidal products containing nanomaterials have to be labelled as such. Under certain conditions[23], objects treated with a biocide that contains nanomaterials also have to be labelled as such.

4.5.2 *Registration in the EU of consumer products containing nanomaterials*

In summary, there is a need (internationally) for a reliable overview of the application of nanomaterials in consumer products. Owing to the lack of progress in the EU arena, a number of Member States have developed national initiatives for the registration of consumer products containing nanomaterials. Each of these initiatives has its own assumptions and content. The commitment is to harmonise them over time to achieve a single EU registration system, a process expected to become more complex as more national initiatives continue to crystallise.

Several EU member States are getting ready to register consumer products that contain nanomaterials, the countries differing in the progress they have made. France, Belgium and Denmark have either passed legislation for compulsory registration, or are well on the way of doing so. For more details and the differences between the registrations in these countries, refer to Table 4.2 Overview of registrations in France, Belgium and Denmark.

[23] This applies to a) treated objects for which a biocidal claim is made, and b) objects treated with a biocide or active substance where approval involved the setting of specific labelling requirements.

Table 4.2 Overview of registrations in France, Belgium and Denmark

	France	Belgium	Denmark
Status	compulsory	compulsory	compulsory
Scope	NM/compound/item (release)	NM/compound/item (release)	Products that release NM
Characterisation	11 phys-chem parameters	11 phys-chem parameters	the same?
Amount	> 100 g/substance	?	?
Data on NM produced	Open: use, annual hvh, confidential: identity of professional downstream users	Open: use, annual hvh, confidential: identity of professional downstream users	/
Data on item/product	/	use category, product volume, hvh nano	use category, product volume, hvh nano
Traceability	yes, name of substance and product (confidential)	yes	no, only importers and producers
Came into force	2013	2013	2013
Initial statements	2013	2014	2014

Norway, Sweden and Italy are each preparing a register, while Germany, the United Kingdom and the Netherlands are studying the feasibility and support among the stakeholders in their respective countries. General conclusions in the various initiatives:

- a harmonised EU register is the most desirable option
- registration of *all* substances, compounds and products is expensive, so that selective registration might be necessary

Rapid action by the EC appears essential, as harmonising an increasing number of national initiatives is becoming a highly complex process. Moreover, achieving consensus among the different stakeholders on a) the objective (transparency for the consumer and/or traceability in the chain, b) the target group for the register in question, and c) the possible alternative structures for a database demands its fair share of time and effort. One possibility for placing a limit is to exclude the registration of products that are already regulated (such as cosmetics and biocides). With this approach, it is important to effectively maintain the links between the various regulatory frameworks. The EC has meanwhile adopted the initiative to conduct an impact assessment on this subject. It will take place in summer 2014 and will hopefully result in the required understanding and action on the part of the EU.

4.5.3 *Registration in the USA*

The USA takes a different approach to the regulation of nanomaterials in consumer products. For example, in contrast to the EU, pre-approval is not needed for the use of a cosmetic ingredient before the product

concerned is marketed. However, the manufacturer has to provide evidence of safety and in specific cases have the FDA[24] conduct a safety assessment. This assessment is at the request of the manufacturer and employs criteria set by the FDA. Accordingly, the ultimate responsibility for the safety of a product is more on the shoulders of the manufacturer. Moreover, testing on animals is still permitted in the USA and the labels on cosmetics do not have to state the nanomaterial content, so that there is less transparency for consumers. In addition, an antibacterial claim makes a product a bactericide. This requires formal approval before putting it on the market.

[24] FDA: Food and Drug Administration

5 Agrofood

5.1 Introduction

Nanotechnology in general including nanostructured materials are becoming increasingly important for the agrofood sector, i.e. the agricultural sector, and the food and feed sector. Of course nano-structures were already present in many food products as a normal (by)product of conventional production methods. These structures often add for example a variety of tastes and textures to many products. However, nanotechnology is developing rapidly and also in the agrofood industry a range of applications is being developed and applied in different stages of the food production and packaging processes.

The benefits of the use of nanotechnology and engineered nanomaterials in the agrofood industry are now widely recognized. The technology enables a large range of new type of products and functionalities. Packaging for example can be made stronger with lower exchange of e.g. oxygen with the surroundings, nano-sensors can detect if products are still fresh and unspoiled, novel production techniques may provide us with food products that are more stable and have longer shelf lives, and new nano-sized materials make the production more efficient and more hygienic.

The presence of nanoparticles in agrofood and the possible consumer exposure also gave rise to some concerns. In this chapter we provide a general overview of the developments of the use of nanoparticles and nanostructures in the agrofood industry. Furthermore we provide insight into the state of play in relation to the several elements involved in risk assessment of nanoparticles. As such this chapter aims to reflect the current state of affairs of the use and possible adverse effects of nanoparticles in the agrofood industry.

5.2 Sources and applications

In summary, potential applications of nanotechnology and engineered nanomaterials can be found throughout the whole production chain of food and food products: from the use in agriculture, to specific applications in processing technology, packaging, and addition as ingredient. Around 275 nanomaterials are confirmed to be used in 55 different types of applications (EFSA, 2014). For several reasons the technology and its applications hold considerable promise for the future. For example specific forms of nano-size food ingredients can add to the shelf life of products and nanomaterials can also play and important role in the controlled delivery of functional ingredients. Uses in packaging e.g. allow for materials that are stronger or less permeable for gaseous substances (e.g. CO_2, O_2).

The role of nanotechnology in agrofood is depicted in Figure 5.1 (Weiss and Gibis, 2013). In Table 5.1 and Table 5.2 we provide a general overview of the types of use, type of nanomaterial and functionality (Sonkaria et al., 2012; Duran and Marcato, 2013; Lopes et al., 2013; Weiss and Gibis, 2013).

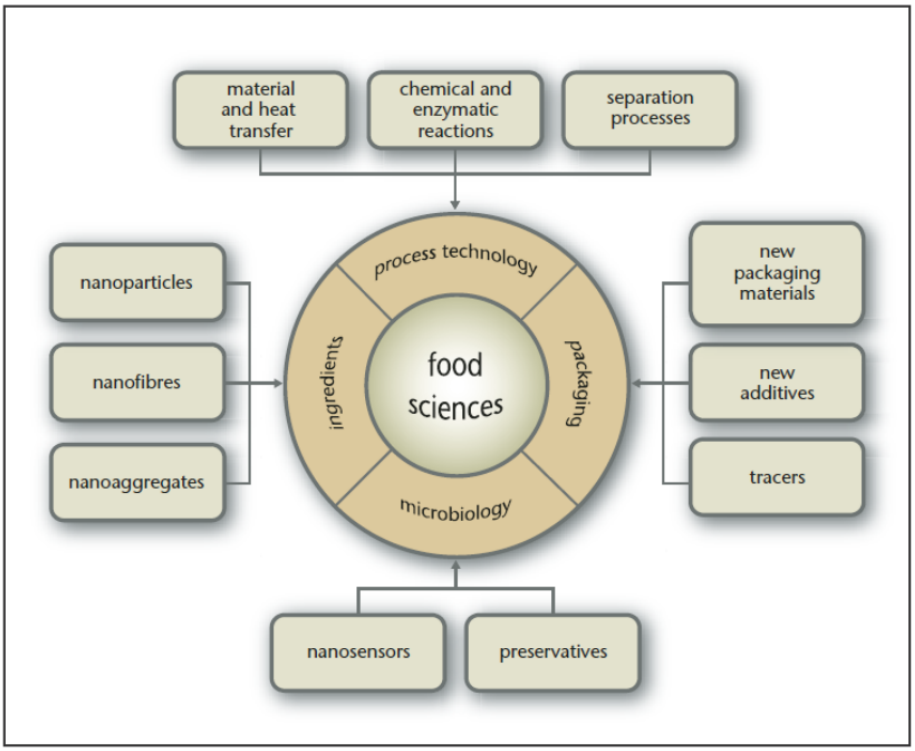

Figure 5.1 Schematic overview of the potential uses of nanotechnology in food (taken from (Weiss and Gibis, 2013))

We distinguish between direct use, i.e. nanomaterials added to foodstuff meant for human consumption and indirect use i.e. to the use of nanomaterials in applications that might come in contact with foodstuff meant for human consumption.

The tables show that possible applications for nanotechnology and –materials in agrofood are developing rapidly, but data on the actual use and occurrence of nanomaterials in foodstuff are scarce (FAO/WHO, 2012; EFSA, 2013). A recent overview of EFSA revealed a total number of 276 of nanomaterials available on the market. Nano encapsulates, silver and titanium dioxide are the most encountered. Applications indicated in the EFSA study are mostly food additives and food contact materials (EFSA, 2014) For indirect and direct use some recent insights on the use of nanomaterials are listed below.

Indirect uses

- A recent overview for nano-applications in chemicals for crop protection (Gogos et al., 2012) shows that – based on a patent scan – a range of new applications is being developed but only a limited number is actually being produced at this moment.
- Nanomaterials for the use in animal feed and veterinary applications have been developed as well. Again data on actual use are limited, but additives like silica/SAS (E551) and titanium dioxide (E171)[25] are known to be used in food are used in animal feed as well, e.g.

[25] Silica and TiO2 contain particulate matter in the nano-size range

Table 5.1 General overview the types of potential use, the used nanomaterial and the specific functionality for the indirect use of nanomaterials.

	Type of use	**Nanomaterial**	**Functionality**
Agriculture	Use in agricultural chemicals (e.g. pesticides,fertilizers)	- Encapsulation of active ingredients - Nano-emulsions - Solid nanomaterials	- Reduction of amount of active substances used; - Less damage to plant systems
Animal related	Use in animal feed, medicine, hygiene	- Encapsulation of ingredients - Use of solid nanomaterials	- Various (see: direct uses for foodstuff)
Nano sensors	Detection of e.g. residues, pathogens, toxins or deterioration products; Several techniques	Predominantly nanotechnology based sensors on active surfaces Incidentally: CNT, gold particles, quantum dots	- Detection of various substances with high sensitivity and selectivity
Packaging	Improving barrier function; anti-microbial functionality	Various, a.o.: nano clays, nano polymers, nanocomposite, nanocellulose, silicates, starch, CNT, silver particles, ZnO, nanosensors	Improved protective function: stronger materials, improved barrier function (gases, UV-radiation), active packaging, incorporating sensor technology*, improved biodegradability, reduced microbial pressure inside the package to increase shelf
Food processing	Optimisation of the various production steps in food processing	Various possibilities; nanotechnology based improvements to enhance material and machine properties (surface coatings/treatment, material design)	- Improved process design using nano-based materials and surface - Reduction of amount of active substances - Easier processing - Longer storage options - Improving catalytic functions of process chemicals
Nano-filtration	Nano-filtration for water treatment (re-use) and separation/isolation technology	Materials with nano-sized pores (as such or in combination	- Increased specificity and capacities in filtration process - antimocobial effect -> longer shelf life

	Type of use	Nanomaterial	Functionality
		with e.g. activated carbon)	(Milk)
Other contact materials	Use of nano-particles with anti-microbial potential in equipment and appliances; Adding specific properties, e.g. adapting surface properties (more hydrophobic/more hydrophilic)	e.g. coatings containing nano-Ag particles, tubing, process related equipment; various coatings/surface treatment to add desired properties	- Anti-microbial activity - increasing process efficiency; easier and more efficient cleaning and disinfecting

*Examples of functionalities are: reduction of gas exchange with environment, active control of the packaged atmosphere, improved UV protection, scavenging of unwanted deteriorating chemicals , improved mechanical properties (abrasion and tear and heat resistance), nano-based carriers systems for e.g. anti-oxidants and preservatives.

Table 5.2 General overview the types of potential use, the used nanomaterial and the specific functionality for the direct use of nanomaterial.

	Type of use	Nanomaterial	Functionality
Encapsulation; nano-emulsions	Incorporation of ingredients in nanostructured particles A huge variety of possible structures with specific characteristics are being devised.	Outer layer of particles is usually made up of biomolecules like proteins, lipids or polysaccharides. Inner ingredients are highly variable, e.g. fragrances, colouring agents, anti-oxidants, biologically active compounds, functional ingredients etc.	- Improved stability under different (processing) conditions – e.g. freezing, dry-freeze - Selective ingredient encapsulations (e.g. enzymes) leading to enhanced shelf life. - Improved control of release of encapsulated ingredient (delivery systems); a.o. masking of unwanted smells and tastes. - Improved control over bioavailability of encapsulated ingredient - Possible reduction of unwanted substances (e.g. salt, sugar)

	Type of use	**Nanomaterial**	**Functionality**
			- Possible new structures, new textures, and new properties
Solid nanomaterial	Use in food additives as e.g anti-caking agent . or food colouring	Often used are: SiO_2 (SAS) and TiO_2[26]	Functionalities like anti-caking, colouring
Edible films	Edible films – nano-layered	Nano-layered films based on various modified biomolecules e.g. proteins, lipids poly saccharides	Improved barrier function, enhancing shelf life

[26] TiO_2 is usually not deliberately added as a nanoparticle. However, some 10-30 % of the added material consists of particles <100 nm.

- In packaging materials nano silver is known to be used as an antibacterial agent (Echegoyen and Nerín, 2013; SCENIHR, 2014a) although not allowed in EU. Nano ZnO applications are being developed for similar applications (Lu-E Shi et al., 2014). Nanoclays to improve e.g. the barrier function of packaging are often mentioned in literature and seem to be regularly used outside the EU (Lopes et al., 2013).

Direct uses

- Nano-silicates are a commonly used ingredient in foodstuff as an anti-caking agent in powdery products, usually in relatively low quantities. Titanium white, which only partly consists of particles within the nano-range is also a common additive to food products.
- Actual product data in literature on the presence of encapsulated ingredients and nano-emulsions are scarce. Recent analysis shows that nano-encapsulates have the highest number of occurrence (EFSA, 2014) in a recent EFSA product inventory/database. The technique seems well developed and several commercial encapsulation systems are available on the market (Ezhilarasi et al., 2013; Lopes et al., 2013).
- Non-mainstream food products e.g. supplements/products for fitness or health purposes are advertised on the internet with a nano-claim.

5.3 Exposure

New products are being developed and claimed to enter the market, but the available data from published sources and databases do not allow verification (FAO/WHO, 2013). Currently an important focus is on inorganic particles (e.g. SiO_2) for their widespread use and potential to accumulate. Measurement techniques have improved but still are costly and complicated.

Indirect

Nanoparticles used in pesticides, agricultural chemicals (e.g. fertilizers), animal feed and veterinary products come in direct contact with crop and animals, which in turn may be used for human food production. Little is known about the lifecycle and the processes governing this lifecycle of the nanoparticles used in these applications (Gogos et al., 2012) and into what extent they end up in foodstuff for human consumption.

