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Assessing health & environmental risks of nanoparticles

An overview

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Colophon

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Foreword

This is the overarching summary of the report 'Assessing health and environmental risks of nanoparticles. Current state of affairs in policy, science and areas of application'. The complete report (nr: 2014-0157) can be found on the RIVM website (www.rivm.nl/en).

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Assessing health and environmental risks of nanoparticles – an overview

'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 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, give a description of the economic development of nanotechnology, present the current state of affairs with respect to the use and risks of nanomaterials/nanoparticles, assess the current state of affairs of our ability to assess the risks of nanomaterials , and conclude with the essential agenda items for the future.

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). 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.

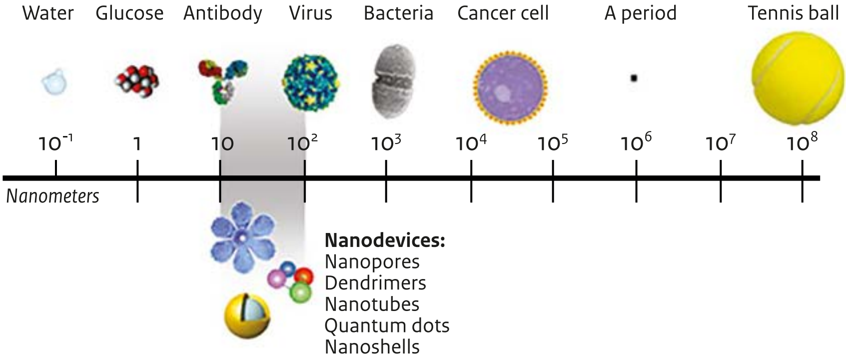

Figure 1.1 Size ranges of different materials; nanoparticles are in the size range of one to one hundred of nanometers (adapted from http://nano.cancer.gov/learn/understanding).

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 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.

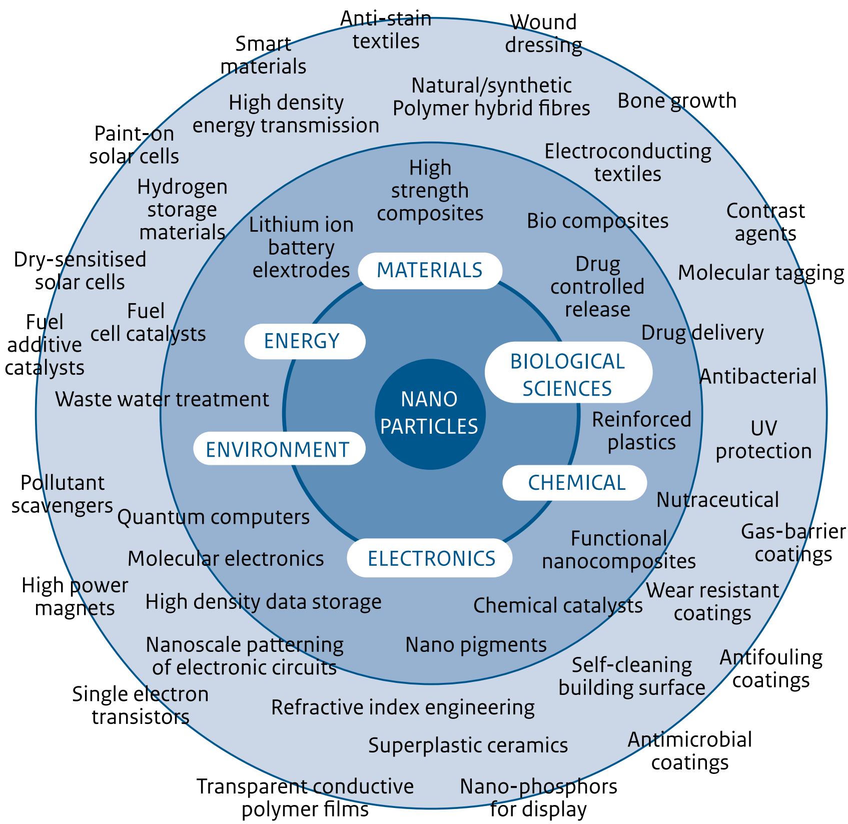

Figure 2 Overview of areas of application of nanomaterials (taken from: (McDermott et al., 2014))

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.

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

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.

1 'From small to great'

2 http://www.nanonextnl.nl/

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).

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 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.

