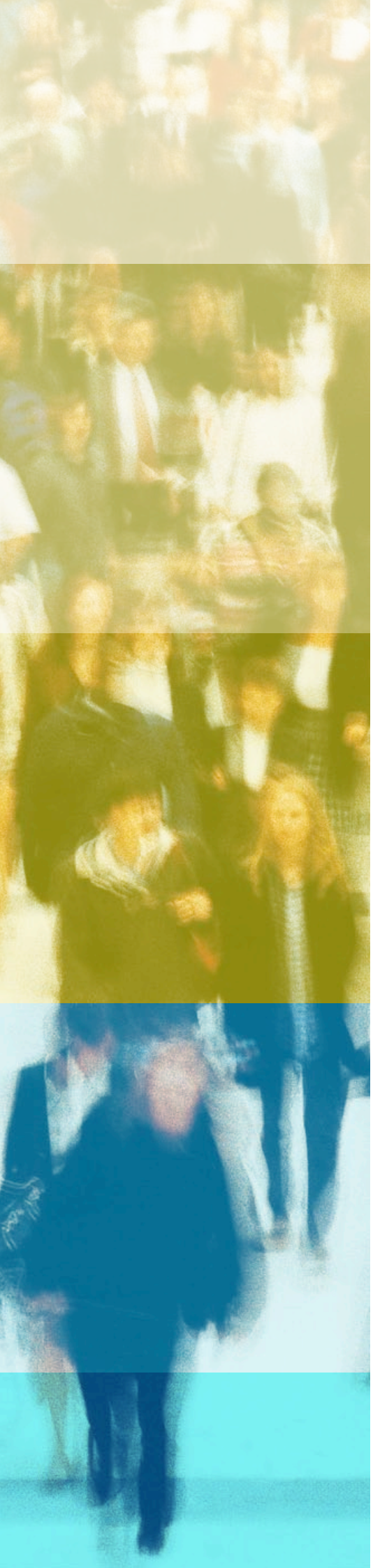

MISTRA
The Swedish Foundation for
Strategic Environmental Research

Mistra Nanotechnology

Report from the Expert group

2013-01-24

The Contents of this background report are the responsibility of the authors.

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Short abstract

Nanotechnology is in rapid development at both the R&D and product levels. The market in 2009 was estimated to be $ 250 billion and is expected to grow by more than an order of magnitude in ten years. Nanotechnology and nanomaterials create opportunities in almost all technology areas. Products include micro-electronics and catalysts, nano-drugs and biochips, solar cells, consumer products like cosmetics, self-cleaning paints and bactericides. Over the past 10–15 years there has been a growing concern that nanomaterials (NM) and nanoparticles (NP) may, besides their many positive effects, pose risks to humans, the environment and ecosystems. NP sizes (1–100 nm) are in the subcellular regime and may interact with and affect cellular processes in organisms. Society in general, including authorities, people on the street and industries, perceives it as important to estimate and handle those risks, especially as they are largely unknown and the knowledge base is fragmented.

The components of a risk assessment system for NM/NP span over a wide range and include:

- Mapping of NMs/NPs and their exposure, transport routes, and uptake paths;
- exposure and hazard assessment;
- toxicokinetics;
- methods and procedures for field and laboratory studies to study NM/NP fate and effects on health, environment and ecosystems;
- dosimetry;
- employing and developing analytical methods to characterize NM and NPs;
- methods to synthesize model systems of NM and NPs;
- methods to remove NM/NP from air and water;
- social science studies of the perception of and attitudes to nanotechnology and safety/risk aspects;
- society organization of assessment and handling of safety/risk aspects, including decision-making and surveillance and regulations/laws.

A Mistra research program can and should not cover all these aspects. The proposed program is based on a selected set of items from the list above plus the topic *"Applying nanotechnology to solve environmental problems"*. Prioritized topics are:

1. *Methods* to collect and characterize nanoparticles from relevant environments (e.g., water, air, soil, tissues, organisms) and their spreading paths and exposures etc., and risk assessment using a life cycle perspective.
2. *Laboratory studies*, including method development, model systems spanning a range from basic ones to more field-like ones, corona effects, dosimetry and toxicokinetics,
3. *Field studies* of the effects of NM/NP on ecosystems (epidemiological studies, toxicokinetics, ...) with emphasis on understanding the underlying principles, i.e. studies beyond dose-effect relationships or just generation of toxicity data.
4. *Social science aspects of nano-risk perception* and appropriateness of risk analysis frameworks.
5. *Applying nanotechnology* to solve environmental problems.

Executive Summary

Nanotechnology is in a phase of rapid development both at the R&D and the commercial/product levels. Publication rates are increasing rapidly. The market in 2009 was estimated to be $ 250 billion and a prognosis from U. S. NSF indicates about a doubling until 2018.

Nanomaterials on the market and in the R&D phase represent a very large variety of materials of different compositions (implying different chemical properties), large size variations (small particles of ca. 1nm with only a few tens of atoms to ca. 100 nm particles with over 10 million atoms) and variations in shape (e. g., rounded versus high aspect ratio). The nanomaterials cover all materials that occur in bulk form, and in addition composite materials that often do not exist as bulk materials. Furthermore, many nanomaterials occur in the dispersed state, e.g. as aerosol or as particles suspended in water or other liquids. Beneficial applications in biomedicine are also extensively explored ("nanomedicine").

Nanotechnology and the use of nanomaterials create opportunities in almost all technology areas. As with all technologies, nanotechnology is expected to create both positive values for society and side effects/problems that need to be addressed and controlled, to avoid or at least minimize negative effects and to optimize benefit/cost ratios. Costs include monetary costs and costs for society, humans and ecosystems.

From a Mistra perspective this situation is primarily projected on environmental and ecosystem aspects. In addition to potential negative effects Mistra should also address opportunities created by nanotechnology to solve environmental problems.

Risks and safety

Over the past 10–15 years there has been growing concern that nanomaterials (NMs) and nanoparticles (NPs) may pose risks to humans and to the environment and ecosystems. NP sizes (1–100 nm) are in the subcellular regime (cells are >> 1 000 nm) and may in a variety of ways interact with and affect cellular processes in organisms via the similarly sized subcellular components and by interfering with nano-biological mechanisms. Society in general, from authorities to people on the street, perceives it as of great importance to be aware of and handle those risks, especially as the risks are largely unknown and the knowledge base is fragmented. Also for most industries it is of interest to have safe products and ways to evaluate and secure their safety, non-toxicity etc., since otherwise their development of nanotechnology products may be hampered or delayed.

Risks that have been identified or are suspected include;

(i) *Health risks* for humans when nanoparticles enter the body through respiration (parallels have been drawn to asbestos-like effects), through food and the digestive system and through the skin (e.g., cosmetics, sun screens). The NP contamination in air, water and food has its origin in emissions from producing industries, waste combustion furnaces, traffic and unintentional

exposure while using e.g. cleaning products containing nanoparticles. A special class here is the intentional use of NPs in cosmetics and sunscreens or nanomaterials used in medicine; e.g. to carry drugs, so called nano-drugs, or the application of nanosized materials for diagnostics (e.g. contrast agents). Exposures can occur at all stages along the life cycle assessment (LCA) chain, e.g., during manufacturing, use, or waste management.

(ii) *Environment and ecosystem effects*, which include effects on vertebrates as well as invertebrates, microorganisms and plants through NPs spreading via air or water or both.