Migration of e.g. nano-silver and nano-copper particles in food packaging has been investigated (von Goetz et al., 2013; Cushen et al., 2014; SCENIHR, 2014a). For commercially available food containers containing nano-silver the released silver was found to be in ionic form; silver nanoparticles were identified as well but the origin (directly released or formation after release) was unclear. Consumer exposure to the total amount of silver released from the food containers is low in comparison with the background silver exposure of the general population, but since natural background concentrations are only known for ionic silver, the exposure to silver nanoparticles is not directly comparable with a safe background level.

It is important to notice that EFSA only assessed a few non-nano silver compounds for use in food contact materials, which are consequently the only ones allowed in food packaging materials. Nano-silver is currently not assessed by EFSA and thus it is not approved for food contact materials sold in Europe.

Direct
First of all, it should be recognized that nanostructures in food (nanoparticles in food) are often normal and desired structures and (by-)products of the food making process. For example, food stuffs containing large amounts of carbohydrates, often contain carbon-based nanostructures (Palashuddin et al., 2012).

TiO_2 has a widespread use as a white pigment in food (E 171) and consumer products. For the food additive, Weir et al (2012) showed for one sample of E171 that 36% of the particles is smaller than 100 nm. Peters et al. (2014) showed for 6 different samples of E171 obtained from producers with different geographic location (a.o. Germany, India, UK) that about 10% of the TiO2 particles are smaller than 100 nm. The additive E171 is used in e.g. chewing gum, toothpaste and candy. The data allow an estimate of the exposure to nano-titanium particles – which within this estimate is most likely larger than exposure to purposely added nano-TiO2 particles in e.g. sunscreens and cosmetics (Weir et al., 2012).

In the SCENIHR opinion on silver nanoparticles (2014), the use of silver nanoparticles in supplements (colloidal metal nanoparticles) is mentioned, and the consequently relatively high exposure due to the oral use. Actual data on use and occurrence are non-existent.

Inorganic nanoparticles, especially SiO_2, have received ample attention during the last years. The widespread use in a variety of food products may result in a sizable exposure of humans, depending on the actual daily intake. The present knowledge is that a sizable portion of SiO_2 is present in nanosize in the gastro-intestinal tract (van Kesteren et al., 2014; van der Zande et al., 2014) . Measurements show that a small fraction does pass the gastrointestinal epithelium and is transferred into the bloodstream, leading to internal exposure in humans. After rapidly distribution to - predominantly - tissues like liver and spleen indications of accumulation at these organs are observed in animal studies. The implications of exposure to such materials for humans need further investigation (Geraets et al., 2014; van Kesteren et al., 2014; van der Zande et al., 2014).

Micellic structures and emulsions are regular components of foodstuffs. In addition to present practices (mayonnaise etc), current technical developments allow these structures to be created and physically handled further at the nanoscale. The diversity of structures is enormous. Nanostructures may lead to enhanced bioavailability, or are even purposely designed to do so. Recent reviews of the patent literature shows a range of possibilities (Ezhilarasi et al., 2013; Lopes et al., 2013). Regulatory constraints from the Novel Food Regulation, that includes materials that are produced with novel fabrication techniques, seem to limit the number of new nano-encapsulates and emulsions.

However, it is possible that most applications remain unnoticed as they can be produced with approved materials and production techniques that are not covered by the Novel Food Regulation (see also the paragraph on regulation).

5.3.1 *Measurement techniques*

Several tools and techniques for measuring nanoparticles are available but numerous aspects still need to be elucidated. A recent review of the EU-based Joined Research Centre (JRC) provides an overview of the current state of the art, focusing particularly on the suitability of the most used techniques for the size measurement of nanoparticles when addressing this new definition of nanomaterials (Calzolai et al., 2012; Linsinger et al., 2012). Additionally, (Szakal C et al., 2014) recently provided a state of the art overview of the challenges of measurement of nanomaterials is food.

JRC also expresses the urgent need for appropriate and fit-for-purpose analytical methods. They identified many challenges to overcome in the chemical-analytical process such as interaction of nanomaterials with matrix constituents, potential agglomeration and aggregation due to matrix environment, broad variety of matrices, etc. They also expressed the need for integrated analytical approaches, for sample preparation (e.g. separation from matrix), and actual characterisation. Also the need for quality assurance tools such as validated methods and (certified) reference materials, including materials containing nanoparticles in a realistic matrix (food products, cosmetics, etc.) was expressed (Stamm et al., 2012).

Considerable improvements are made in measurement techniques for nanomaterials, also in complex matrices such as food. Several techniques are reviewed by ISO and are in a process of harmonisation. Methodologies and user interfaces/guidances are available and the costs of equipment is within reach of most standard laboratory facilities, but proper characterization remains complex and expensive. Skilled expertise is of course a prerequisite. Further progress can be expected in the years to come.

5.4 Hazards

From a hazard perspective the inorganic nanoparticles in food products receive the most attention at present. Recent toxicological studies show that a small part of the orally administered nano-particles (SiO_2, TiO_2) does enter the bloodstream and reaches liver and spleen and to a smaller extent other tissues (Geraets et al., 2014; van Kesteren et al., 2014; van der Zande et al., 2014). There are serious indications that accumulation of these particles occurs in these specific organs when exposure occurs regularly. Whether or not this internal dose results in long term toxicological effects is at present topic of further study (Geraets et al., 2014; Peters R.J.B et al., 2014).

Furthermore, toxico-kinetic studies show that, due to a variety of agglomeration processes in the gastro-intestinal tract, the oral dose and the internal dose are poorly correlated (or may even show a plateau). Thus, an oral uptake of a higher dose may in effect not result in a higher

concentration in tissues. Thus care should be taken when making use the high oral dose in a risk assessment (van der Zande et al., 2014).

Nano-encapsulates and nano-emulsions are usually based on naturally occurring substances and ingredients already used in foodstuff. Most of the used materials will be destroyed early in the digestive process, reducing the nano-structure to its individual components and therefor no specific, nanomaterial based hazard is to be expected. There is some safety concern however in case of more stable nano-encapsulates – these structures may either enter the body intact as a particle-like structure or release their content further down the intestinal tract. The precise mechanisms are unknown and need further elucidation. (Bouwmeester et al., 2009; Weiss and Gibis, 2013). For a detailed and comprehensive description of nano-delivery systems, see (Borel and Sabliov, 2014).

5.5 Risk Assessment

A recent FAO report gives a comprehensive overview of the world wide state of the art with respect to risk assessments and risk governance of food ingredients and food contact materials (FAO/WHO, 2013). The report shows that there is limited information on risk assessment of nanotechnologies in the food and agricultural sectors. The EFSA corroborates this result in a recent suvey (Peters et al., 2014). The FAO finds that more data seem to be available for dermal and inhalation exposure and less for ingestion exposure, and that nanomaterial risk assessments need to be made on a case-by-case basis.

Indirect use
SCENIHR (2014) and others have identified the use of nanosilver in food packaging (not allowed in Europe). A number of migration studies (from packaging to food) have been identified by SCENIHR, and migration of nanosized silver particles was confirmed, but in very low concentrations. However, specific human risk assessment for silver nanoparticles is not feasible as information on possible long term effects are lacking (SCENIHR, 2014a). Additionally, more exposure data are necessary; as well as data on all products containing silver nanoparticles and data on exposure levels during use of silver nanoparticles containing products.

An example of a more general approach is developed in Switzerland, where a precautionary matrix was drafted. The approach allows a preliminary evaluation of the potential risk based on a limited number of data (potential effects, potential exposure, basic characteristics). The results are indicative and may support e.g. decision making and product development in e.g. applications for agriculture (Gogos et al., 2012).

Direct use
As indicated before, current risk assessment focus is on inorganic nanomaterials in food, dedicated data collection on e.g. bio-kinetics of particles in the human body, accumulation in the human body, and the assessment of adverse effects and risks are underway. These particle types are also under scrutiny in the REACH substance evaluation process

(e.g. SiO_2, and silver). The SCCS[27] has been mandated to provide an opinion on the use of silicate in cosmetics, and has already provide opinions on the dermal use of TiO_2, 2 types of UV-filters for sunscreens and carbon particulates. Note that the SCCS opinions are for non-oral applications.

Nano-encapsulates and nano-emulsions are, in most cases, expected to reduce to their molecular constituents when entering the gastro-intestinal tract. Risk assessment therefore poses no specific methodological problems, and the standard toxicological approaches and considerations can be used. However, more stable encapsulates may lead to an altered bioavailability of the encapsulated ingredient, which requires a separate assessment (Cockburn et al., 2012).

EFSA is in the process of re-evaluating the possible risk as a result of the established food additives. This evaluation process will include nano-forms of the additives and is scheduled to be finished in 2020.

Other developments
The European Food Safety Authority drafted a guidance for the safety assessment of applications involving the application of nanoscience and nanotechnology to food and feed (EFSA, 2011). The document highlights that physio-chemical behaviour and the identity of ENM particles may change depending on their specific surroundings which should be incorporated in the characterisation of the ENM.

The ILSI-project project ' NanoRelease Food Additive'[28] (US-branch) also focuses on the development of test methods for the risk assessment of food additives. The project is comparable to the EFSA initiative, but here it concerns a public-private cooperation, securing the input of industry, science and policy, and making a broad implementation possible.

In 2010 EFSA established a European Network for Risk Assessment of Nanotechnologies in Food and Feed was established (EFSA, 2013). Current activities are: contributing to the making of inventory lists of applications of nanomaterials already present in the food/feed chain, assessments and recommendations on the adequacy and relevance of specific toxicity test methods and drafting a list of national laboratories that have equipment and know-how for analysing certain nanomaterials in complex matrices.

As medicines and food represent fields with increasing overlap (e.g.functional foods), developments within the world of medicine may stand model for those in the field of food products. Block co-polymers can form structures that stay intact throughout the gastrointestinal tract can be used both in the field of medicine and agrofood. It is recommended to keep track of the developments within other application domains and in particular medicines.

[27] http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm
[28] http://www.ilsi.org/ResearchFoundation/RSIA/Pages/Nanotechnology.aspx

5.6 Risk communication and labelling

Nanotechnology and nanomaterials are relatively new developments, much of which still belong to the scientific and policy communities. The use in consumer products is however growing and there is an increasing potential for new applications. Direct and indirect applications in food and feed show similar potential.

Apart from the technical and scientific potential, the acceptance of new technologies and innovative ideas is very much prone to judgment of the general public. The attitude of the consumer with respect to nanotechnology and the use of nanomaterials, in food but also from a broader perspective, is a topic of much research throughout the world (Duncan, 2011; Ronteltap et al., 2012).

Generally, within the EU nanotechnology and its implications are still relatively unknown with the public, there is however a significant variation throughout the different European countries. Generally, applications, which show e.g. health or other personal benefits are usually preferred over applications with no evident additional personal value, such as applications that are beneficiary in the production process. With respect to food, consumers want to be informed about the ingredients and the general opinion is that this should be reflected on the label somewhere. A recent study in the US showed that consumers are inclined to accept the use in food contact materials (e.g. packaging) more quickly than the use in food products itself (Brown and Kuzma, 2013).
The EU-labelling obligation for nanomaterials as laid down in the proposed FIC-regulation (see below), may answer the consumers' desire for transparency and adequate information. Obligatory nano-labelling might however hamper innovation as companies may wish to stay away from labelling their products, and thus will refrain from using nanomaterials.

5.7 Legislation

The European food legislation relevant for nano particles centres around four legislative frameworks.

Regulation on Food Information to Consumers (EU 1169/2011)
This regulation considers labelling of food, which also includes the labelling of nanoparticles. In order to distinguish when labelling should be applied, 'engineered nanomaterial' was defined in 2011. As the EU Recommendation on the definition of a nanomaterial was released later, and due to other developments, the Commission has drafted an amendment for this definition of 'engineered nanomaterial' (see chapter 2). In this proposal a selection of nano-materials already used in food products as additives[29] are exempted from the labelling obligation. Furthermore, nanomaterials should be intentionally manufactured, meaning that nanomaterials are manufactured to perform/fulfil a specific function or purpose. This amendment of a definition was however

[29] More specifically it concerns those nanomaterials which were already allowed before the entrance into force of the Food additive regulation (EU/1333/2008) and are listen on either EU/1129/2011 or EU/1130/2011

rejected by the European Parliament (March 2014). In effect the labelling provisions as stipulated in EU 1169/2011 now remains to be valid.

Novel food regulation (EC/258/97)

This regulation focuses on foods and food ingredients that were not used for human consumption to a significant degree in the EU before 15 May 1997 (novel foods and novel food ingredients). The proposed amendment (December 2013) by the European Commission includes nanomaterials for food applications. These nanomaterials have to be authorised by the Commission before use in food products is allowed. For the definition of nanomaterials use is made of the definition as is foreseen in the Regulation on Food Information to Consumers (EU 1169/2011). Furthermore, novel production methods may yield ingredients in the nano-sized range. Whether or not these nano-sized particles are covered by the Novel food regulation is still open to interpretation (Sprong et al., 2014).

Food contact materials

Food contact materials and articles are regulated by:

- Framework Regulation (EC 1935/2004) - general requirements for all food contact materials
- Legislation on specific materials - groups of materials and articles listed in the Framework Regulation
- Directives on Individual Substances or groups of substances used in the manufacture of materials and articles intended for food contact
- National legislation covering groups of materials and articles for which EU legislation is not yet in place

EFSA has adopted a guidance document clarifying the data to be provided when submitting an application dossier for a nanomaterial to be incorporated in food and feed (Antunović et al., 2011).

Food additives (*1333/2008/EU*)

This regulation covers food additives used as ingredients during the manufacture or preparation of food and which are part of the finished product and listed in one of the categories in Annex I (a "food additive" being any substance not normally consumed as a food itself, the intentional addition of which results in its becoming an ingredient). The only substances which may be used as food additives are those included in the approved lists and then only under the conditions of use mentioned in those lists (e.g. preservatives, emulsifiers, sweeteners, raising agents). Additives are as such strictly regulated and are only to be used in food after approval, i.e. after an assessment of possible health risks by the European Food Safety Authority.

EFSA, has adopted a guidance document clarifying the data to be provided when submitting an application dossier for a nanomaterial to be incorporated in food and feed (Antunović et al., 2011). EFSA will re-evaluate all additives by 2020. In this process nano-aspect and associated risks, if relevant, will be evaluated as well. Based on EFSA's scientific advice, the European Commission and Member States may decide together to change the uses of additives or if needed to remove them from the EU list of authorised food additives.

Outside EU

Recently, a comprehensive review paper described the worldwide development of several aspects of nanoparticle related food regulations. As the field and applications are developing, the regulations are also dynamic and globally developing. A range of countries are currently addressing the regulation issue, most notably: Argentina, Australia and New Zealand, Brazil, Canada, China, EU, Japan, Mexico and the USA (Magnuson et al., 2013). The main focus in these countries is related to the development of approaches to risk assessments.