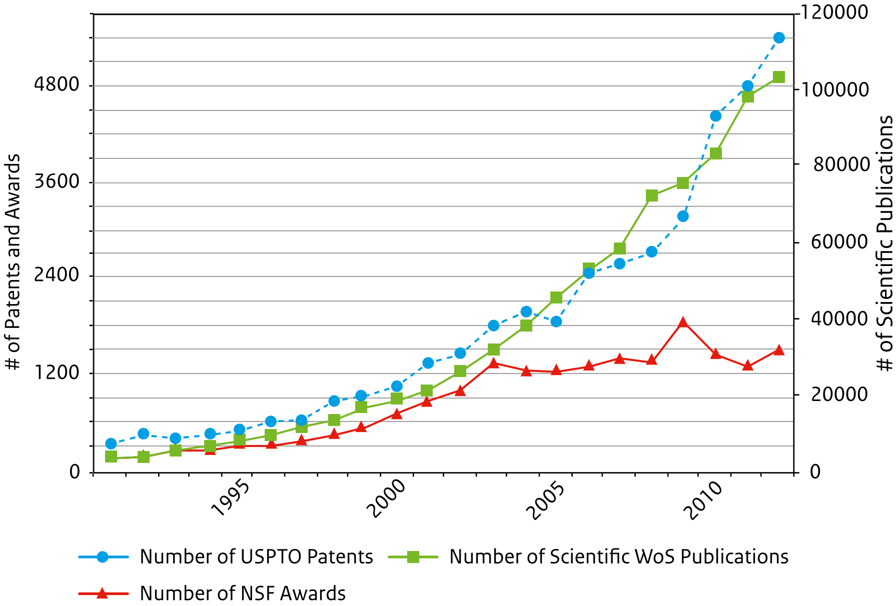

Figure 3 Development of nano-related patents, and publications from 1991 to 2012 (taken from (Chen et al., 2013). USPTO=United States Patent and Trademark Office; NSF=National Science Foundation (USA); WoS=Web of Science

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).

Materials containing nanoparticles: uses and uncertainty about risks[3]

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

Occurrence and exposure

Table 1 gives an overview of the different potential uses of nanomaterials in consumer products, agrofood and nanomedicine applications[3]

[3] The information in this paragraph is based on the individual chapters from the main report (Westra, 2015).

Table 1 Generalized overview of the potential use of nanomaterials in several use categories[3]

Use category	Nanosized material	Product type	Functionality
Consumer products[3]	Particles (e.g. TiO_2, Ag, ZnO, SiO_2, carbon black) Carbonanotubes	Diverse (e.g. cosmetics, personal care products, textiles)	Colour pigments, antibacterial activity strength, durability,
Agrofood Direct use[3]	Inorganic solid particles (SiO_2; TiO_2)[1]	Diverse (powdery foodstuff; sweets)	Anti-caking agent, food colouring
Agrofood Direct use[3]	Encapsulated active ingredients	Regular foodstuffs (diverse)	Improved stability of foodstuffs; improved shelf life; improved control of bioactive ingredient, etc.
Agrofood Indirect use[3]	Encapsulated active ingredients	Animal feed, fertilizers, pesticides, animal medicine, animal hygiene	improved control of active substance; reduction of active substance
Agrofood Indirect use[3]	Particulates (SiO_2, silver, clays, starch, polymers)	Animal feed, packaging, various equipment	Anti-caking, improved packaging (e.g. strength, barrier function) anti-bacterial activity

Use category	Nanosized material	Product type	Functionality
Nanomedicine[3]	Encapsulated active ingredients	Therapeutics (medication)	Improved control of active ingredient Targeting of active ingredient Reduction in amount of active ingredient
Nanomedicine[3]	Particulates (various)	Cements, filling materials (e.g. for bone; dentistry); instruments, medical appliances	Improved strength, improved biocompatibility, anti- bacterial activity

** TiO_2 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 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.

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[4] provided an overview of a number of important toxicological findings for non-soluble (water) nano-sized particulate matter (SCENIHR, 2009).

[4] Scientific Committee of Emerging and Newly Identified Health Risks

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 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, SiO_2, 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[5] . 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[6] 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.

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5 (Quantitative) structure activity relationship

6 Scientific Committee on Consumer Safety

- EFSA[7] 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., 2013), 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.

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, 2008). 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.

[7] European Food Safety Authority

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.

Current state of affairs [3]

Introduction

Nanotechnology, and nanomaterials as a subset, has a great deal to offer to improve the quality of life. 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.

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 need 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.

Four needs to 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.

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 corners-tone 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 premar-ket - 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.

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