(iii) One can also include potential effects of NPs on weather and climate, e.g. via particles that are spread in the atmosphere from volcanic activity and combustion processes, although this subarea is generally less considered than (i) and (ii).

(iv) In addition to intentionally produced nanomaterials and nanoproducts, there are also nanoparticles that have natural origins (e.g., dust storms, forest fires, volcanic activity, ….) or that are unintentionally created through processes involving bulk materials (e.g., wear products from tires and asphalt and combustion processes, …) or formed by combustion processes(e.g., diesel particles, or particles emitted by wood burning stoves). Such particles can provide epidemiological information about NP effects.

Risk assessment of NM and NP involves a long chain of different components directed towards assessing exposures and hazards; from identification and characterization of NM, to their use, spreading and transport paths, toxicokinetics and effects on humans and the environment (including, e.g., animals, plants, microorganisms, and ecosystems). Issues and challenges under discussion are, e.g., definitions of NM and NPs, how to express dosage, whether total amounts (numbers or weight) or surface area are most important, the importance of size and shape, "corona effects" (surface adsorbed materials like biomolecules or chemicals carried by the NPs into organisms), how to collect representative sets of NPs from environmental systems, methods to characterize them, methods to synthesize model NPs, and in vitro and in vivo test methods in the laboratory.

There are several proposed approaches to handle the safety aspects and risks associated with NM. A common approach is to consider NM as similar to chemicals and apply the same approaches as for chemicals like the EU regulations REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) and CLP (Classification, Labeling and Packaging of substances and mixtures). There are many arguments in favor of this "standard" approach, such as the similarity in the type of questions that arise and in the large variation in occurrence and spreading of chemicals as well as in NM/NPs. There is rather general consensus that this may be a viable long-term approach as a foundation for the risk assessment and control work to be done. However, it is also realized that REACH and CLP need to be significantly modified to include and cover the nano-aspects in a proper way. NMs and NPs exhibit different biological effects (e.g. a cellular uptake of NPs, in contrast to the bulk materials) and also follow different distribution pathways after release into the environment.

Questions are also raised whether there may be a need for additional, parallel approaches for more pro-active and faster governance and decision-making concerning NM and NPs. The latter is based on the observation that the "standard" approach most likely will take a very long time to establish and requires extended and costly research and assessment efforts, while new NM and NPs will enter the market more rapidly. In other words, it is argued that the standard approach alone may be too slow and therefore will lose control over, or at least lag behind the development on the market. Suggestions have therefore been put forward

about developing and adding a more responsive and supportive system for (faster) decision-making as a complement to the standard approach. The extreme alternative, i.e., to ban all NM and NPs until their risks are fully assessed is, to say the least, problematic, given the huge economic potential of nanoscience and nanotechnology.

The components of a complete risk assessment system for NM/NPs span over a wide range and include:

(i) *Mapping* of all the NMs/NPs that exist and are likely to appear and compilation of databases about their occurrence, uses, *exposure potentials, transport routes and uptake paths*.

(ii) *Exposure and hazard assessment* in a life cycle perspective.

(iii) *Field studies:* Methods and procedures to study NM/NP fate and their effects on the environment and ecosystems.

(iv) *Laboratory studies*, including method development, model systems, corona effects, toxicokinetics and dosimetry, to evaluate the effects of NM and NPs on organisms.

(v) Employing and developing experimental *analytical methods to characterize* NM and NPs in laboratory test systems and in environmental samples.

(vi) *Methods for collection of representative samples* of NPs from various environments (work environment, ecosystems, organisms, body fluids, tissues, ...), in order to analyze types and occurrence.

(vii) *Methods to synthesize* representative model systems of NM and NPs.

(viii) *Methods to remove NM/NP* from air and water.

(ix) *Health effects*.

(x) *Studies of the perception of and attitudes to nanotechnology* and safety/risk aspects including analysis of appropriate *risk analysis* procedures.

(xi) Society organization of assessment and handling of safety/risk aspects, including decision-making and surveillance and regulations/laws.

As an additional topic Mistra has decided to include the topic:

(xii) Applying nanotechnology to *solve environmental problems*.

A research program of the type that Mistra is considering to launch cannot cover all these aspects – it would mean spreading the resources far too thin. The Mistra program should be based on a selected set of items from the list (i)-(xii) above.

Based on MISTRA's main mission, which is in the environemental area, and noting that the largest volume of ongoing research world wide is related to human health aspects, we suggest to exclude this area, except that the program, whenever appropriate, should take advantage of existing knowledge in this field (effects as well as methods). For example, this area provides valuable data basis, appropriate model systems and other input for several of the other items above. Area (xi) above is currently subject to a governmental investigation and coming report (E Forsberg), where the report is expected in about one year and is therefore not explicitly included in the suggested program.

All other areas above are in principle open for proposals. It is suggested that the call for proposals for the planned Mistra Nanotechnology program is particularly focused on

1. *Methods* to collect and characterize nanoparticles from relevant environments (e.g., water, air, soil, tissues, organisms) and their spreading paths and exposures etc. and risk assessment using a life cycle perspective.

2. *Laboratory studies*, including method development, model systems spanning a range from basic ones to more field-like ones, corona effects, dosimetry, and toxicokinetics.

3. *Field studies* of the effects of NM/NP on ecosystems (epidemiological studies, toxicokinetics) with emphasis on understanding the underlying principles, i.e. studies beyond dose-effect relationships or just generation of toxicity data.

4. *Social science aspects of nano-risk perception* and appropriateness of risk analysis frameworks.

5. *Applying nanotechnology* to solve environmental problems.

Comment regarding point 5. It is said from the beginning that the program, in addition to addressing safety and risk problems and problem solving in the area of nanotechnology, should also open up for proposals that concern the *employment of nanotechnology to remedy environmental problems*. Here, several methods based on NPs are explored today or even applied commercially. Among the most well known examples are catalytic exhaust cleaning from vehicles, remediation of groundwater contaminations with nano-scale zero-valent iron and photo-catalysis involving e.g., titania nanoparticles and either artificial or solar light. In the near future, there may also be other very different examples where nanotechnology can help to solve environmental problems, e.g., the nano-formulation of pesticides for controlled release of active substances or the detection of toxic compounds using nano-sensors. These are just a few examples illustrating point 5. above.

Table of Contents

Short abstract 2

Executive Summary 3

Risks and safety 3

1. Background 8

1.1 Mistra's mission 8

1.2 Mistra's interest in nanotechnology . 8

1.3 Background to this report 9

2. Overview of Nanotechnology 10

2.1 Definition of nanomaterial 10

2.2 General overview, historical aspects and recent developments 12

The origin of Nanoscience and Nanotechnology 12

Current and future trends 15

2.3 Nanomaterials as perceived and managed by society 18

2.4 Swedish nanoresearch and its relation to European and international nanoresearch 19

Bibliometry 19

2.5 Examples of nanomaterials with different functions and their applications 21

a) Selected examples of nanomaterials . . 21

Carbon nanomaterials 21

Silver nanoparticles 22

Gold nanoparticles 23

Titania nanoparticles 23

Other oxide nanoparticles than titania 24

Polymer nanoparticles 24

b) Selected existing or potential application areas based on nanomaterials 24

Catalysis and photocatalysis: Nanocatalysts for environmental cleaning purposes 24

Removal of environmental contaminations: Remediation of ground water 26

Agriculture: Nanoparticles for release of nutrients, pesticides, and biocontrol organisms 27