6 Nanomedicine

6.1 Introduction

The UK Royal Society and Royal Academy of Engineering have defined nanotechnologies as the design, characterisation, production and applications of structures, devices and systems by controlling shape and size at the nanometre scale (Royal Society & Royal Academy of Engineering, 2004). The field of nanomedicine has been defined by the European Science Foundation as the science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body (ESF, 2005). Nanomedicine can thus be interpreted as the application of nanotechnologies to healthcare. Innovative applications of nanotechnologies are increasingly used in medical practice and are expected to have a major impact on healthcare in the future (Geertsma et al., 2008). These new nanotechnology applications relate to both medicinal products and medical devices and are intended for diagnosis or treatment, monitoring or prevention of diseases. Also products combining different functions are being developed (Rizzo et al., 2013).

Nanotechnology applications in the field of medicinal products, so called nanomedicinal products, are new or existing active pharmaceutical ingredients in formulations with features at the nanometre scale. The products may contain all kinds of drugs, and an increasing range of nanostructures are being applied (Duncan and Gaspar, 2011). The *in vivo* biological behaviour of such nanostructures can be influenced by engineering the properties of the nanomaterials, leading to the optimal effect (Duncan and Gaspar, 2011). It is expected that nanomedicinal products will provide novel solutions for a broad range of indications, including cancer, infections, auto-immune diseases and inflammations.

Nanotechnology applications in the field of medical devices span a wide range of very diverse products, technologies and application areas (ETPN, 2013). Their intended use can be therapy, diagnosis, monitoring or prevention of disease. Devices can be non-invasive or invasive, contacting any kind of tissue. Nanomedical devices can involve the use of nanomaterials, however, nanotechnologies also enable innovative devices without using nanomaterials, for example by applying nano-electronics or lab-on-a-chip technologies (Geertsma et al., 2008). All medical disciplines are benefiting from nanomedical devices, especially orthopaedics, dentistry, oncology, and cardiology. Also a number of innovations in clinical chemistry laboratories are enabled by nanotechnology (Hermsen et al., 2013).

Together, nanomedical applications can contribute to solving some of the grand challenges in healthcare. For example, developments in nanotechnology may enable reduction of costs, thereby aiding efforts to achieve a sustainable healthcare system. In this context, development of more methods for early diagnosis, and more effective therapies are important, and also technologies supporting the increasing trend of self-

management by patients. Furthermore, therapeutic selection can increasingly be tailored to each patient's profile, thus enabling the concept of personalized medicine (Lammers et al., 2012).

While the advantages are highly desirable, the emergence of innovative nanomedical products also gives rise to questions whether currently used risk assessment strategies and testing methods provide a sound scientific basis for an adequate evaluation of the quality, safety and efficacy of these products within the current regulatory frameworks (EMA, 2010; Ehmann et al., 2013a; SCENIHR, 2014b). It is important to have clear insights into the state of affairs with regard to the availability of nanomedical products and their specific properties, not only for regulators and industry, but also for physicians and pharmacists. The following paragraphs will provide an overview of specific applications, potential for exposure, identification of hazards, description of risk assessment issues and developments in regulation and standards.

6.2 Applications

Apart from the regulatory classification in medicinal products and medical devices, various ways to categorise the products can be used. The European Technology Platform Nanomedicine has published roadmaps for nanomedicine in 2009 (ETPN, 2009), and is currently developing these into a strategic research and innovation agenda. As the three largest areas of application for nanomedicine, ETPN distinguishes: Nanotherapeutics (including drug delivery), Regenerative Medicine and Biomaterials, Nanodiagnostics and Imaging (ETPN, 2013). In order to include an additional number of applications we consider important, we add a category of Medical Instruments. The diversity of the various types of nanotechnology applications is shown in Table 6.1.

Table 6.1 Overview of nanotechnology applications in medical products

Category	**Application**	**Nano-enabled features**
Nanotherapeutics (incl.drug delivery)		
Drug delivery	Nanoformulation of drugs	- More accurate targeting - Decrease in side effects - Improving solubility/bioavailability - Controlled (sustained) release - Crossing blood brain barrier - Personalized medicine
	Nano-needle arrays	- Painless drug injection
Injectable devices	Nanoparticles used in hyperthermia/ thermo-ablation/ radiation therapy	- Tumour destruction - Enhancing efficacy of radiation or chemotherapy

Category	Application	Nano-enabled features
Active[30] implantable medical devices	Pacemakers, hearing devices, retina implants	- Improved batteries - Nano-electronics enabling functionality
Devices with nanosilver component	Wound dressings	- Antibacterial activity - Faster healing
Regenerative medicine & biomaterials		
Biomaterials	Dental materials	- Optimal material properties for i)usability by dentist and ii)performance in teeth
	Bone cements & fillers	- Rapid integration in patient's bone
	Coatings on implants	- Rapid integration in patient's tissue
	Improved biomaterials	- Increased durability/better flexibility - Light weight biomaterials
Nanosilver component	Bone cement, other biomaterials	- Antibacterial activity
Regenerative medicine	Scaffolds mimicking extracellular matrix	- Enabling/promoting cell growth in and on the tissue constructs
Nanodiagnostics and Imaging		
In vivo imaging	Imaging equipment	- Improved batteries - Novel superconductive magnets - Small X-ray sources - Improved & earlier detection of abnormalities
	Contrast agents	- Enhancing images - Improved & earlier detection of abnormalities
In vitro diagnostics	Lab-on-a-chip technology	- Faster test results - Multiplexing - Point-of-care diagnostics - Personalised medicine
Medical Instruments		
Surgical & dental	Scalpels, saws, burs and	- Improved cutting

[30] 'active' means that the device is relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity

Category	Application	Nano-enabled features
instruments	similar instruments	behaviour, wear resistance, handling properties
Minimally invasive therapeutic & diagnostic instruments	Catheters, canula's for a range of applications	- Improved mechanical properties - X-ray visibility
Devices with nanosilver component	Operation textile & gowns, catheters & other devices	- Antibacterial activity

6.2.1 *Nanotherapeutics (including drug delivery)*

In the area of nanotherapeutics, the most prominent category of applications in terms of number of individual products is drug delivery. Products may consist of nanoparticle forms of the active pharmaceutical ingredient itself, nanoporous carrier materials engineered to achieve a controlled release of their payload, or nanoparticles used as a carrier material for drug delivery, either with the drug encapsulated inside or attached onto the surface (Duncan and Gaspar, 2011). Nanostructures being applied include well-known examples like liposomes, micelles, nanosilver and iron oxide nanoparticles, but also more novel structures like dendrimers and block-copolymer micelles are being investigated (Ehmann et al., 2013a). Nanotechnologies potentially can contribute to solve one of the major issues of drug administration: delivering the right drug, in the right dose, to the right spot at the right moment.

Especially therapies with drugs producing considerable side effects may benefit from nanotechnological solutions, as for example demonstrated with several highly toxic cytostatic drugs. The active pharmaceutical ingredient may be targeted more accurately, and it may be shielded until reaching the target where a controlled release takes place (Lammers et al., 2008). These features lead to a higher efficacy and a decrease in side effects. Application of nanostructures may also provide new options for drugs with solubility problems and increase their bioavailability, enabling more efficient dosing (Merisko-Liversidge and Liversidge, 2011; Onoue et al., 2014). They may also be instrumental in transporting drugs to targets that are difficult to reach, e.g. by enabling passage of the blood brain barrier (Alyautdin et al., 2014).
A very recent overview by Noorlander et al. (Noorlander et al., 2014) identified 175 unique products, of which 43 were approved by the European Medicines Agency (EMA), 71 were approved by United States Food and Drug Administration (FDA) and 101 products were in various phases of clinical trials. The first nanomedicinal product approved by the EMA dates back to 1994, and between 1994 and 2013 at least 1 nanomedicinal product was approved each year.

Most products were found to be used for cancer treatment, followed by infectious diseases (Noorlander et al., 2014). Other application areas include cardiovascular disorders, degenerative disorders and inflammatory/immune disorders. Liposomes, polymer conjugates and protein nanoparticles were identified as the most frequently used

structures. The high number of liposomal products currently under investigation might be connected to the fact that patents have expired for some of the older, successful innovator products. Part of the liposomal products now under development are probably follow-up products or "nanosimilars" (Ehmann et al., 2013a). An example of a product where the active pharmaceutical ingredient has been formulated as a nanocrystal in order to increase dissolution velocity and thus bioavailability, is naproxen, an anti-inflammatory drug used to treat pain associated with inflammation (Junghanns and Müller, 2008; Merisko-Liversidge and Liversidge, 2011).

An interesting innovative technology expected on the market within a few years is a needle that is built of hollow nano-needle arrays (ETPN, 2013). This could enable transdermal delivery of drugs into target tissue with minimal pain.

A specific type of nanotherapeutics which are considered medical devices are injectable nanoparticles used in cancer treatment for hyperthermia therapy, thermo-ablation or to increase the efficacy of radiation therapy. When the injected metal based particles have accumulated in a tumour, they can be heated by an external energy source for hyperthermia/thermo-ablation, or will serve as a multiplier of the radiation dose during radiation therapy. Examples of the first type of products are gold-silica nanoshells heated by near-infrared radiation (Nanospectra, 2011) and iron oxide nanoparticles heated by applying an alternating magnetic field (Magforce, 2010). A product based on this last principle obtained a CE certificate, i.e. the approval to put a product on the market, in 2010, after finalising a clinical trial to prove safety and efficacy (Magforce, 2010; Maier-Hauff K et al., 2011). An example of a product used in radiation therapy is using hafnium oxide (Nanobiotix, 2012). A phase I clinical study with this product was successfully completed recently (Nanobiotix, 2014).

A variety of medical devices use nanosilver particles or coatings as a component because of their antibacterial properties (Wijnhoven et al., 2009; SCENIHR, 2014a). In the category of nanotherapeutics, a well-known example is wound dressings containing free nanosilver particles.

6.2.2 *Regenerative medicine and biomaterials*

In the area of regenerative medicine and biomaterials, applications range from straightforward, sometimes well-established biomaterials to smart biomaterials with or without cells integrated before administering them to a patient. One of the oldest applications of nanomaterials in medical devices is as a component of dental materials. Some of these products have been on the market for thirty or forty years, although innovative new varieties are still being developed. The branch organisation of the European dental industry recently compiled an overview of all dental materials containing nanomaterials (FIDE, 2014). This overview identified almost 3,500 individual products in 30 categories on the market, including for example various types of cements, filling materials and sealants, but also plastic materials for bite registration and preparations for tooth cleaning and polishing.

Other well-known medical device applications are bone cements and bone filler materials with hydroxyapatite and tricalcium phosphate nanoparticles facilitating rapid integration with the patient's bone (Zhang et al., 2008). Furthermore, also aiming at better integration with the body, implants have been modified with nanocoatings or nanostructures (grooves and ridges) on the surface which direct cell growth, e.g. hip and knee prostheses and coronary stents (Arsiwala et al., 2013; Thakral et al., 2014). Nanocoatings on implants are also increasingly used to enable the sustained release of a drug with an ancillary function to that of the implant, for example the prevention of infection or the promotion of tissue growth around implants, or the prevention of restenosis after placement of a stent (Gultepe et al., 2010).

A variety of medical devices use nanosilver particles or coatings as a component because of their antibacterial properties (Wijnhoven et al., 2009; SCENIHR, 2014a). In the category of biomaterials, a well-known example is nanosilver mixed in bone cement.

For regenerative medicine, micro- and nanotechnology fabrication techniques are used for engineering a 3D architecture of scaffolds used as analogues for the natural extracellular matrix. Products can consist of scaffolds only, or of constructs incorporating living cells. Often bioactive materials are used to build the scaffolds, promoting the tissue self-healing. As an example, nanofibres are used to produce scaffolds for in situ heart valve regeneration in the Dutch iValve project (Simonet et al., 2011; BMM, 2014). Since most of the extracellular matrix features are on the nanometre scale, advanced bio-inspired materials should incorporate nanometre surface features and also internal structures like nanopores. This is necessary for optimal integration into the body, uptake of nutrients and release of waste products from the cells.

6.2.3 *Nanodiagnostics and Imaging*

The area of clinical diagnostics can be divided into "*in vivo*" and "*in vitro*" technologies. In both areas there is a demand for increased sensitivity and earlier detection of disease. In the "*in vivo*" imaging area nanotechnology contributes both to the scanning equipment and to contrast agents which are injected into the patient's blood circulation in order to enhance the images and to improve the detection of abnormalities (ETPN, 2013). These features lead to earlier diagnosis of diseases, in particular of cancer (both primary tumours and metastases) (Fortuin AS et al., 2014). Currently, the only nanomedical products on the market in the area of imaging we could identify are contrast agents for MRI. Two of these so-called ultra-small superparamagnetic iron oxide nanoparticles (USPIONs) are currently registered as a medicinal product (Noorlander et al., 2014). In the area of contrast agents, a lot of research has been going on for many years, and more developments are expected, especially MRI and optical imaging applications (ETPN, 2013). In the coming years, nanotechnologies are expected to improve imaging systems equipment by for example enabling novel superconductive magnets, specialised batteries, new image processing and small X-ray sources based on carbon nanotubes (ETPN, 2013). Also in the further development of combining imaging and therapeutic modalities, nanotechnologies can play a role, for example in image guided therapy

by embedding nanomaterials as contrast agents in the wall of a guidewire for (trans)vascular interventions (Ariens et al., 2013) or in the development of bifunctional nanoparticles that can be used both as contrast and as therapeutic agent for example in hyperthermia therapy (ETPN, 2013).

In the area of *in vitro* diagnostics, nanotechnology plays a role in enabling important trends like near patient rapid testing, often indicated as point-of-care diagnostics, which enable a fast diagnosis and early start of treatment. In this context, lab-on-a-chip (LOC) technologies are crucial. In addition, LOC technologies are also applied in large analysers, which are used in clinical chemistry laboratories. An overview of available LOC devices was recently published by Hermsen (Hermsen et al., 2013). The inventory comprises 75 companies with 154 devices on the market and 33 devices under development. Many of these applications concern devices for blood glucose and electrolytes analysis, HIV diagnostics and determination of cardiac markers. Multiplexing, i.e. simultaneous screening of multiple parameters, will be further developed using for example DNA or protein array technologies. Also the development of so-called "companion diagnostics" using biomarkers for personalised medicine is seen as an important trend (ETPN, 2013; Hermsen et al., 2013). Nanotechnology aspects include the biosensor components, nanoscale reagents, and nanopores for specificity in sequencing.

6.2.4 *Medical Instruments*

Nanostructures are used on surgical and dental instruments to enhance the cutting behaviour and wear resistance of cutting instruments, e.g. scalpels, needles, catheters, burs (SCENIHR, 2014b). Nano-diamond coatings have been used to create non-sticky surfaces to facilitate handling and placement of materials (Dearnaley and Arps, 2005). Nanomaterials can also be embedded in a matrix in order to improve the mechanical characteristics, e.g. carbon nanotubes in catheters for minimally invasive surgery. A quite common application was identified recently by the European branch organisation for medical devices: Barium sulphate is a widely used x-ray visible agent added to the bulk material of a long list of products to make them x-ray opaque, e.g. a latex Foley catheter. When present in latex or plastic, it is in the form of an aggregate that can most likely be defined as a nanomaterial (Eucomed, 2014).

A variety of medical devices use nanosilver particles or coatings as a component because of their antibacterial properties (Wijnhoven et al., 2009; SCENIHR, 2014a). Well-known examples are operating gowns and textile to cover patients in the operating theatre, catheters, contact lenses or tracheatubes with a nanosilver coating.

6.3 Exposure

Nanotechnologies are enabling technologies with very broad applications in medical products, as shown in the previous paragraphs. Importantly, there are great differences in risk profile between applications using e.g. nanoelectronics – even if they are applied in implants - and applications using nanomaterials (SCENIHR, 2014b). For the sections on exposure,

hazard and risk assessment, the focus is on the use of nanomaterials. In relation to nanomedical products, mainly health care professionals and patients are potentially exposed to nanomaterials. The potential for exposure depends on the product and its intended use, especially with regard to the level of invasiveness, types of tissue involved and the duration of contact. The highest exposure potential occurs with applications using free nanomaterials, followed by coatings and embedded nanomaterials (SCENIHR, 2014b).

Health care professionals are generally exposed to low or negligible levels of nanomaterials from medical products (SCENIHR, 2014b). Often no direct contact with the nanomaterial occurs because of packaging and the use of tools to administer drugs and devices. In other cases, exposure is minimized by the use of protective clothing and gloves when handling the products. Generally, medical products are not airborne, and other exposure routes besides dermal and inhalation are highly unlikely. An exception could be a potential low exposure to airborne particles created during the polishing of dental fillings (Van Landuyt et al., 2012; Van Landuyt et al., 2014).

For patients, the highest potential for exposure is associated with nanotherapeutics, including nanomedicinal products and medical devices that contain or consist of free nanomaterials, which are actually intended to be administered in a way as to achieve maximum exposure. This is also true for contrast agents used in medical imaging procedures and for biomaterials such as bone fillers and dental materials. For the latter, it is important to note that most of the dental products containing nanomaterials have relatively low potential for release of free nanoparticles, and if there is release, the exposure route is estimated to be mostly through ingestion and a low potential for inhalation (FIDE, 2014).

In case of biomaterial applications where nanomaterials are present as coatings on the surface of implantable medical devices, exposure to the fixed coatings is maximal, while there is also the possibility of exposure to free nanomaterials due to the release from or loosening of the coating material. The level of exposure to the free nanomaterials is very much depending on the particular device and on any wear of the device. In addition, exposure to nanomaterials from implantable biomaterials/medical devices may also result from degradation or wear processes, even when no nanomaterials were used in the manufacture of the device.

A well-known example are wear particles from hip implants, some of which are in the nanoscale. In the case of scaffolds for regenerative medicine purposes, there is also maximum exposure intended to the material. In this case, the nano features are mostly surface topography or internal structures, not leading to exposure to free nanomaterials. Since these scaffolds are usually absorbable, a degradation and absorption process will most likely take place over time. Nanomaterials may result as intermediate products during this process, however, since this is only a temporary exposure, this generally should not be considered an issue.

Surgical instruments with nanotechnological features either embedded in a matrix or fixed on the surface in order to optimize cutting behaviour or wear resistance provide a low potential for exposure to free nanomaterials. Finally, *in vitro* diagnostic devices provide a negligible potential for exposure of patients to nanomaterials. See Table 6.2 for a summary of the estimated exposure potential in relation to the various categories of medical products.

Table 6.2 Potential for exposure of patients to free nanomaterials from medical products

Category	**Application**	**Estimated exposure potential**
Nanotherapeutics (incl.drug delivery)		
Drug delivery	Nanoformulation of drugs	High
	Nano-needle arrays	Low
Injectable devices	Nanoparticles used in hyperthermia/ thermoablation	High
Active[31] implantable medical devices	Pacemakers, hearing devices, retina implants	Low
Nanosilver component	Wound dressings	High
Regenerative medicine & biomaterials		
Biomaterials	Dental materials	Generally low, some medium
	Bone cements & fillers	High locally in the bone, medium to low systemically, depending on device
	Coatings on implants	Medium to low, depending on device
	Improved biomaterials	Medium to low, depending on device
	Implants subject to wear	Medium to low, depending on device
Nanosilver component	Bone cement, other biomaterials	High locally in the bone, medium to low systemically, depending on device
Regenerative medicine	Scaffolds mimicking	Low

[31] 'active' means that the device is relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity

Category	Application	Estimated exposure potential
	extracellular matrix	
Nanodiagnostics and Imaging		
In vivo imaging	Imaging equipment	Low
	Contrast agents	High
In vitro diagnostics	Lab-on-a-chip technology	Low
Medical Instruments		
Surgical & dental instruments	Scalpels, saws, burs and similar instruments	Low
Minimally invasive therapeutic & diagnostic instruments	Catheters, canula's for a range of applications	Low
Nanosilver component	Operation textile & gowns, catheters & other devices	Medium to low, depending on device

6.4 Hazards

Hazards related to nanomaterials used in nanomedical products are the same as hazards related to nanomaterials used in other types of products. See Chapter 3 for a description of nanomaterial hazards in general. Hazards related to nanomedicinal products that are different compared with other types of medicinal products are associated with the particulate character of the nanomedicinal product formulations. Likewise, for nanomedical devices, specific hazards are related to the possibility for the release of free (nano)particles.

Especially the toxicokinetic profile of nanoparticles is quite different from that of dissolved chemicals. Blood clearance generally appears quite quickly, unless the products were designed to stay in the blood circulation for an extended period of time (see paragraph 6.2.1). Therefore, blood levels (i.e. concentrations) are less important than the ultimate tissue and organ levels. In addition, consideration should be given to the potential for tissue accumulation and persistence of a nanomaterial (ISO, 2014; SCENIHR, 2014b).

Hazard evaluation for individual medicinal products and medical devices has to be performed on a case-by-case basis. For both product types, guidance documents are available to help designing the required toxicity testing strategy and performing the needed toxicity studies. It should be noted, however, that none of currently available test methods, both *in vitro* and *in vivo*, have been validated specifically for nanomaterials (EFSA, 2011; SCCS, 2012a; SCENIHR, 2014b).

When in contact with the biological environment, nanomaterials interact with proteins at quantitative and qualitative levels that are dictated by

the nature of the physiological environment (e.g., blood, plasma, cytoplasm, etc.) and nanomaterial characteristics. Similarly, when exposed to testing media, nanomaterials are expected to interact and/or interfere with the environment depending on their inherent nature and the conditions of exposure; they may then display different behavior from bulk corresponding materials (ISO, 2014).

There are several known pitfalls in toxicity testing of nanomaterials that should be avoided, and in the future more testing pitfalls may come to light. Although methods used for chemicals in bulk form can be adapted, for example specific attention should be given to the detection method. While knowledge on this and other pitfalls will keep evolving, some useful guidance is already available (EFSA, 2011; Crist et al., 2012; SCCS, 2012a; ISO, 2014; SCENIHR, 2014b).

Nanomedicinal products consist of a large variety of nanostructures with variable characteristics including size, shape, and chemical composition. In addition, many nanomedicines include as an integral component a non-covalently or covalently bound coating with different levels of complexity, which may have a great effect on their efficacy and safety (Ehmann et al., 2013a; EMA, 2013c). Also for nanomaterials used in and/or released from medical devices a large variety of properties can be expected.

Knowledge regarding "nanospecific" safety aspects of nanomedicinal products and nanomedical devices is still emerging. A complicating factor in this is the fact that it is often not easy to distinguish whether an observed adverse effect is due to the nano-formulation or to the active pharmaceutical ingredient. Distribution studies with various types of nanomaterials show that they are mostly taken up by cells of the mononuclear phagocytic system (MPS) as part of the immune system (ISO, 2014). Indeed, from literature, the most frequently reported side effect after injection of (liposomal) nanotherapeutic agents seems to be an acute hypersensitivity reaction, which may be caused by activation of the complement system and denoted by Szebeni (Szebeni, 2005a; Szebeni, 2005b) as complement activation-related pseudo-allergy (CARPA).

6.5 Risk Assessment

Risk assessment on a case-by-case basis is required for all medical products. Any nanospecific issues should be carefully considered and included in the overall risk assessment. Although the general principles of chemical risk assessment are considered applicable to nanomaterials (SCENIHR, 2009; Hristozov et al., 2012; OECD, 2012; Macphail and Grulke, 2013), they present some special challenges, including unique physicochemical properties, greater compositional uncertainty, changing properties in biological systems, exposure measurement difficulties, and appropriate dose metric decisions that may require specific guidance (ISO, 2014). The greatest challenges for medicinal products, as identified by regulatory risk assessors from the European Medicines Agency and international colleagues (Ehmann et al., 2013a), are associated with the novel, "next generation" nanomedicinal products, e.g. based on dendrimers or other complex, hybrid structures produced

by new manufacturing techniques. In contrast with first-generation nanomedicines, including liposomal formulations, iron-based preparations and drug nanocrystal technologies in oral dosage forms which have been established as safe and effective for many years, few data are available for these novel, complex products.

Additionally, challenges are foreseen for the generic versions of first generation products, e.g. based on liposomes or iron oxide nanoparticles, which have been indicated by the term "nanosimilars". Although data from the originator products may be used for the safety evaluation, such products must demonstrate equivalence in terms of quality, safety and efficacy before a market authorization can be granted. Given the degree of complexity of many nanomedicinal products, special scientific considerations may be needed to ensure this equivalence (Schellekens et al., 2011; Ehmann et al., 2013a).

Guidance on how to deal with the challenges in risk assessment of nanomedicinal products and nanomedical devices is under development (EMA, 2011; Ehmann et al., 2013a; EMA, 2013a, b, c, d; ISO, 2014; SCENIHR, 2014b).

6.6 Governance, Regulation & Standards

The regulatory systems for medicinal products and medical devices are different. Both systems contain requirements for quality and safety of the products. In their second regulatory review of nanomaterials of October 2012 (EC, 2012b), the European Commission takes the view that current legislation on medicinal products allows an appropriate risk/benefit analysis and risk management of nanomaterials. For legislation on medical devices, actions currently under consideration are included in a proposal published in 2012 (EC, 2012d). For purposes of joint knowledge building, improving regulatory science and international regulatory convergence, the EMA, the European Commission and the European Food Safety Authority (EFSA) have regular meetings with their international colleagues from Australia, Canada, Japan and the United States on application of nanotechnologies in the areas of medicinal products, medical devices, cosmetics and food (CLINAM, 2014). This kind of governance activities have been indicated as being important in the field of nanomedicine (Dorbeck-Jung, 2013). Equally important are other governance activities related to the application of nanotechnologies within the specific areas of medicinal products and medical devices, such as exchange of scientific knowledge in meetings and conferences, development of guidance documents, interpretation of the existing regulatory framework and the preparation of new requirements if necessary (Dorbeck-Jung, 2013). Such activities are described in the specific sections below.

6.6.1 *Nanomedicinal products*

The regulatory system for medicinal products is based on the provisions of Directive 2001/83/EC (EC, 2001a) that details the EU marketing authorisation system. This directive is supplemented with 13 Directives, 21 Commission Regulations and several legal reference documents. Specific rules govern medicinal products for paediatric use, orphan drugs, herbal medicinal products, blood products and advanced therapy

medicinal products. The legislation is supported by a series of Community guidelines published in 'The rules governing medicinal products in the European Union' which includes both regulatory and scientific guidelines (EC, 2014a, b).

The current regulatory framework for medicinal products has no specific provisions for nanomaterials. The European Medicines Agency (EMA) does, however, recognise nanotechnology as a topic in the area of medicines and emerging science on their website (EMA, 2014) . EMA has established an Ad Hoc Expert Group on Nanomedicines to support the Agency's activities with specialist input on new scientific knowledge and to contribute to the review of guidelines on nanomedicines. In 2010, the EMA organized a large international scientific workshop on nanomedicines, where some 200 European and international participants from 27 countries including Australia, Canada, India, Japan and the United States discussed the benefits and challenges arising from the application of nanotechnologies to medicines. Participants included representatives from patients' organisations, health care professionals' organisations, academia, regulatory authorities and pharmaceutical industry. The participants of the workshop shared experience, reviewed existing and emerging nanomedicines and discussed a number of specific aspects, including the characterisation, biodistribution and interactions of nanomedicines with biological systems, to identify gaps in scientific knowledge and to prepare for the evaluation of future nanomedicines (EMA, 2010).

Interesting to note is the EMA's view on the definition of nano. The European Commission has issued a Recommendation defining a nanomaterial as follows (EC, 2011): 'Nanomaterial' means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm–100 nm. EMA currently states on its website that 'nanotechnology is the use of tiny structures - less than 1,000 nanometres across - that are designed to have specific properties (EMA, 2014). The website introduces two major differences: a limit of 1,000 nm instead of 100 nm, and the additional qualification of 'designed to have specific properties'.

The EMA has also published 'Reflection Papers' on nanomedicine in general (EMA, 2006), for general issues related to surface coatings of nanomedicines (EMA, 2013c) and for specific product classes: liposomal products developed with reference to an innovator product (EMA, 2013d), nanosized colloidal iron-based preparations developed with reference to an innovator product (EMA, 2011, 2013a) and block copolymer micelles (EMA, 2013b). These reflection papers and the general perspective of European regulators on nanomedicines were discussed in a scientific paper by Ehmann (Ehmann et al., 2013a).

Legislation on medicinal products requires careful risk assessment and risk management on a case-by-case basis before products can be brought to the market. Even though the specific risks of nanomedicine products are not as yet fully known, they are to be thoroughly evaluated

in registration dossiers. The availability of alternatives and the clinical benefits of the products will also be taken into account in this process.

6.6.2 *Nanomedical devices*

Currently, procedures for market access of medical devices are set out in three Directives:

- Active Implantable Medical Devices Directive [90/385/EEC; EU, 1990]
- Medical Devices Directive [93/42/EEC; EU, 1993]
- In-Vitro Diagnostic Medical Devices Directive [98/79/EC; EU, 1998c]

These directives are supplemented by fifteen amending or implementing legislative documents (EC, 2014a). The legislation is supported by a series of (MEDDEV) guidelines, consensus statements and interpretative documents; also, there is an important role for 'harmonised standards' (EC, 2014a).