Food: Nanoparticles as food additives and as packaging materials 27

Cosmetics: Nanoparticles as active substances, carriers and formulation aids 28

Medicine: Nanoparticles as drug carriers and gene transfection vectors 28

Textiles: nanofibres and composite materials 30

Electronics: Nanosized components in electronic devices 31

Sensors: Biochips and detection of chemical compounds in air and water 31

Energy: Nanomaterials in solar cells, fuel cell electrodes, and battery electrodes . . . 32

3. Environmental and Health Risks caused by Nanoparticle Emission 34

3.1 Nanomaterials in the environment 34

Naturally occurring nanomaterials: Nanoclays 34

Antropogenic nanoparticles in the environment: Combustion produced soot, wear particles, … 35

Manufactured nanoparticles in the environment 36

3.2 Exposure models for nanomaterials in the environment 37

3.3 Potential beneficial and adverse effects on human health 38

Classical examples of diseases caused by nanoparticle exposure 38

Improved treatment of diseases by nanodrugs 38

Nanotoxicology 38

3.4 Nanoecotoxicology 40

4. Experimental Methods to study Nanoparticles 41

4.1 Nanoparticle interaction and "effect" studies 42

4.2 Collection of nanomaterial samples from the environment 42

4.3 Characterisation/analysis 43

4.4 Synthesis and availability of model nanoparticles 44

5. Ethical, Legal, and Safety (ELSA) Aspects 46

5.1 Ethical aspects of nanotechnology . 46

5.2 Chemicals regulations to secure safe handling of nanomaterials 46

Industrial chemicals legislation 46

Pesticides legislations 48

The rules and their applicability to nanomaterials 50

An EU common mandatory reporting system for nanomaterials 51

6. Areas of Specific Interest for Mistra and Proposed Areas for Research in a Mistra Program . . . 53

6.1 List of potential topics 53

Topics deemed to merit lower priority 54

Additional comments on topics (i)-(xii) . 54

6.2 Prioritized topics 56

7. References 58

1. Background

This report has been compiled during 2012 as part of the second step in one of Mistra's programme initiation processes.

1.1 Mistra's mission

The aim of the Foundation for Strategic Environmental Research (Mistra) is to support research of strategic importance for a good living environment. The foundation should promote the development of robust research environments with high international class that will have a positive impact on the competitiveness of Sweden. The researched financed by the foundation should play a significant role in solving major environmental problems and contribute to the development of a sustainable society.

Mistra invests approximately 200 million kronor annually in multidisciplinary environmental research. Mistra aims to fund up to 15 programmes concurrently, with each programme running from 4 to 8 years, i.e. 1–2 calls are announced every year. Mistra strives to find areas where the funding from Mistra can make a difference next to larger funding agencies, with the ultimate goal to strengthen the competitiveness of Sweden. A Mistra programme is considered to be a success when scientifically advanced research is implemented by authorities, organisations or businesses in such a way that there is a measurable return on the investment.

1.2 Mistra's interest in nanotechnology

Nanotechnology is a relatively new and massively expanding area, which is expected to have a huge impact on society. The market potential of nanotechnology-based products is estimated to be more than 250 billion dollars (2009), and is expected to grow by more than an order of magnitude within the coming decade (see e.g. report by Roco et al.). There is thus ample room for new, innovative ideas to be realized. An investment in nanotechnology-based innovations, which contribute to a sustainable development, coupled with surveys regarding risk benefit analysis, decision-making processes and consumer attitude towards nanotechnology would fill several purposes. In particular, it would:

- Give Swedish researchers the opportunity to strengthen their position in the international research arena
- Give Sweden the opportunity to establish a leading position in certain niche areas related to environmental aspects of nanotechnology
- Illustrate the benefits of considering environmental aspects in the early development stages of emerging technologies.

Mistra's board of directors has identified four nanotechnology programme areas of interest for upcoming calls, where idea processes have been initiated together with experts;

(i) Release of nanomaterials into the environment,

(ii) Nanotechnology as part of a solution to environmental problems (remediation),

(iii) Nanomaterials in a sustainable society, and

(iv) Agricultural application of nanomaterials.

1.3 Background to this report

The idea behind Mistra's interest in a nanotechnology programme call is twofold, i.e. either to solve actual or perceived environmental problems caused by nanotechnology or to promote the solution of environmental problems using nanotechnology. A steering group consisting of internationally renowned scientists and representatives from public authorities has been assigned to review this area and to suggest specific topics of interest for Mistra, as described in Table 1.

TABLE 1 Members of the group compiling the present report.

	Affiliation	Expertise
Members of the steering committee:		
Prof. *Bengt Kasemo* (chair)	Dept. of Applied Physics, Chalmers University of technology, Sweden	Nano(bio)technology, Surface Science, Energy technology.
Prof. *Matthias Epple*	University of Duisburg-Essen, Germany	Synthesis and biomedical application of inorganic materials (especially nanoparticles). Biomaterials.
Dr. *Agneta Falk-Filipsson*	KemI (Swedish Chemicals Agency)	Nanomaterials. Toxicology. Chemicals legislation.
Prof. *Markku Leskelä*	Dept. of Chemistry, University of Helsinki, Finland	Nanocatalysis. Inorganic chemistry.
Prof. *Anders Baun*	Technical University of Denmark	Nanoecotoxicology.
Mistra representative:		
Dr. *Christopher Folkeson Welch*	Mistra	
Secretariat:		
Dr. *Sofia Svedhem*	Dept. of Applied Physics, Chalmers University of technology, Sweden	Nanomedicine, nanobiotechnology.
Dr. *Michael Zäch* (until July 2012)	Dept. of Applied Physics, Chalmers University of technology, Sweden	

As a result of its work, this group has authored the present report with Sofia Svedhem and Bengt Kasemo as co-ordinating authors. Input to the report has also been obtained during an open workshop at Mistra on May, 24th in 2012.

2. Overview of Nanotechnology

The development of engineered nanomaterials has resulted in a broad range of new commercial products. There is, in parallel with the many beneficial effects of nanotechnology also a growing concern about the effects both on humans and on the environment caused by intentional and unintentional exposure to nanomaterials. In order to manage the future of nanomaterials and the whole area of nanotechnology, there is a need both for definitions of what nanomaterials are and of a detailed understanding of how nanotechnology has developed, its current status, as well as its future potential and applications.

2.1 Definition of nanomaterial

A nanomaterial is sometimes defined as a material with at least one dimension in the range of 1–1000 nm. A more common definition is that the size of at least one dimension is limited to 1–100 nm. According to ISO, nanomaterials are categorized as *nano-objects*, objects with any dimension in the nanoscale, or *nanostructured materials*, materials with an internal structure or surface structure in the nanoscale (ISO 2010).The dominant motivation for a nanomaterial definition is the wish to ensure safe use of engineered nanomaterials, by the development of sensible regulations. In order to achieve this goal, it can be argued that a definition should focus on nanomaterial properties rather than on size alone (Maynard 2011).

Regarding the upper size limit suggested in the definition(s), it is motivated by the changes in physical properties that occur for some materials in this size range and/or the way the material or object is recognized by its surrounding, e.g., in a cell or soil. As examples very small nanoparticles may have a lower melting temperature compared to the corresponding bulk material, and there is also a change in chemical reactivity both due to the inherent change in physical properties and due to the relative increase in surface area. These factors, combined with the difficulty of manipulation and control of nanoparticles in the aforementioned size range, and the observation that such particles cannot be observed by conventional optical microscopy, make the nanomaterial range quite unique. The upper size limit may actually change somewhat with specific particle type and it is therefore in scientific work, wise to not have a too sharp upper size boundary, but a boundary somewhere in the range of a few hundred nanometers. If regulations require a sharp boundary it should be set large enough. Regarding the lower limit, 1 nm, this is the boundary regime to what we rather classify as molecules – nanomaterials are at this limit composites of atoms that we normally do not consider as molecules, but there is inevitably a grey zone between molecules and nanoparticles at this size range. In addition one or even two dimensions might be below 1 nm, as in the case of single graphene sheets, where one dimension is significantly smaller than 1 nm.

The recommendation of the definition of a nanomaterial adopted by the European commission in October 2011 (EC 2011) is based on size and defines a nanomaterial as:

"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."

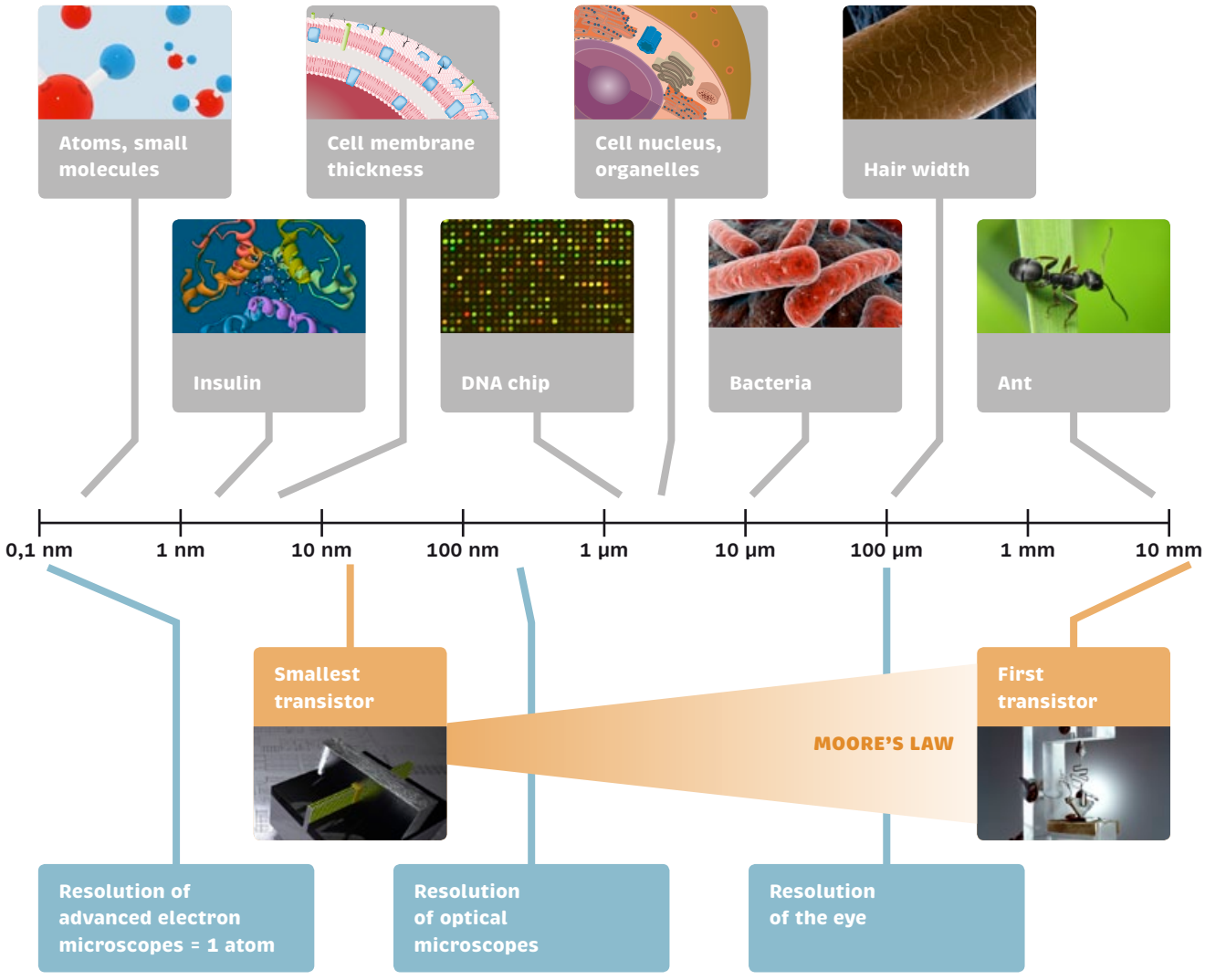
"In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %."

In the present report we adopt the above definition, however, well aware that important grey zones exist and may need to be taken into account in specific cases.

The European Commission will review the definition in December 2014, focusing on the number size distribution threshold, which may at this point be increased or decreased.

Proper implementation of any nanomaterial definition requires appropriate tools and methodologies, as discussed in a recent report for the Joint Research Centre (JRC) (Linsinger et al. 2012)(see also Section 2.5).

FIGURE 1 An illustration of the size regime dealt with in nanoscience and nanotechnology.



2.2 General overview, historical aspects and recent developments

The origin of Nanoscience and Nanotechnology

One can trace nanoscience and nanotechnology back to several sources. Richard Feynman made the often quoted statement "there is plenty of room at the bottom" at an American Physical Society meeting at Caltech on December 29, 1959, suggesting that there is much to discover and exploit at sizes between the size of an atom and a macroscopic object. This size regime is illustrated in Figure 1.

The birth of nanoscience and nanotechnology can also be traced back to more "hands on" events related to microelectronics and this areas transition decades later into the nanosize regime. Since the discovery of the transistor around 1947 and of the integrated circuit (IC) at the end of the 1950ies (both discoveries awarded Nobel Prizes), electronic components (transistors, diodes,..) on an IC have steadily shrunk in dimensions. The number of functional units per unit surface area, and the functional speed (e.g., like mathematical operations per unit time) have increased according to the empirical relation called Moore's law after the founder of Intel, Gordon Moore (Figure 2), after the founder of Intel, Gordon Moore. Source: Intel.). Already at the turn of this century, twelve years ago, transistors were smaller than 100 nm (Figure 3), a size commonly set as the approximate upper dimensional limit of nanotechnology. Today the transistor size is down to 20 nm in commercial circuits.

The development of IC technology over many decades successively created a large and sophisticated set of instruments and tools for manufacturing and control of the microelectronics and eventually nanoelectronics components.

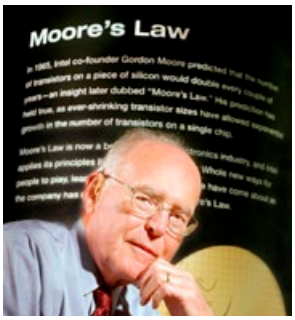


FIGURE 2 Graphical representation of the empirical relation called Moore's law(Moore 1965), after the founder of Intel, Gordon Moore. SOURCE: INTEL.