The current regulatory framework contains no specific provisions for nanomaterials. The European Commission does, however, recognise nanotechnology as a topic in the area of medical devices. The European Commission has installed the New & Emerging Technologies Working Group in medical Devices (NET WG) to ensure that they are kept abreast of innovations, specifically including application of nanotechnologies, in the development of medical devices (NET-WG, 2014). The 2007 report by the NET WG on medical devices manufactured utilising nanotechnology concluded that the regulatory framework was suitable for such products (NET-WG, 2007). However, the Working Group recommended introducing a classification placing nanoproducts in the highest risk class. The Working Group also recommended developing regulatory guidance because risks are partly new and not known to all stakeholders. Furthermore, the European Commission has asked its Scientific Committee for Emerging and Newly Identified Health Risks to develop an opinion providing guidance on the risk assessment of medical devices containing nanomaterials. The preliminary opinion was recently published for consultation (SCENIHR, 2014b). At international level, a working group has been created under the umbrella of the International Organisation for Standardisation (ISO/TC194/WG17) to develop a guidance document for biological evaluation of medical devices utilising nanomaterials. Such a document is also relevant within the European system. The first draft of the document was sent out for voting and comments recently (ISO, 2014).

Currently, a revision process of the regulatory framework is ongoing. The European Commission has published two proposals for revision of the medical devices legislation: a Proposal on medical devices (EC, 2012d) and a Proposal on *in vitro* diagnostic medical devices (EC, 2012c). These proposals include a definition of nanomaterial taken from Commission Recommendation 2011/969/EU on the definition of nanomaterial (EC, 2011) and provisions on the risk classification, the labeling and the instructions for use of medical devices containing nanomaterial. In addition, the general safety and performance requirements contain a specific requirement to design and manufacture medical devices in such a way as to reduce to a minimum the risks linked to the size and the properties of particles used. Special care shall

be applied when devices contain or consist of nanomaterials that can be released into the patient's or user's body. The risk classification influences the stringency of the conformity assessment procedure that is required to obtain a “CE-certificate”, which manufacturers need to be able to place a medical device on the market. The proposals are still under negotiation in Council and Parliament, and are thus subject to changes.
Legislation for medical devices requires that careful risk assessment and risk management is carried out on a case-by-case basis before products are brought onto the market. Even though the specific risks of nanomedical devices are not as yet fully known, they should be thoroughly evaluated in the technical documentation required by the directives. The availability of alternatives and the clinical benefits of the products are also be taken into account in this process.

7 Nanomaterials and Occupational Health Risks

7.1 Introduction

Nanotechnology is a still growing field of research and development, and more and more products are entering the market or are expected to enter the market at a relatively short term time scale. Within the field of nanotechnology, the use of nano-materials and nano-particulate matter is becoming increasingly common. Nanotechnology has a potential application in a wide range of industries. Therefore, more and more workers are potentially exposed to nanoparticles.

In this chapter we focus on recent developments within the area of occupational health and nanotechnology – and specifically nanoparticulate matter - since 2008 (Van Zijverden and Sips, 2009). We discuss these developments in the light of the current and future needs in occupational risk assessment and risk management. In the following we provide a description of the current state of the art following the basic risk assessment paradigm: the potential sources of nanoparticulates, aspects of hazard and exposure, risk assessment and risk management. For each item, the important developments are described and remaining gaps are discussed. With regard to future perspectives, advice is given with regard to priority setting for further research.

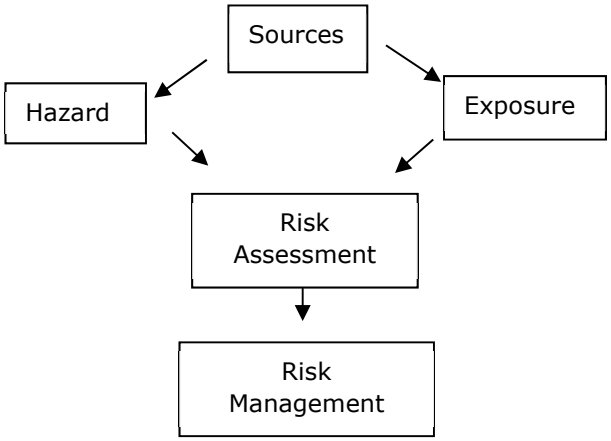

Figure 7.1 Risk Assessment Paradigm

7.2 Sources and applications

In summary, currently we have a generalized idea of the most important industries and branches that produce and/or use nanomaterials. However, nanotechnology and its potential applications are rapidly evolving, and at the moment there is still no comprehensive overview of all branches that produce and use nanomaterials. Similarly, a lack of clear labeling and a limited flow of nanoparticle-oriented information through the supply chain, leaves downstream users and workers ill-informed about the nano-character of the materials and substances they work with.

Applications and economic sectors
Nanomaterials are used for a large variety of applications (see Table 7.1). In order of largest use, they are used as a reinforcing agent (mainly carbon black) for tyres and other rubber goods, as fillers in polymers (synthetic amorphous silica, but also other metal oxides and silver), in electronics, cosmetics and biomedical applications. Nanomaterials are furthermore used in a wide range in paints and coatings, catalysts, solar and fuel cells, etc.(EC, 2012a)

Table 7.1 Use of engineered nanomaterials takes place in, amongst others, the following sectors.(Gressler and al, 2012; Leppänen et al., 2012; Schlagenhauf et al., 2012; Nowack et al., 2013; Schutz and Morris, 2013)

Sectors	**Applications**
Aerospace	lightweight materials, resistant paints, coatings
Automotive & Transport	scratch-resistant paints and coatings, lubricants, fluids, car-repair, tire production
Agrifood	sensors to optimise food production
Construction	insulation, stronger building materials (cement, coatings, isolation of noise and energy and fire distinguishing materials)
Energy generation & Storage	Photovoltaics, fuel cells and batteries
Environment	soil and groundwater remediation
Cosmetics	Sunscreens, tooth paste, face creams
Health, medicine and nanobiotechnology	targeted drug delivery
Information and communication technologies, electronics and photonics	semiconductor chips, new storage devices and displays
Plastics	Mechanical working of plastics (shaving, cutting, flexing, polishing)
Security	sensors to detect biological threats
Textiles	protective clothing, stronger, self-cleaning or fire resistant fibres

In the appendix, two figures are added that give an overview of the number of companies per sector in the Netherlands (Bekker et al., 2013). that produce or use nanomaterials,

Potential for exposure of workers
The engineered nanomaterials (ENM) which have the highest potential for exposure per sector are shown in Figure 7.2. Whether or not there is an EHS (environment, health and safety) impact, and how big the impact is, depends on the application, as well as on the specific ENM.

Hazard depends on both the type of application and on the type of ENM, whereas exposure depends mainly on the type of application (Nowack et al., 2013)

		Metal oxides									
	CNT	All oxides	TiO_2	ZnO	Fe-oxides	SiO_2	Metals (Ag, Au, Fe)	QD	Clays	Nanocomposites	Carbon-based (not CNT)
Agrifood	x	x	x	x		x	x	x	x	x	
Automotive	x	x								x	
Environment		x	x		x		x				
Security	x	x	x	x		x	x	x	x	x	x
Chemistry/Materials	x	x	x	x	x	x	x	x	x	x	x
Construction		x	x			x					
Energy	x	x	x	x		x		x			x
ICT	x	x		x		x		x			x
Textiles	x	x		x			x		x		
Health	x	x	x	x	x	x	x	x		x	x

CNT, Carbon nanotubes; QD, Quantum dots; ICT, Information and communication technologies.

Figure 7.2 nanomaterials identified as carrying highest potential for exposure per sector within 10 considered technology sectors (Nowack et al., 2013)

With regard to the presence and emission of nanoparticles a main distinction is made between engineered nanoparticles and process generated nanoparticles.

Engineered nanoparticle:
nanoparticle intentionally engineered and produced with specific properties.

***Process generated nanoparticle**:*
nanoparticle unintentionally released in a production process.

An important observation is that nanoparticles, so called Process Generated Nanoparticles (PGNP's), can be unintentionally released in a variety of production processes. PGNP's can be formed , e.g. by electrical instruments (engine-generated), by combustion and heating (combustion-derived) and can be released as a result of working and processing of nanomaterials (e.g. abrasion, sanding). With regard to the toxicity of PGNP's, as with engineered nanomaterials, this is strongly depending on the material characteristics like chemical composition, size, and other properties (SER, 2012).

7.3 Exposure

Size of potentially exposed population

In summary, only few studies have focused on the potentially exposed population. The current knowledge on the exposed worker population is still limited to qualitative assessments based on general surveys. Quantitative data of exposure levels (to engineered nanomaterials) is usually not available. Since nanotechnology develops very fast, this data is outdated very quickly. New surveys may present more accurate and up-to-date data with regard to potential exposure to nanoparticles in the worker population.

In 2008 Borm et al. conducted a survey with the main objective to draft an overview of the current state of the art with regard to nanomaterials in Dutch working environments (Borm et al., 2008). Borm found that 400 workers (1% of the research population) have a regular contact with engineered nanomaterials.
A survey conducted by Pronk et al. in 2011 (Pronk et al., 2011) elaborated on this result and found that an extra 3000 workers were potentially exposed to nanomaterials, which was based on an estimated market penetration of 1% (percentage of companies in the specific sector/branch that uses nanomaterials). In 2014 Cornelissen et al published a report focusing on the use of engineered nanomaterials in Dutch research institutions (Cornelissen et al., 2014). They estimate that in 2013 about 800 employees in these institutions work regularly with nanomaterials (equal to 1.6% of the total number of employees in this sector).

In other countries comparable surveys were conducted. A Swiss survey concludes that about 0.08% of the total worker-population is potentially directly exposed to nanomaterials (Schmid et al., 2010). In the Swiss chemical industry this percentage equals to about 0.5% of the workers.

Honnert et al. conducted a survey in two industrial branches in France and found that about 50% of the workers are potentially exposed to nanomaterials (Honnert and Grzebyk, 2014). Furthermore they detected a difference in potential exposure between producers of, and users of nanomaterials. Differences in exposure reduction measures between production facilities and user facilities are expected to cause this difference in exposure.

Potential moments of exposure

In summary, the highest risk of exposure to nanoparticles in workplaces is during production and the main route of exposure is by inhalation. Most research data with regard to exposure is focused on the inhalation route.

Occupational exposure to engineered nanomaterials can be roughly divided into two main settings: within industrial environments (production of nanomaterials and application in products) and within research environments (research and university laboratories). Generally, the highest risk of exposure to nanomaterials is to workers at the production stage. Nowack et al. investigated the potential moments of workers exposure to nanomaterials in the lifecycle of products that

contain nanomaterials (Nowack et al., 2013). The main pathways of potential exposure across all sectors were considered to be:

- Inhalation of powder, or aerosolised ENM during production and use;
- Dermal exposure to spills or dusts;
- Exposure following any degradation, abrasion or wear and tear;
- At disposal or recycling of the product if this allows release of ENM.

Exposure assessment methods
In summary, there are still many gaps that need to be filled for quantitative exposure assessment, amongst others; most workplace studies have focused on the emission of nanoparticles rather than on immission and they do not take into account the transformations of nanomaterials that may occur. Despite all uncertainties, there is an increase in workplace related exposure measurements. A general impression is that the existing data come from experimental setups rather than from practical situations and different dose metrics are used (a.o. mass, total particle number, particles per size-classes, surface area).

Recently published papers focus on exposure measurements of specific nanomaterials (metals, metaloxides like TiO2, CeO, carbon-based CNT/CNF and Silica) (Lee et al., 2011; RISS, 2011; Leppänen et al., 2012; Schutz and Morris, 2013). These specific materials are also extensively investigated by international research programs (OECD sponsorship programs a.o.) based on their industrial relevance and relatively large production volumes. Most current research is limited to potential exposure to engineered nanoparticles. More recently, in the Netherlands more attention is given to process generated nanomaterials (EU-OSHA, 2009; Broekhuizen et al., 2012).

Occupational exposure is less likely if nanomaterials are bound in a matrix or enclosed in equipment. However, in this bound state, exposure may still occur at the waste stage or during specific operations such as abrasion or machining of the matrix. The identification of the particles themselves (engineered vs process generated) is important for assessing exposure and health (Savolainen et al., 2013).

One important factor to characterize exposure is whether nanoparticles occur as free particles, in aggregates or agglomerates, bound in a matrix or enclosed in equipment. Often, nanoparticles aggregate or agglomerate, thereby changing their specific properties. Once inhaled, the aggregates/agglomerates may be released.

Several (combinations of) techniques are available for detecting specific properties of nanoparticles. However, since large knowledge gaps exist on the right dose metrics and toxicological relevance of these properties, it is currently not possible to establish one general protocol for all nano-focused risk assessments.

All exposure measurements that have been conducted so far have only focused on short term exposure to nanomaterials and were limited to stationary exposure (or even release) related measurements.

For a more accurate exposure assessment, a more person related exposure measurement should be developed and optimized, leading to reliable results that can be used in health studies and/or risk management. Some efforts have already been taken in this area; amongst others, scientists in Taiwan and the US have developed a mobile personal sampler that gives the possibility to measure nanoparticles in the breathing zone and distinguish between engineered and process generated particles within the laboratory (Tsai et al., 2012). The Japanese TASC (TASC, website) has described a method to analyse nanoparticles (carbon nanotubes) and makes a distinction between engineered and process generated nanoparticles (TASC, 2013).

At on national level (TNO, IVAM, Arbo-Unie) as well as international level (EU, OECD) measurement strategies are being developed rapidly. The development of exposure scenarios is needed for comparative assessments of processes and should be developed in a harmonized way. Within the NANOSH project (Brouwer et al., 2009) a harmonized approach was developed. There is an increasing need for harmonized measurement methods and techniques that can be translated into official guidances and norms (e.g. CEN of ISO).

7.4 Hazards

The main developments within the hazard area are not specific for occupational risk assessment. They will therefore be presented in another chapter in this document. Within the context of occupational health there are few studies that have focused on health effects due to exposure to nanomaterials. Song et al. (2009) aimed to examine the relationship between a group of workers with airway related symptomatic findings and their nanoparticle exposure (silica) (Song et al., 2009). Although no valid proof has been given with regard to health damage caused by nanosilica, nanoparticles were detected in the lungs of the patients. This might indicate that nanosilica has played a role in the development of these health effects.

7.5 Risk Assessment

In summary, in order to assess the risks of possible health effects of hazardous substances in workplaces, quantitative and qualitative assessment methods can be used. However, in the area of nanomaterials there is no consensus what testing strategies and methods of risk assessment can be applied. Mainly due to a lack of hazard and exposure data, it is generally acknowledged that for most nanomaterials quantitative risk assessment will be impossible at the short and mid-term time scale. To overcome the time needed to fill these gaps, alternative qualitative risk assessment approaches are being developed (a.o. control banding techniques), that can be used in risk and safety management.

Exposure to nanomaterials may take place along several routes; via airways, gastro-intestinal tract or skin. For the worker population inhalation is generally seen as the dominant exposure route. Next to health effects, nanomaterials (powder) may have self-igniting (pyroforic) properties because of the large surface-mass index and the

corresponding reactivity TU Delft has developed some practical guidelines on this (TNW, 2008).

7.5.1 *Quantitative Risk Assessment*

Quantitative Risk Assessment
Quantitative exposure data should be compared to an existing health based limit value for the specific nanomaterial. These limit values are set using scientific toxicity data. If the actual exposure of workers is lower than the health based limit, no adverse health effects are expected for workers. If exposure is higher than the limit value, possible health effects cannot be excluded.

Occupational Exposure Limits
Occupational Exposure Limits (OELs) help to control exposure to dangerous substances in the workplace, by setting the maximum amount of (air) concentration of a substance that can safely be allowed. OELs are set by competent national authorities and other relevant institutions, but also by industry. OELs can be binding (meaning that they must be met), or indicative (giving an idea of what should be achieved), and they can apply both to marketed products and to waste and by-products resulting from production processes.

The quantitative risk assessment principle is assumed valid but not yet applicable for nanoparticles, due to the lack of limit values and exposure data, which in turn traces back to more fundamental knowledge gaps. Therefore, no binding regulatory limit values have been derived, and are not expected to be derived on the short and medium term. For a few nano-substances indicative limit values were derived (Table 7.1)

Table 7.2 Nano-related limit values for occupational exposure

	Type	**Value (unit)**	**Source**	**Status**
TiO2 (nano)	REL	0,3 mg/m3	NIOSH (US)	Recommended
CNF/CNT	REL	0,001 mg/m3	NIOSH (US, 2013)	Recommended
TiO2		1,2 mg/m3	NEDO	private
CNT	DNEL	0,007-0,020 mg/m3	ENRHES (EC2010)	
MWCNT [baytubes]	OEL	0,050 mg/m3	Bayer (Germany)	private
MWCNT [nanocyl]	OEL	0,0025 mg/m3	Nanocyl (Belgium)	private

TRGS=Technische Regel für Gefahrstoffe 900 (Arbeitsplatzgrenzwerte); REL=Recommended Exposure Limit; DNEL=Derived No-Effect Level; OEL=Occupational Exposure Limit.

Private OELs, set by industry, are not always publicly available because of intellectual property rights.

Categorical limit values
Once no individual limit values are present, so called reference values can be determined for groups of nanomaterials by categorizing the nanomaterial in one of several classes using some specific properties, amongst others biopersistence and density. They represent pragmatic guidance levels, but are not health based.

The Dutch Trade unions (FNV and CNV) and the Confederation of Netherlands Industry and Employers (VNO-NCW) commissioned a pilot project involving a feasibility study on the practical application of provisional nano reference values. This project was carried out by research agency IVAM, the University of Twente and IndusTox Consult (van Broekhuizen, 2011).

Provisional Nano Reference Values are based on a generic approach in which a limit value for each different type of nanomaterials is set. They can be used as temporary pragmatic benchmark levels, but should not be regarded as safe health based occupational exposure limits. When sufficient data are available, the use of health based occupational exposure limits is preferred.

Next to the Dutch Nano Reference Values, British Standard Institute (UK) and the German Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA) have also established categorical limit values. In table 7.3 an overview is given of these reference values.

Table 7.3 Proposed workplace exposure limits for different ENPs (all data refer to concentration per cubic metre, when not otherwise specified)(Pietroiusti and Magrini, 2014).

ENPs	BSI (UK)	IFA (Germany)	DMSAE (The Netherlands)	NIOSH (USA)	SWA (Australia)	AIST (Japan)	KML (Korea)
Fibre-like ENPs							
Rigid, biopersistent CNTs	10^4 f	10^4 f	10^4 f	0.007 mg	10^5 f	0.03 mg	
Fibre-like metal oxides	10^4 f				10^5 f		
CNTs with explicitly excluded asbestos-like effects		4×10^7 p	4×10^7 p				
Biopersistent granular ENPs with a density <6000 kg/m³							
Titanium dioxide	0.066× WEL*	4×10^7 p	4×10^7 p	0.3 mg	0.03× Australian inhalable or 0.1× Australian respirable WEL	0.61 mg	
Carbon black	0.066× WEL* or 2×10^7 p	4×10^7 p	4×10^7 p		3 mg		3.5 mg
Silica	0.066× WEL* or 2×10^7 p	4×10^7 p	4×10^7 p		2 mg (fumed silica)		
Fullerene	0.066× WEL* or 2×10^7 p	4×10^7 p	4×10^7 p		0.03× Australian inhalable or 0.1× Australian respirable WEL	0.39 mg	
Zinc oxide, aluminium oxide, dendrimers, polystyrene, nanoclay	0.066× WEL* or 2×10^7 p	4×10^7 p	4×10^7 p		0.03× Australian inhalable or 0.1× Australian respirable WEL		
Biopersistent granular ENPs with a density >6000 kg/m³							
Cerium oxide, gold, iron, iron oxide, silver, cobalt, lanthane, lead, antimony oxide, tin oxide	0.066× WEL* or 2×10^7 p	2×10^7 p	2×10^7 p		0.03× Australian inhalable or 0.1× Australian respirable WEL		
Insoluble ENPs for which WEL* is not available					0.3 mg		
CMAR ENPs							
Nickel, cadmium containing quantum dots, chromium VI	0.1× WEL*	2×10^7 p	2×10^7 p		0.1× WEL*		
Beryllium, arsenic, zinc chromate	0.1× WEL*	4×10^7 p	4×10^7 p		0.1× WEL*		
CMAR ENPs for which WEL* is not available					0.003 mg		
Liquid and soluble ENPs							
Fat, hydrocarbons, syloxane		Same WEL*	Same WEL*				
Sodium chloride	0.5× WEL*	Same WEL*	Same WEL*		0.5× WEL*		
Other soluble ENPs	0.5× WEL*	Same WEL*	Same WEL*		0.5× WEL*		
Soluble ENPs for which WEL* is not available					1.5 mg		

f, fibres; p, particles; WEL*, work exposure limit of coarse material.

Alternative approaches

In 2012, during a meeting in Washington (US), the participants agreed on the fact that waiting for more and enough data to set regulatory limit values, is no option (Gordon et al., 2014). Some alternative methods have been presented, among which the setting of pragmatic or temporary limit values. Several of the approaches discussed at the workshop may be appropriate depending on the specific properties of the nanomaterial, the types of toxicity data available, whether an OEL exists for the larger material, whether the OEL is intended to be a non-regulatory provisional value or a regulatory limit, and other considerations.

7.5.2 *Qualitative Risk Assessment*

During the past years several guidances and instruments have been developed to help in the qualitative assessment of possible risks of nanomaterials in workplaces. Although there remain many uncertainties with regard to the possible risks of nanomaterials, some clues are available with regard to the exposure and hazardous potential of

nanomaterials. Performing risk assessment on the use of materials with limited knowledge on the potential hazards and lack of quantitative exposure data can be performed by methods like Control Banding, which is a concept combining a qualitative evaluation of the hazard posed by the nanoparticle with an estimate of the probability of workers exposure. Thus chemical substances and exposure to them are grouped in categories of toxicity (hazard bands) and exposure (exposure bands).

Control Banding: Control banding has been developed as a pragmatic tool to manage the risk resulting from exposure to a wide variety of potentially hazardous substances in the absence of firm toxicological and exposure information (Brouwer, 2012).

In appendix 5, table 1, an overview of guidances has been listed. In 2012, Vervoort (Vervoort, 2012) documented the worldwide availability of 32 nano risk assessment tools. The risk level outcome referring to one specific process can deviate considerably for each tool. These differences can be clarified by the following facts: the use of various criteria and, differences in criteria interpretation,and whether or not risk reducing measures are taken into account during risk assessment. This illustrates the need for standardization of risk assessment.

Summarizing the needs in the area of risk assessment:

- Need for standardised limit and reference values and methods or strategies to set these values. So far there are only a few health based limit values for nanomaterials
- Need for more nanospecific hazard data
- Need for harmonised and standardized risk assessment tools (a.o. control banding based)
- Future research on further development and harmonization of methods and strategies for risk assessment and/or OEL's.

7.6 Risk Management

In summary, during the past few years, within the area of risk management, the number of guidances has grown notably. Next to this increase, the research on the efficacy of risk reduction measures has also grown. Last but not least, efforts have been undertaken to setup and improve risk communication.

Prevention of occupational risks is the employer's responsibility. Due to the current missing information and knowledge gaps, employers as well as employees have an urgent need for risk management guidances and measures to avoid exposure within the area of uncertain risks of nanomaterials.

The control banding approach can be applied at workplaces to assess exposure in case of missing occupational limits or missing exposure data. A further instrument of risk management is the Material Safety Data Sheet[32]. The German VCI issued guidance on submitting

[32] A Material Safety Data Sheet (MSDS) is a document that contains information on the potential hazards (health, fire, reactivity and environmental) and how to work safely with the chemical product

information along the supply chain of nanoscale products (VCI, 2008). ECHA has developed a (not nano specific) guidance that aims to explain in simple terms the obligations which downsteam users have to fulfil to comply with the REACH Regulation.

7.6.1 *Guidances*

In the past few years many risk management guidances have been developed worldwide. As the body of knowledge is rapidly growing, the information is continuously updated. Different approaches and reference values are being used in different countries in Europe, Therefore, there is a growing need for harmonization in approaches. In appendix 5, table 2 an actual list of guidances is presented.

7.6.2 *Risk Reduction Measures*

There is a variety of possible risk management measures to avoid exposure at the workplace. Due to the uncertain risks of exposure to nanomaterials the precautionary principle (EC, 2000a) is used by policy makers to justify decisions in these situations thereby avoiding the rejection of certain risk management measures by employers based on this uncertainty.

In situations where exposure is a realistic scenario, in Europe, the hierarchy of control measures as provided by directive 98/24/EC on the protection of health and safety of workers gives priority to reduction of the risk at the source. Directive 2004/37/EC provides more stringent measures related to exposure to carcinogens or mutagens at work; process control, local ventilation and control measures, organizational measures and, as last resort, personal protective equipment (EC, 2012a).

In case of personal protection equipment (ppe), knowledge of the ppe type and its efficacy with regard to nanoparticles has increased. The most recent information focuses on the efficacy of respiratory protection (Vo and Zhuang, 2013) (NIOSH-US) and penetration potential of nanoparticles through gloves (Dolez and al, 2013). At this moment, however, there is still limited knowledge on the efficacy of risk reducing measures.

"Safe by Design" is a preventive conceptual method within the context of risk reduction. Safe by Design is the integration of hazard identification and risk assessment methods early in the design process of nanomaterials to eliminate or minimise the safety and health risks throughout the lifecycle of nanomaterials.
A safe design approach begins in the conceptual and planning phases with an emphasis on making choices about design, materials used and methods of manufacture or usage to enhance the safety of the finished product. The designer needs to consider how safety can best be achieved in each of the lifecycle phases[33].

[33] http://www.hse.gov.uk/construction/cdm/safety-by-design.pdf

7.6.3 *Medical Surveillance*

Some countries have investigated the value and use of health registration systems and thereby providing a database that might be useful if a correlation between health and exposure is actually established on the long term.

Epidemiological studies and findings of occupational medicine offer insights into effects on workers who are exposed to nanomaterials. Schulte et al discussed the role of occupational medicine as a tool to limit adverse health effects of nanomaterials (Schulte et al., 2008). Schulte concludes that first priority should be to implement appropriate primary preventive measures. Additional efforts to monitor workers' health may be warranted. Continued research is needed, and the collection of such information for exposure registries may be useful for future epidemiologic studies.

The French institute for Health surveillance (InVS) has recommended the implementation of an epidemiological surveillance system for workers who are exposed to nanomaterials (Boutou-Kempf, 2011). The Health Council in the Netherlands has recommended the installation of an exposure registration system and the integration of this system with existing health registration system within industries that work with nanomaterials (Health Council of the Netherlands, 2012). Since the worker population in the nanotechnology area is relatively small, Riediker et al. have recommended the pooling of international cohorts (Riediker et al., 2012). A valid registration relies on the usefulness of a valid characterization of exposure. The practical set up of an exposure registration system will therefore be a challenging task.

7.6.4 *Risk Communication*

There is an urgent need to increase awareness of the potential risks of exposed workers in the area of nanotechnology. Efforts in this area have been focusing on increasing the availability of information with regard to the presence of nanomaterials. Next to that the information exchange to small and medium-sized enterprises (SME's) with regard to the safer use of nanomaterials has become more extensive and specific.

The European Risk Observatory has reviewed existing literature focusing on risk perception and communication with regard to nanomaterials in the workplace (Brun, 2012). Following risk management, effective worker protection requires awareness within the workplace that nanomaterials are being handled. This is clear at facilities where the materials are manufactured. However, organisations lower in the supply chains may not always be fully aware of the different components of materials that are being handled. Workers of these organisations and facilities may consequently be at risk of exposure to nanomaterials.

In the Netherlands in 2011, the Labour Inspectorate has inspected 43 institutions that work with nanomaterials. The inspections showed that some companies are unaware they are using nanomaterials. This is partly due to the lack of information provided by the suppliers of these companies (Arbeidsinspectie, 2011).

Increasing awareness of workers and employers within the field of nanotechnology is one of the major goals of nano-communication. Several countries and institutes have contributed to this goal during the last couple of years. Some examples of these contributions are: the development of guidelines that focus on safe handling of nanomaterials, the improvement of (guidance on) Material Safety Data Sheets and the development of training modules (NIOSH-US) (Kulinowski and Lippy, 2011)and the development of a guideline that focuses on the self-management of nanomaterials by workers themselves (Institute of Occupational Health in Taiwan).

7.7 Legislation

The Occupational Safety and Health Framework is internationally a nation-specific framework with different approaches to legislation, regulation and enforcement. Within the European Framework of Worker Legislation, the Framework Directive for Occupational Safety and Health (EEC, 1989) and the daughter Chemical Agents Directive (CAD, EC, 1998) set the obligations for employers to ensure safe use of chemicals at the workplace. Nanomaterials are not specifically mentioned but implicitly included. In addition, REACH (EC, 2006) provides the legal framework for generating the information needed on the hazards, exposure of workers and safety assessment for the majority of chemicals (including nanomaterials). Adaptation of REACH will be beneficial for worker protection as well.

At present, there are discussions on how to regulate nanomaterials at the European level. Based on these discussions, the RIVM has identified a number of building blocks for such legislation. With regard to the CAD and REACH a number of adaptation proposals were defined (Bleeker et al., 2013). In chapter 2 of this document a more detailed review of the gaps and future perspectives in this legislation area is described.

8 Nanomaterials and the environment

8.1 Introduction

Nanoparticles occur naturally in all environmental compartments (e.g. in volcanic ash and ocean spray) and have contributed to the evolution of natural ecosystems. Humans have also adapted to the presence of natural nanoparticles in their habitats, albeit that the adaptation is not complete. Especially in the event of disasters and prolonged exposure – the most extreme examples being volcanic eruptions and smog episodes during which large as well as small particles cause problems – the exposure to particles is too high for adaptation.