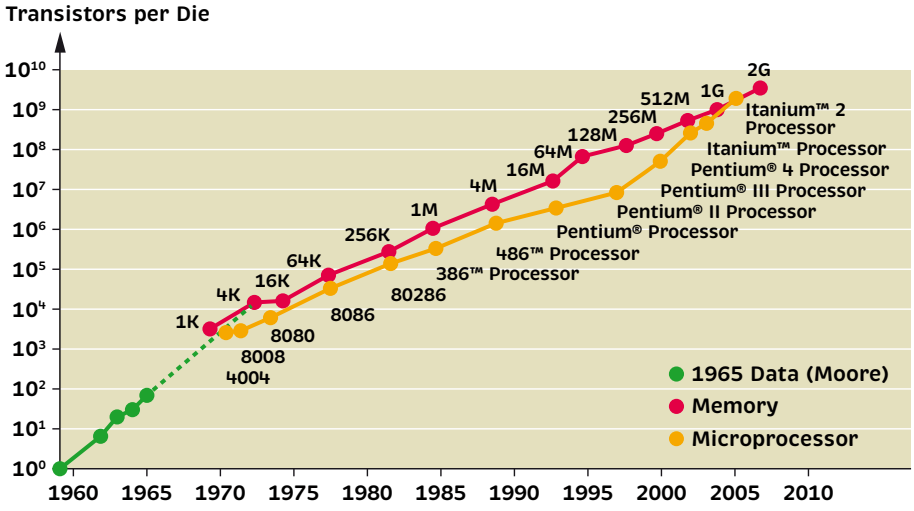


TABLE 2 Examples of areas where the miniaturization toolboxes from microelectronics combined with the push from Moore's law created many spin-off effects.

Nanotechnology areas benefiting from the development of microelectronics	
Nanoelectronics (Moore's law)	
Optics and optoelectronics	
Nanobiotechnology, Nanomedicine	Implants and tissue engineering
	Drugs
	Sensors, diagnostics, imaging
Materials Science & Technology	

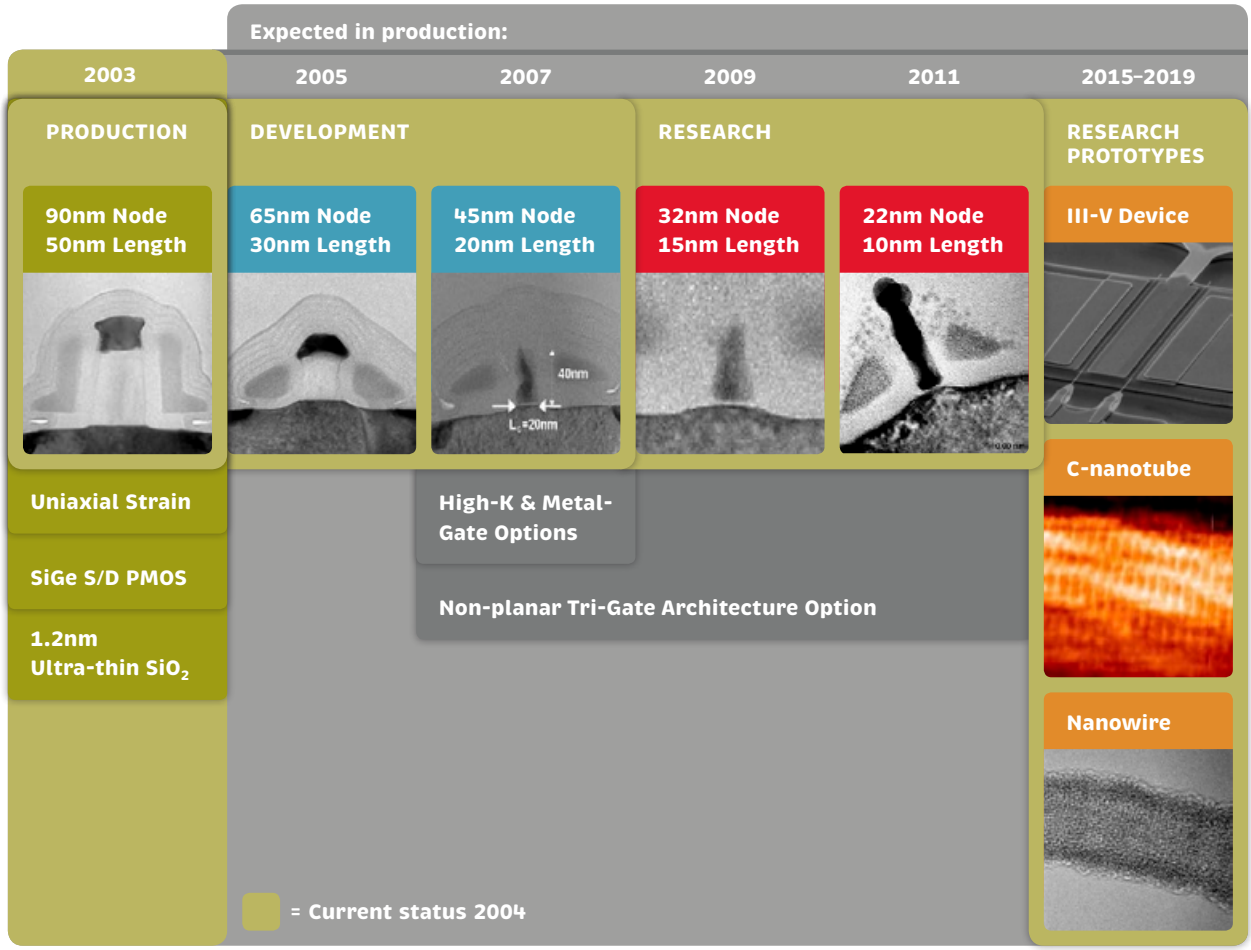


FIGURE 3 An illustration of transistor scaling and research roadmap.
PREPARED BY ROBERT CHAU, INTEL, 2004.

Researchers interested in totally different areas of science and technology of course exploited this already developed "tool box" for their quite different purposes, in optics, materials science, sensors, biomedical devices, catalysts and many others. It is, e.g., highly unlikely that photolithography and the large variety of nanolithography methods for micro- and nanofabrication that exists today, had been even close to the current sophistication and precision, without the push from micro-and nanoelectronics. Some areas that took advantage of this "free ride" are shown in Table 2 (for more application areas see later).

Similarly many of the experimental analytical instruments that were developed came out of the microelectronics industry development. Most prominently, the scanning tunnelling microscope (STM, Nobel prize in 1986) and its sister instrument, the atomic force microscope (AFM), were both developed at IBM Research laboratories. Both these instruments have, although developed for analyses, also been demonstrated to have fabrication/preparation power at the atomic scale, much in the spirit of Feynman's words above.

The nanofabrication tools that came out of microelectronics were originally developed to sculpture, modify, deposit etc. structures in or on silicon wafers for IC circuits. They constituted a kind of nano- and atomic level craftsmanship (atomslöjd). This fabrication approach is often referred to as the *top-down approach*.

It is contrasted by the totally different *bottom-up approach*, especially developed within certain branches of chemistry, e.g. organic and inorganic synthetic chemistry and colloidal chemistry, where one instead of the "brute force" of nanosculpturing, tries to create conditions, where molecules and small particles self-assemble into desired and often complicated architectures. Some types of particles of this kind are shown in Figure 4. Current nanoscience and nanotechnology exploit both these approaches – top-down and bottom-up – to create new, sophisticated structures and functions, sometimes in combination.

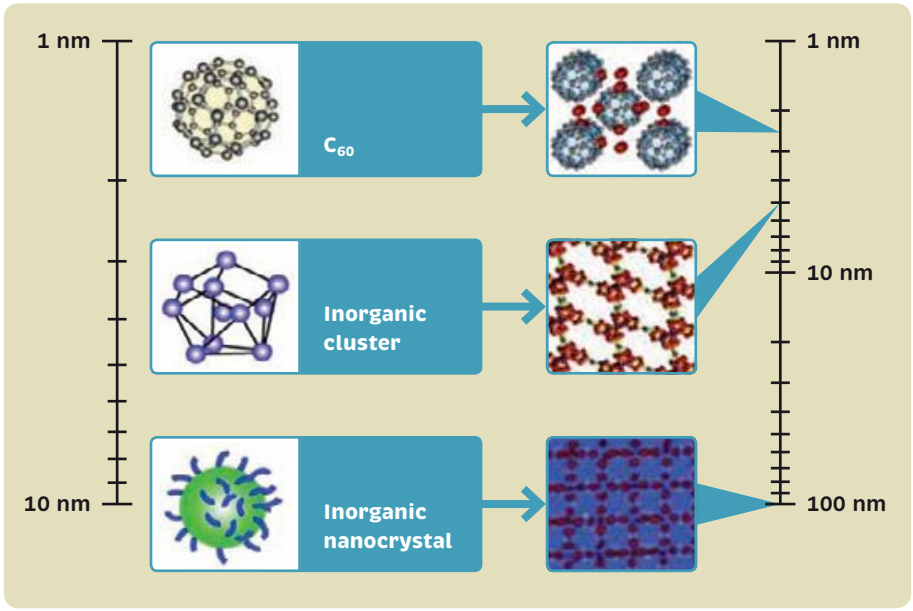


FIGURE 4 Fullerenes, atomic clusters, and larger inorganic crystals can be assembled to create materials and devices with tailored properties.

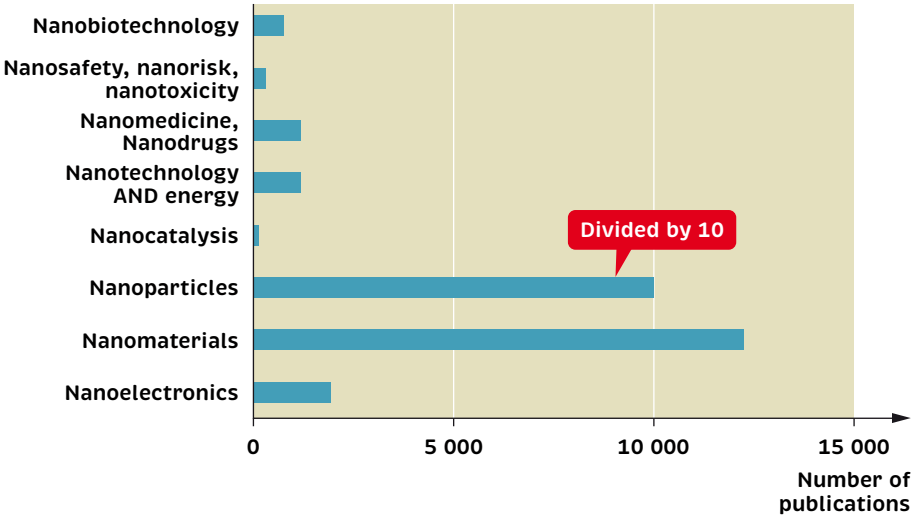


FIGURE 5 Overview of research publications in the nanoarea divided into subtopics by keyword searches. Note that the length of the bar corresponding to the search term *"Nanoparticles"* has been divided by 10 to fit at the same scale as the other bars.

RESEARCH PUBLICATION SEARCH USING ISI WEB OF SCIENCE IN 2011.

From the point of view of potential risks with nanomaterials and nanoparticles (see further below) the top down and bottom up approaches are quite different in the following respects. The top down approach most often (but not always) consists of working on bulk materials, originally on silicon single crystal wafers, with etching agents (acids, ion beams, cold plasmas,), where the removed material is taken care of as "normal" chemicals, and the made structures are firmly attached to their original host/bulk material (like the transistor on an IC chip). The exposure risks with such components and nanomaterials are extremely small, especially when the fabrication is made in closed systems.

At the other extreme, with the bottom up approach, individual nanoparticles are synthesized in solution or even in gases, and deliberately surface-treated to avoid agglomeration or attachment to surfaces, so that they can be used as half-fabricates for later processing and use. Without precautions the exposure risks may then be very high. The same may hold even after further processing/use of the materials, if the final functional device, where the nanoparticles are used, consist of loosely attached nanoparticles on a surface or dispersed in a liquid or gel as in cosmetics, sun-screens etc. Exposure risks thus exist at several stages along the life cycle chain of such nanoparticles/nanomaterials. The importance of this comment underlined by a literature search for different subtopics in the nano-area and their publica-

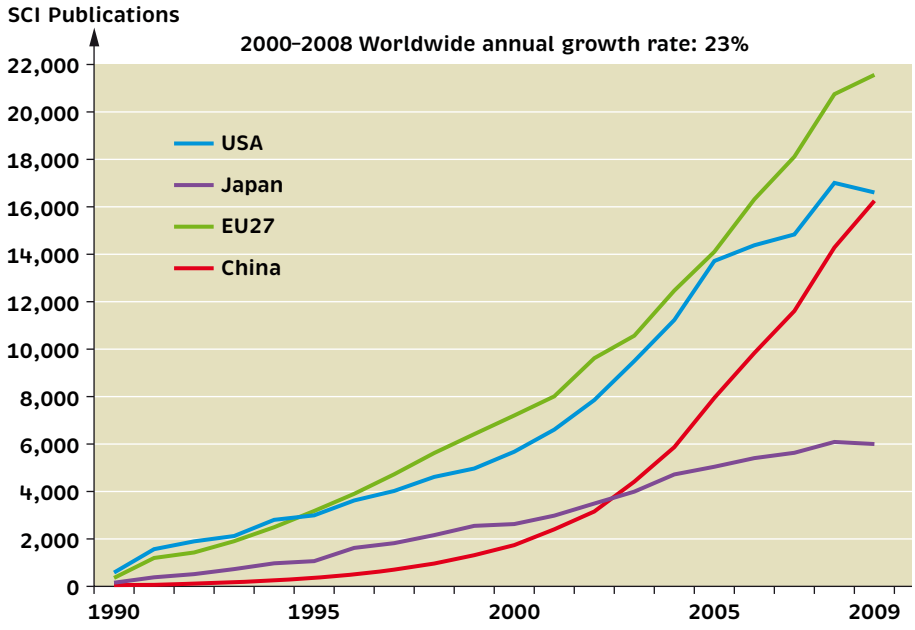


FIGURE 6 Nanotechnology publication in the Science Citation Index 1990–2009.
ROCO 2010.

tion rates, Figure 5. From this search it is found that the keyword *"nanoparticle"* is about 10 times more common than nanomaterial and even more compared to other common nano keywords used in the scientific literature. This search was done in 2011 – a newer search for the ratio of *"nanoparticle*"/"nanomaterial*"* publication numbers yields a ratio even larger than 10.