A feature of recent decades has been technological developments resulting in almost exponential growth in the production of engineered nanoparticles, possibly resulting in an exponential increase in the amount of these particles in the environment. Engineered particles have in common that they are produced with a particular purpose in mind, and for this reason they have specific properties. The main source of concern about the environmental risks posed by engineered nanoparticles relates to the issue of whether these specific properties cause specific interactions within an ecosystem, and hence specific effects on parts of the system, in such a way that the impact is different from that of conventional substances. From an environmental standpoint, the question is whether the variation in chemical composition and the increased variation in types of nanoparticles resulting from their introduction into the environment, enlarge the effects on the ecosystem concerned. To answer this question, it is necessary to qualify and quantify the risks arising from the emission of engineered nanoparticles in relation to the chain of "emission -> distribution in the environment -> exposure -> impact".

8.2 Sources of nanoparticles and applications

The variety among engineered nanoparticles is steadily increasing, accompanied by the expectation that the number of applications will grow even further[34]. In line with the increase in applications and in the volumes of nanoparticles produced, the number of sources and emissions in absolute terms will also steadily grow. In principle, emissions into the environment can occur throughout the entire life cycle of a product containing nanoparticles, including during the waste phase (Wiesner and Plata, 2012).

The level of emissions varies from product to product, possibly fluctuating strongly in the course of the life cycle. This point can be explained by the following:

[34] The global investment in nanotechnology from all public sources for 2008 exceeded $7 billion (Lux Research Inc (2009). Nanomaterials of the Market Q1 2009. Cleantech's Dollar Investments, Penny Returns), whereas the market size for nanotechnology is expected to grow to over $3 trillion by 2015 (National Science Foundation: see Red Herring (2001): 'The Biotech Boom: the view from here').

1. In the case of advanced, tailor-made engineered nanoparticles, manufacturers and users alike will often do their utmost to minimise emissions during the production and use phases of the product and/or nanoparticles. Emission of nanoparticles usually occurs only in the waste phase, which is often also controlled. Some examples from this category are particles used in energy extraction and energy storage, and water treatment. In most cases, these applications involve relatively expensive nanoparticles.
2. In the case of particles primarily intended for single use, the emissions into the environment are often substantial during the use phase. Some examples are particles in sunscreens, particles used as crop-protection agents (in the controlled output of pesticides), particles present in personal care products, and free particles such as nanosilver in textiles and in medical products such as wound dressings (Rezi, 2011; Walser et al., 2011).
3. For particles employed non-specifically in the manufacture of sustainable products, emissions occur mainly during the use and waste phases. Although these widely varying emissions can be substantial in a quantitative sense, they are significantly smaller in comparison with the emissions due to nanoparticles in for instance sunscreens.
4. Apart from the above product-related sources, there are process-related sources. Depending on the emission-reducing measures implemented, these sources might emit particles in all stages of production, processing and storage, as well as during the waste phase. Nanoparticles could also be formed during the processing of waste, something that occurs if incineration is not fully effective. Moreover in this case, hydrophobic organic contaminants such as polycyclic aromatic compounds (PACs) and dioxins are not entirely eliminated from the waste gases, owing to sorption to the nanoparticles (Verejano et al., 2013).

For the risks associated with emitted nanoparticles, also the emission route together with the behaviour of particles in the environment is of importance:

1. Particles released into the air will often be transported to all other environmental compartments (By analogy with fine particles in air, there is in this case the option of potentially direct effects of air-borne particles on for instance birds);
2. Particles emitted directly into the soil will usually pose no risks for other environmental compartments, unless leaching, run off, rinsing or dispersion occurs;
3. Particles entering the environment via a waste water treatment plant will only create risks for the microbial processes taking place in the plant itself, for the receiving surface water and associated sediment, and indirectly for seas, oceans and the marine ecosystem; sewage sludge may be used as fertilizer and may subsequently create terrestrial risk
4. Particles emitted directly into water will only create risks for water and sediment.

The foregoing means that, apart from quantitative information on the emissions of nanoparticles during their life cycles, it is also necessary to know the fate of the particles following release.

Currently, there is no reliable method for quantifying nanoparticle emissions. In the case of conventional substances, emission factors can be calculated based on the production process and the usage scenario for a particular substance. A comparable method for nanoparticle emissions into the environment is still lacking for two reasons: the products in which nanoparticles are applied are not sufficiently identified, and the processes involving nanoparticles are not sufficiently documented. It is known in a general sense that the maximum emissions occur during a product's use and waste phases. The emissions for each application are still in need of quantification, however.

8.3 Determining exposure

In summary, owing to the lack of analytical methods specifically designed for nanoparticles, it is virtually impossible to determine the exposure of ecosystems to nanoparticles. Despite this drawback, exposure models have been developed that, based on laboratory data, provide an initial estimate of the principal exposure processes and the expected concentrations of nanoparticles in the environment. Most of the information available is for the nanoparticles that have been studied the most: nanoparticles of metals such as Ag, Cu and Zn, carbon nanotubes, fullerenes.
Current research into modelling the diffusion of nanoparticles in the environment focuses either on developing specific analytical methods for the above-mentioned nanoparticles, or on improving and quantifying the process for deriving exposure estimates. In broad terms, the main processes that are decisive for the exposure of organisms to nanoparticles have been identified. However, there are still insufficient basic data to quantify the various processes.

To determine the exposure of organisms in ecosystems to nanoparticles, the ideal requirement is to have measurements on the occurrence of engineered nanoparticles in the various environmental compartments. Although considerable effort is expended on developing methods specifically for nanoparticle analysis, almost no measurement methods yet exist specifically for engineered nanoparticles in the environment. There are actually three basic problems:

- Isolating nanoparticles from the "soup" of natural and engineered particles found in each environmental compartment (the least problematic being the air compartment).
- Distinguishing between natural and engineered nanoparticles.
- Analysing small nanoparticles (smaller than about 30 to 40 nm).

After nanoparticles have been emitted, they diffuse within and among the various environmental compartments. The result of this diffusion will be a specific concentration to which organisms are exposed. Given the typical properties of nanoparticles, the vast majority of them are likely to settle finally in the soil and in sediment. Unless the particles break down, they will form aggregations in these compartments. The process of aggregations does not rule out that, after emission, exposure will occur in the water and air compartments of the environment. Although this exposure cannot be quantified at present, the processes that determine the fate and effective exposure of nanoparticles are certainly known.

To illustrate the point, Figure 8.1 presents a diagram of the relevant diffusion and conversion processes that nano-iron oxide undergoes following its release into the aquatic environment. Praetorius (Praetorius et al., 2012) carried out a systematic study to identify the key processes for the diffusion of TiO_2 in the Rhine. These processes were then incorporated in a fate model specifically for the river Rhine. Owing to the lack of measurement methods, it is not yet possible to validate the model.

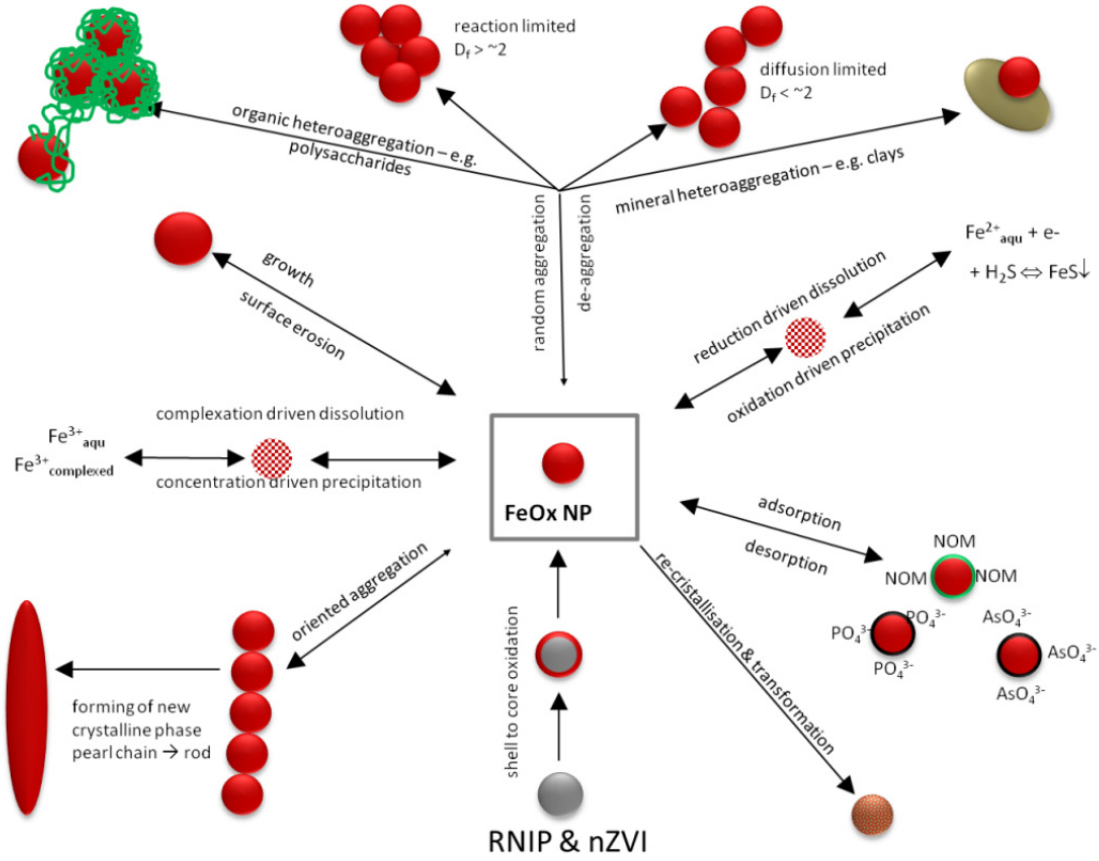

Figure 8.1 Diagram of the typical conversion and diffusion processes that nano-iron oxide undergoes following its release into surface water (RNIP = Reactive Nanoscale Iron Particles, nZVI = nano zero valent iron). Source: (Peijnenburg et al., 2014).

Figure 8.1 typifies our knowledge about the exposure to nanoparticles in the environment, showing that the main processes are known in broad terms, but there are insufficient basic data to quantify all the processes individually:

1. In principle, nanoparticles are insoluble in water and aggregate in aqueous media. However, solid nanoparticles that do dissolve in water lose their particle characteristics and then behave in water like 'conventional' soluble substances.
2. Clusters of particles will precipitate, the rate of precipitation increasing as they become larger. Following precipitation, organisms

that live in sediment can become exposed to these clusters of particles.
3. Individual nanoparticles can also react with other components in surface water, such as dissolved carbon, which is present everywhere. This causes the particles to stabilise, resulting in exposure of water-borne organisms. For a given particle and for surface water of known composition, it is not yet possible to quantify the degree of aggregation.
4. Particles released into the air will end up in water and soil through the effect of deposition. Although there is literature describing precipitation as, amongst others, a function of the concentration of nanoparticles, in general little is known about the deposition rate of nanoparticles in the air.
5. Nanoparticles entering the soil because of deposition or direct emission will usually remain there. Leaching or run off into ground and surface water is also possible, and the particles may be degraded. For these processes, too, there is a lack of quantitative information.

As a final remark on exposure to nanoparticles, it is to be noted that nanoparticles can also adsorb pollutants from the environment. As a result of this specific adsorption process, the exposure of organisms to these adsorbed pollutants (and hence their risks increases in the presence of nanoparticles. This is referred to as the Trojan Horse effect of nanoparticles (Choi and et al, 2007).

8.4 Hazards

In summary, the available (laboratory) observations indicate that environmental impacts of engineered nanoparticles cannot be ruled out (Khin et al., 2012; Vandevoort and Y., 2012; Manzo et al., 2013). In parallel with the growing interest in nanoparticles, information on their effects on humans and the environment is increasing rapidly as well. Most of the available information concerns the water compartment. Virtually no information exists on the hazards of nanoparticles in soils and sediments. The diversity of impact data makes it impossible to form a consistent opinion on the hazards of specific nanomaterials. Exploratory studies indicate that, of the most investigated nanoparticles, nanosilver is at present the most likely source of a threat to the environment. There is increasing attention to the hazards of transformation products, which are formed after the introduction of a nanomaterial into the environment. This, too, concerns silver, as well as complex nanoparticles that can break down into different toxic components. As part of the 7th Framework Programme, the EU is coordinating focused research into the hazards presented by a wide range of nanoparticles.

A bottleneck in determining a common feature of the bulk of the available data is the lack of systematically generated impact data. The limited data that are available:

- apply to a range of test organisms;
- apply to a wide variety of endpoints;
- are often the outcome of non-standardized protocols, including sample preparation;

- apply to a range of non-identical/non-comparable nanoparticles (as regards type, chemical composition, applied coating, presence or absence of stabilisers, etc.);
- apply to nanoparticles not fully characterized;
- apply to doses far beyond realistic exposure amounts.

Although ecotoxicology focuses on the protection of the ecosystem by utilising data for different organisms, a relatively large volume of data has been collected on the antimicrobial impact of nanosilver, partly due to the release of silver ions. From an environmental perspective, one reason for doing this resulted from model calculations that did not exclude the possible effects of nanosilver following its initial use in water treatment plants (Johnson et al., 2011).

In a general sense, the available data enable a rough estimate to be made of the impact of these nanoparticles, based on their chemical composition. What emerges in practice, however, is that the wide variety of additions to the basic material and the wide range of coatings applied often constitute a larger factor for the toxicity of specific particles than the primary chemical composition does. As things stand, it is also not yet possible to apply accepted alternative estimation methods for conventional substances to nanoparticles. To give some examples: QSARs (quantitative structure-activity relationships); the use of *in vitro* data to generate *in vivo* information; and read-across methods that utilise information on nearly identical substances or particles as a guideline for estimating the impact and/or behaviour of a particular substance or particle for which no or virtually no experimental data are available. The concept of nanoparticle dosimetry also needs further development, to find the best way of expressing their effective toxic dose. In this context, sufficient data show that the common dose expression of mass for conventional substances is not valid for nanoparticles (Oberdörster et al., 2007). A further limitation is that the scant information available on the effects of nanoparticles is only valid for the water compartment. As regards soil and sediment, there are almost no data at all on the hazards of nanomaterials (Waalewijn-Kool, 2013).

Despite these limitations, the following general principles are known:

1. Small particles are usually more toxic than large particles;
2. Small organisms are usually more sensitive than large organisms;
3. The composition of the environment affects toxicity. For example particles that are stabilised in the aquatic environment through the action of organic carbon and hence remain in the water for a longer period of time, are potentially more toxic for water-borne organisms than particles that are not stabilised and precipitate almost immediately (Park et al., 2013; Quik, 2013).

Of the nanomaterials identified thus far, the hazards are generally assumed to be the greatest for nanosilver. However (as stated above), added functionality can modify the toxicity of a nanoparticle. This means that some functionalised nanosilver particles are less toxic than their pristine (non-functionalised) counterparts. For the same reason,

depending on the composition of the applied coating, other functionalised nanosilver particles are more toxic.