Current and future trends

The current state and trends of nanoscience and nanotechnology is very well described in the U.S. National Science and Technology Council reports *Nanotechnology Research Directions: Vision for Nanotechnology in the Next Decade* ("Nano 1") and the follow up report *Nanotechnology research directions for societal needs in 2020: Retrospective and Outlook* ("Nano 2")[1] (Roco 2010). These are follow-up studies of Bill Clinton's nanoscience and nanotechnology initiative, called the *"Next industrial Revolution"* launched in 2000. Some interesting aspects in the report are quoted below:

Publication rates as a function of time illustrate the growth of nanoscience and nanotechnology, see Figure 6. A notable fact is that China has just been passing USA in this area (the publication number ratio for 2012 until mid December was *"nano*"* (China)/*"nano*"* (US) = 1.35). Europa as a whole has still a larger publication rate than these two countries. Japan has a significantly slower rate than the three aforementioned regions.

In terms of market size, the estimates done in connection with Clinton's initiative in 2000 have hold up to promise and the projected growth is very rapid, Figure 7. (Note the logarithmic scale indicating exponential growth) The type of products on the market is expected to change over time from rather simple components and devices to more and more advanced systems and characterized by so-called converging technologies, i.e., products that are based on combined knowledge and technology from many disciplines and technologies and are based on extensive research (academia) and development (predominantly in rather large companies).

At the other end of this spectrum of sophisticated and advanced products are a whole set of more or less serious consumer products, mostly marketed by smaller companies and often with limited or no scientific base for the claimed function. Inspecting the web site *http://www.nanotechproject.org/inventories/* one finds almost 2000 products as different as textiles, silver impregnated socks, anti-graffiti

1 *http://wtec.org/nano2/Nanotechnology_Research_Directions_to_2020/*

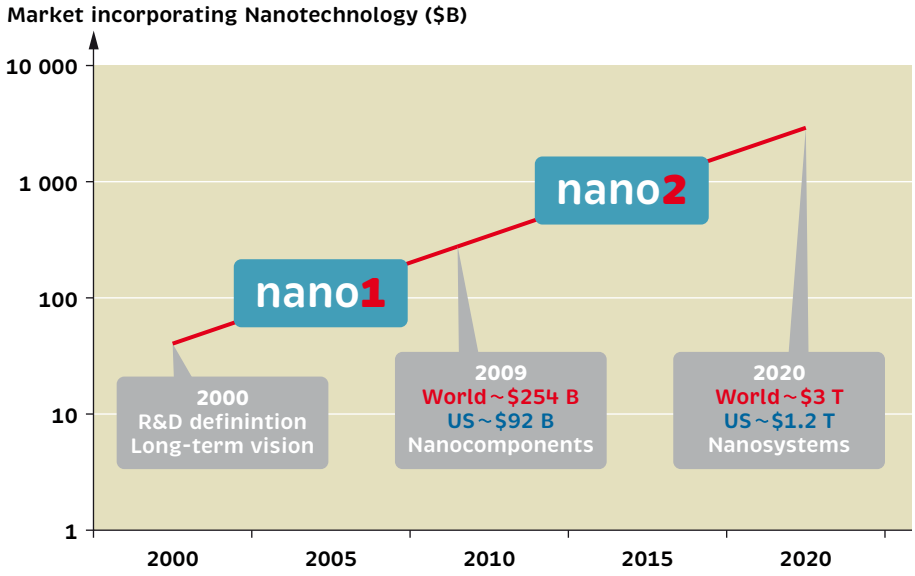


FIGURE 7 Market of final products incorporating nanotechnology: the long-term vision for 2000–2020 and outcomes in 2009. The R&D focus evolves from fundamental discoveries in 2000–2010 (Nano1 in the figure) to applications driven fundamental and nanosystem research in 2010–2020 (Nano2).
ROCO ET AL. 2010.

FIGURE 8 Examples of nanoproducts from the inventory at *http:/www.nanotechproject.org/inventories/* **(a)** 260 Den Nano Silver Far Infrared Anti-odor Healthy Socks fromTsung-Hau Technology Company, **(b)** Acnel Lotion N "Acnel: Nano-Lotion for dry acne skin" from DERMAVIDUALS® U.S.A., **(c)** Ag Nano Phytoncide Toothpaste from SH Pharma Co Ltd, **(d)** Nanometer-Silver Foam Condom from Blue Cross Bio-Medical (Beijing) Co., Ltd., **(e)** All Day Suncare SPF 15 from Kara Vita, **(f)** AIRION State-of-the Artifical intelligent Air Purifier from Shinah Electronics Co., Ltd.

paint, self-cleaning paints, condoms, anti-acne, air purifiers, ski-waxes and many more. Some examples are shown in Figure 8.

It is interesting to note that, while the small companies, which are marketing consumer products, tend to put the label "nano" up front as a (positive) sales argument, large companies are reluctant to do the same, most likely because of the ongoing discussion and concerns on safety and risk aspects, which the latter companies do not want to be associated with. It would be highly undesirable to forfeit the high potential of nanotechnology as outlined above, due to a biased public perception, which is in turn due to a poorly informed society. Therefore, a clear evaluation, estimation and communication of both possibilities and risks towards the public is necessary, which fits ideally into Mistra's mission.

A far from complete selection of products/areas, where one can expect nanoparticles to appear and potentially cause exposures are listed in Table 3 (more detailed version of Table 2). We note that the examples cover a broad range of technologies from electronics to chemical industry to energy technology to consumer products. One example, the wear products from tires and asphalt, illustrate nanoparticles that are unintentionally produced and do not originate from nanomaterials, but are produced from bulk materials (tires, asphalt) or bulk liquids/gases (soot formation from fuels).

In parallel with development of nanoscience and nanotechnology, originally within microelectronics and then spreading into almost any technology area, there was a growing awareness that risks might be associated with some of the nano-

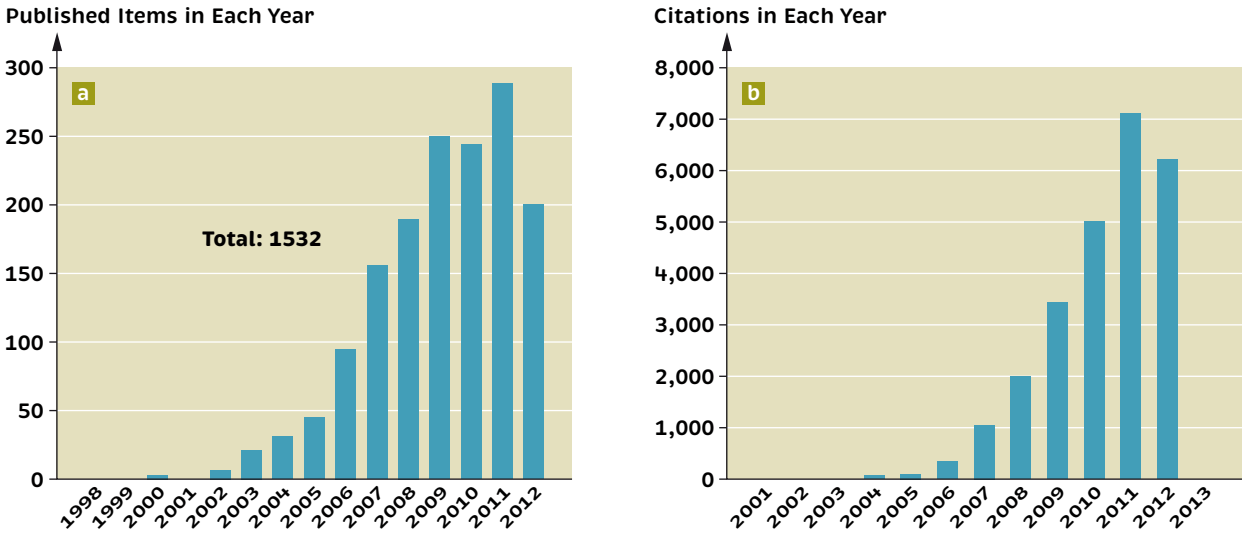
technology-based products. Two fiction books that amplified and to some extent ignited a broader interest were Eric Drexler's *Engines of creation: the coming era of nanotechnology* (1986) and Michael Crichton's *Prey* (2002).