A trend is currently discernible of increased attention being directed towards the hazards of nanoparticles resulting from their breakdown following the emission into the environment. This concerns not only nanosilver (release of toxic silver ions), but also quantum dots (formation of toxic metal ions such as Ga and Cd) and nano structures of greater complexity (formation of nano structures that can enter into complex interactions with biota). A large part of the research in question is being coordinated by the EU under the 7th Framework Programme.

8.5 Risk assessment

In principle, the paradigm of risk assessment in which the risks are stated to be proportional to the degree in which the exposure level of an environmental contaminant exceeds the effect level, also applies to nanoparticles.

Accordingly, risk assessment in the case of nanoparticles needs to focus on determining or predicting the effective exposure levels and the impact levels. The considerations expressed in the preceding paragraphs determining the exposure and impact due to nanoparticles, underline the fact that it is currently not possible to quantify the risks ensuing from the presence of nanomaterials in the environment. At best, qualification of risks is possible.

Within the framework of REACH, only a small number of nanomaterials has been registered for which a hazard or risk assessment should have been performed (see chapter 2). Detailed questions on the physical-chemical properties and some of the hazardous properties of e.g. silica in nano form, nanosilver and TiO_2 are being prepared within REACH. An initial risk analysis under the NANOFATE project (www.nanofate.eu) concerning metallic nanoparticles showed that the ration between exposure and impact levels for nanozinc oxide are so small that risks attributable to nanozinc are unlikely to arise in European waters. Taking the same approach regarding nanosilver, the emergence of undesirable effects could not be ruled out. Although the risk assessment in neither case conformed to the REACH specifications, the results are indicative for the nanoparticles that will currently present the greatest risk.

A major bottleneck for the risk assessment is the lack of guidance for assessing the risks specifically associated with nanosized materials. It is worth mentioning that such a bottleneck is not unique to an environmental risk assessment for nanoparticles, but also occurs in connection with food and health & safety. With the creation of an EU definition for nanomaterials, the first step has been taken to producing the above-mentioned guidance (see chapter 2) (EC, 2011). For the time being, the aforementioned bottlenecks stand in the way of further steps. By means of directed actions within the OECD Working Party on Manufactured Nanomaterials (WPMN), the development of test guidelines specifically for nanomaterials is being carried out. These guidelines can underpin the collection of basic data needed for future risk assessments. In addition, ongoing projects under the EU's KP7

research program and pending HORIZON2020 projects are engaged in developing guidance specifically for assessing the risks of nanomaterials. These projects not only consider the integration of information on exposure and hazards, but also include the development of alternatives to experimental testing.

8.6 Risk management

As concluded above, the risks that nanoparticles pose cannot be identified 'in the field' at this point. Risk management is confined to the accepted risk-limiting activities from a precautionary point of view (such as preventing, monitoring and reducing emissions, and preventing or reducing diffusion and exposure). Of importance in this context is the increased interest in defining the concept of safer-by-design for nanoparticles. Within this concept, two approaches are underway. The first is to focus on the development of particles that are expected to present lower risks for the environment. The second is minimising unnecessary industrial investment in the development of high-risk particles.

As regards legislation (see chapter 2), REACH is in principle the most important European instrument for assessing the risks posed by nanoparticles in the environment. However, the production volumes of most nanoparticles are below the tonnages set within the REACH framework as triggers for conducting an environmental risk analysis. However, such an analysis can still be initiated if there are concerns about aspects other than tonnage level. An evaluation of the nano forms of silica is currently underway, with the emphasis on physical-chemical properties and the human exposure. For nanosilver, an evaluation is in preparation, with environmental aspects being at the forefront of concern.

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Annex A: additional information on occupational safety and health

Figure A1: Overview of the identified sectors, exposure scenarios, and number of workers potentially exposed to MNM during the production of MNM-enabled end products in the Netherlands (Bekker et al., 2013)

Sector	Functionality	Exposure situation	Market penetration (%)	Average number of companies per sector	Average number of potentially exposed workers per company	Number potentially exposed workers
Production of wet concrete	Fumed silica for strength	Mechanical mixing of nanoconcentrates and nanocomposites (powder and liquid) with relatively low energy levels	10	190	8	152
Production of cosmetics	TiO_2 and ZnO for UV absorption		Not applicable	Not applicable	4	12*a*
Paint production	TiO_2 for absorption of pollutants		20	112	1.7	37
Paper production	Nano cellulose for strength and durability	Not available	1	29	2	1
Plastics/synthetics production	Nanoclay or nanosilica for strength and durability, Ag for antibacterial effect, ZrO_2 in scratch-resistant coating	Mechanical mixing of nanoconcentrates (powder and granules) with relatively low energy levels Manual application of liquid MNM-enabled end products	1	878	6.3	56
Tire production	Carbon black as filler and nanosilica for strength and durability	Mechanical mixing of nanoconcentrates (powder) with relatively low energy levels	100	150	1	
Toner production	Rheological properties	Not applicable	Not applicable	Not applicable	Not applicable	90*b*
Total						498

[a]Total number of companies working with MNM-enabled end products attained from cosmetic production sector organization = three companies.
[b]Number of workers potentially exposed to MNM adopted from Borm *et al.*, 2008.

Figure A2: Overview of the identified sectors, exposure scenarios, and number of workers potentially exposed to MNM during the professional application of MNM-enabled end products in the Netherlands (Bekker et al., 2013).

Sector	Functionality	Exposure situation	Market penetration (%)	Average number of companies per sector	Average number of potentially exposed workers per company	Number potentially exposed workers
Automotive						
Car body repair	Self-repairing, dirt-repelling coating	Manual application of liquid MNM-enabled end products	15	1503	2.7	609
		Spray application				
Car garages	Oil additive and polishing agent	Manual mixing of liquid nanocomposites	5	7584	1	379
		Manual application of liquid products				
Cleaning	Protective coating	Manual application of liquid MNM-enabled end products	1	Not available	2	15*a*
Construction						
Concrete repair	Strong mortar					
	Members sector organization	Mechanical mixing of nanocomposite (powder) with relatively high energy levels	83	14	39	913*b*
	Non-members sector organization	Manual application of liquid MNM-enabled end products	50	46	40	
Concrete prefab	Anti-dirt and anti-water coating	Mechanical mixing of nanocomposites (liquid) with relatively low energy levels	10	106	2.5	27
Metal industry	Nano silicon for anti-corrosion coating	Mechanical mixing of nano-concentrate (powder) with relatively high energy levels	5	328	4	66
		Manual application of liquid MNM-enabled end products				
Painters/ coaters	Anti-algae and anti-graffiti coating	Manual application of liquid MNM-enabled end products	5	Not available	2.5	321*c*
		Spray application				
Shoe repair shops	Anti-dirt and water impregnating agent	Spray application	20	615	2	246
Textile cleaning	Anti-dirt and water impregnating agent	Manual application of liquid MNM-enabled end products	5	246	1	12
Total						2588

Number of non-member sector organization (46) * market penetration (50%) * 40 workers potentially exposed per company = 920 workers
Maximal total exposed = 920 + 453 = 1373. Minimal total exposed = 453. Therefore, average total exposed = 913 workers.
[a]The number of potentially exposed workers was calculated as follows: the number of members of the sector organization (650) * market penetration (1%) * 2 workers potentially exposed per company = 13 workers out of 120 000 workers makes 1.1%. This percentage issued to calculate the number of potentially exposed workers among all workers in the sector (150 000 according to statistical data), resulting in maximal 16 potentially exposed workers. Therefore, the average number of potentially exposed workers is 15.
[b]The number of potentially exposed workers was calculated as follows: the number of members of the sector organization (14) * market penetration (83%) * 39 workers potentially exposed per company = 453 workers.
[c]Number of potentially exposed members of the sector organization: 2000 companies * 5% * 2.5 employees = 250 of a total of 19 700 company employed workers (20 500 minus 800 self-employed) is 1.3%. This percentage is extrapolated to the number of potentially exposed workers among all members including self-employed workers (20 500) and among all workers in the sector (30 000), resulting in minimal 260 and maximal 381 potentially exposed workers, respectively. Therefore, the average number of potentially exposed workers is 321.

Table A1. Nano-related Guidances

Control Banding Nanotool	Zalk, et al Evaluating the Control Banding Nanotool: a qualitative riskassessment method for controlling nanoparticle exposures. J Nanopart Res 11:1685–1704 (2009); Zalk et al. Control Banding and Nanotechnology. The Synergist Volume 21 No. 3 (2010);
Handleiding veilig werken met nanomaterialen en –producten	Cornelissen, et al. Handleiding veilig werken met nanomaterialen en –producten (2010); Cornelissen, R.T.M. Veilig werken met nanomaterialen. Safety! nr. 1. 2011;
Stoffenmanager nano 1.0	Duuren-Stuurman, B et al. Stoffenmanager Nano: Description of the conceptual control banding model. TNO Report V9216. 2011
Precautionary Matrix for Synthetic Nanomaterials	Höck J. et al.: Guidelines on the Precautionary Matrix for Synthetic Nanomaterials. Version 2 Federal Office of Public Health and Federal Office for the Environment, Berne 2010 http://www.bag.admin.ch/themen/chemikalien/00228/00510/05626/index.html?lang=en;
Control Banding Tool for Nanomaterials	Expert Committee (CES) on Physical Agents. Developing of a specific Control Banding Tool for Nanomaterials. ANSES Request no. 2008-SA-0407 Control Banding. 2010;
NanoRiskCat	Foss Hansen et al. (2012) NanoRiskCat – A Conceptual Decision Support Tool for Nanomaterials. Environmental Project No. 1372 2011. Danish EPA;
ANSES	Riediker, M et al. (2012) Development of a control banding tool for nanomaterials. Journal of Nanomaterials, vol. 2012
EPFL-model	Groso, A.et al. (2010) Management of nanomaterials safety in research environment. Particle and Fibre Toxicology 2010
Nanotoolkit	California Nanosafety Consortium of Higher Education (2012) Nanotoolkit. Working safely with engineered nanomaterials in academic research settings;

Table A5.2 Guidances most recently developed and listed per country.

Country / Institute (year)	**Guidance**
ISO (2014)	Nanotechnologies – Occupational risk management applied to engineered nanomaterials – Part 2: use of control banding approach
US-NIOSH (2014)	Protecting the Nanotechnology Workforce: NIOSH Nanotechnology Research and Guidance Strategic Plan, 2013 – 2016
WHO (2014)	Development of guidelines for protection of workers against potential risk of manufactured nanomaterials
Germany – BauA (2013)	Recommendation safety and health protection of workers
UK-NanoSafety PG (2012)	Working Safely with Nanomaterials in Research & Development
Switzerland – Innovation society (2012)	Trainings modules for safe working with nanomaterials
NL-IVAM (2011)	GUIDANCE WORKING SAFELY WITH NANOMATERIALS AND NANOPRODUCTS - THE GUIDE FOR EMPLOYERS AND EMPLOYEES
NL (2012)	Specific guidance by industry on presence and occurance of NM (maritime industry).
US-NIESH (2012)	Training Workers on Risks of Nanotechnology
UK-BSI (2013)	Nanomaterials and nanotechnology-based products. Guide to regulation and standards
ISO (2011)	Technical Committee 229 – development of guidance for risk assessment and risk management nanomaterials
US-CDC / NIOSH (2013)	Current strategies for engineering controls - Nanomaterials production and Downstream Handling processes
Taiwan- IOSH (2013)	Guidance for the safe use of nanomaterials
US-OSHA (2013)	Working Safely with Nanomaterials
Canada – Canadian standard Association (2013)	Nanotechnologies – Exposure control program for engineered nanomaterials in occupational settings
US-NIOSH (2011)	NIOSH Nanotechnology Strategic Plan for Research and Guidance Nanotechnology
Australia-Safework Australia (2012)	SAFE HANDLING AND USE OF CARBON NANOTUBES
Germany-BAuA (2012)	Leitfaden für Tätigkeiten mit Nanomaterialien am Arbeitsplatz
US-NIOSH / CDC (2012)	General Safe Practices for Working with Engineered Nanomaterials in Research Laboratories

The different guidances in the table differ slightly in their specific focus but in general provide information on how to work as safely as possible with nanomaterials

Annex B

During the drafting of this report, the contents of the report and/or that of the individual chapters was discussed in several expert-stakeholder meetings.

Nanotechnology expert group on occupational health and safety (2014)
L.T. Kuijpers (TNO)
S. Dekkers (RIVM)
D.H. Brouwer (TNO)
B.J.K. Bennink (Ministry of Social Affairs and Employment)
H. Heussen (Cosanta BV)
M. Groenewold (RIVM)
P. van Broekhuizen (IVAM)
R.T.M. Cornelissen (FOM)
R.C.H. Vermeulen (UU)
C. van Gulijk (Delft University)
E.L.J.P. Tielemans (TNO)
S. Evertz (RIVM)
E.K. Zondervan-van den Beuken (TNO)

Ad-hoc nanotechnology expert group on environment (2014)
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A. van Wezel (KWR)
I.M. Kooter (TNO)
C.A.M. van Gestel (VU)
D. van de Meent (RIVM/RU)
N. van den Brink (WUR)
E.A.J. Bleeker (RIVM)
W.J.G.M. Peijnenburg (RIVM)

Nanotechnology expert group on consumer products and agrofood (2014)
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J. Castenmiller (NVWA)
F.W.H. Kampers (WUR)
I.M. Kooter (TNO)
H.J.P. Marvin (WUR)
M.M. Nijkamp (RIVM)
R.J. Vandebriel (RIVM)
G. Visser (DSM)
W.P. van der Vossen-Wijmenga (Voedingscentrum)
A.M. Walhout (UT)
S.W.P. Wijnhoven (RIVM)
E.K. Zondervan-van den Beuken (TNO)
K.G.J. Beaumont (Ministry of Public Health)
H. Bouwmeester (WUR)
S.J. Beukema (Ministry of Economic Affairs)
P. A. Dekker (NVWA)
S. Dekkers (RIVM)
R. Donker (Ministry of Economic Affairs)

A.R.H. Fischer (WUR)
F.J. Gaikema (NVWA)
W.H. de Jong (RIVM),
B. Koops (Tilburg University)
C.J.M. Rompelberg (RIVM)
A. Rip (UT)
A.J.A.M. Sips (RIVM)

Stakeholder policy reflection group on risks of nanomaterials (klankbordgroep risico's nanomaterialen)
Ministerie van IenM (tevens secretariaat van de Klankbordgroep)
Ministerie van SZW
Ministerie van VWS
Ministerie van EZ
NVWA
VNO-NCW
Vereniging van de Nederlandse Chemische Industrie (VNCI)
Nederlandse Cosmetica Vereniging (NCV)
Federatie Nederlandse Levensmiddelen Industrie (FNLI)
Ondernemersorganisatie voor de Technologische Industrie (FME)
Verbond van Verzekeraars
DSM
Unilever Nederland
Lionix BV
FNV Vakcentrale
Consumentenbond
Vereniging Leefmilieu
Stichting Natuur en Milieu
WECF
GGD IJsselland
Stichting voor Fundamenteel Onderzoek der Materie (FOM)

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