However, making a bibliometric search for *"nanotechnology"* combined with either of the words *"safety"*, *"toxic"*, or *"risk"* yields quite few publications at ISI Web of Science before the turn of the century. The publication rate then takes off very steeply around 2002–2003 as shown in Figure 9 (using *"nano*"* as search work instead of *"nanotechnology"* gives more early publications in the nineties and

TABLE 3 A selection of product areas, which can be expected to contain nanomaterials and to give rise to nanomaterial exposure.

Nanotechnology areas benefiting from the development of microelectronics	
Cosmetics, sun screens	
Drugs and medical products	
Traffic	Wear from tires and asphalt
	Soot
Erosion from construction materials	Carbon fibers, carbon nanotubes
	Powder metallurgy
	Nano-sized fillers in composites
Energy	Used solar cells
	Batteries
	Fuel cells
	Catalysts
	Conductive materials
Industrial manufacturing processes, working environment	
Electronics, sensors	
Agriculture	
Food packaging	
Sport goods	
Anti-bacterial impregnation agents and coatings	
Self cleaning surfaces and paints	

FIGURE 9 Research publication search using search words *"nanotechnology"* AND (*"risk"* OR *"safety"* OR *"toxic"*).
WEB OF SCIENCE 2012.



less dramatic rise at 2002–2003). This rapidly growing interest is illustrated by the citation frequency of articles containing the above search words.

One can thus conclude that the research area of safety, risk and toxicology related to nanotechnology is a young science, which also explains why the knowledge and databases are still fragmented and incomplete. The same statement consequently applies to the legislative, authority and political situation in the area – most of the work remains to be done and the whole area should be labeled immature.

2.3 Nanomaterials as perceived and managed by society

Although increasing familiarity with the term "nanotechnology" among the public has been reported (Simons et al. 2009), many studies and opinion surveys make it clear that the awareness and knowledge of nanotechnology is low (Siegrist et al. 2007; Pidgeon et al. 2009; Priest et al. 2010). Scarce knowledge and ambivalence combined with technological optimism and hopes about benefits has been shown to dominate public opinion about nanotechnology (Pidgeon et al. 2009; Siegrist et al. 2007). In contrast to risk issues pertaining to for example GMO, pandemic flu, radiation, vaccines, and food additives, nanotechnology appears to be a set of technologies where risk is socially attenuated rather than amplified (Priest et al. 2010). Pro-technological attitudes have been found to be associated with positive views on nanotechnology (Kahan et al. 2009). Several studies further suggest that public attitudes vary according to contextual dimensions such as area of application, cases in focus being food and food packaging, health care and medicine, digital information, surveillance, war, and management of environmental pollution (Pidgeon et al. 2009; Siegrist et al. 2008).

A consistent finding is that news media coverage of nanotechnology is overall positive in tone, and that there is an emphasis on benefit rather than risk (Anderson et al. 2009; Boholm and Boholm 2012). US newspapers have a greater tendency to emphasize benefit by giving salience to positive aspects of nanoscience and technology, while European reporting contains a slightly higher level of reported concern about risks and (negative) effects in society. Moral views and religious orientation have been argued to explain differences in public attitude towards nanotechnology in Europe and the US.

Another area of social science research concerns regulatory issues and risk communication targeted to the public. It has been pointed out that risk communication in the area of nanotechnology is precarious since regulation presupposes norms, definitions, categorization and standardization (Boström and Löfstedt 2010). Studies on regulation of risk (or rather its absence) associated with nanotechnology has focused on the path dependency of policy and institutional performance, and on national differences especially when it comes to the US and Europe (Bosso 2010). It has been pointed out that regulations follow historical trajectories where new regulation must align to already existing regulation.

Nano risk regulation lacks a globally accepted governance structure, and where national regulation is often fragmented into sectorial policy areas like work place safety, chemicals, food, drugs, and environmental protection, the regulatory challenges are substantial. In September 2006, the OECD council established the Working Party on Manufactured Nanomaterials (WPMN) to address the implication of manufactured nanomaterials on the human health and the environmental safety (OECD 2010). This working party aims to ensure that the approach to hazard, exposure and risk assessment of manufactured nanomaterials is of an internationally harmonized standard. In the EU, substantial work is ongoing to incorporate risk management of nanomaterials within the REACH chemical regulation program (see Chapter 5 below). Difficulties here relate to the establishment of standardized char-

acterizations of chemicals at nanosize and agreed-upon comprehensive protocols for assessing toxicity. In the literature on risk regulation of nanomaterials, various modes of self- regulation and "soft law" approaches have been considered as possible future models, although identified as problematic since nanotechnology, being a vast and multifarious area of emerging technology, lack overarching industry or branch.

2.4 Swedish nanoresearch and its relation to European and international nanoresearch

Swedish research and development activities on nanomaterials currently in progress were recently mapped in a report from the Swedish Chemical Agency (KemI 2012). No national strategy has so far been developed, but there are various efforts to gather actors in networks, such as the one organised by SwedNanoTech (*www.swednanotech.se*).

Here, as a simple means to compare Swedish nanoresearch to similar activities in other countries, some bibliometry was collected, together with some information about European nanosafety research.

Bibliometry

The Swedish share of research publications estimated through a database search in the Web of Science using the search word *"nano"* or *"nano*"* is ca. 1 %. (*"nano*"* gives a much higher number of publications because it is a broader search, but it makes no difference for the Swedish percentage share of publications). Swedish nanoresearch, as measured by publication numbers, is in Table 4 compared to international nanoresearch measured by the same method.

The publication trends for three of the most publishing countries, USA, China and Germany and for Sweden are shown below. They certainly miss many references but still illustrate the rapid development – and interestingly show a sign of slowing down in the US and a very rapid increase in China.

Database searches are useful tools to get an overview over on-going research in a particular topic. Specifically, such searches are helpful to find trends and to divide activities to different subareas. In this way, it was found that Sweden demonstrates an excellent per capita output and a rapidly rising number of publications over time, as well as an increasing number of citations (Figure 10). On average, each publication was cited 19 times, which is an impressive number. Stockholm, Göteborg, Uppsala, Lund and Linköping are the top-5 national players (Table 5).

Strong/popular research areas in Sweden include: photovoltaics (thin film, Grätzel cells, organic, nanowires), transparent conductors, surface-enhanced Raman spectroscopy, biosensing, nanooptics / nanoplasmonics, nanomagnetism, gra-

TABLE 4 Published items and citations related to nanoresearch worldwide (*"nano*"* NOT *"nanosecond*"* NOT *"nanogram*"*). The total number of items is about 800,000. Sweden is compared to top-5 countries. Note that these search criteria are quite wide, and that the result will change somewhat with more narrow search terms. WEB OF SCIENCE 2012.

	Country	No. of publications	Publications per capita (*10–6)
1	USA	170'587	556
2	China	127'040	95
3	Japan	59'237	464
4	Germany	51'164	625
5	South Korea	35'924	737
...			
21	Sweden	7'344	**789**

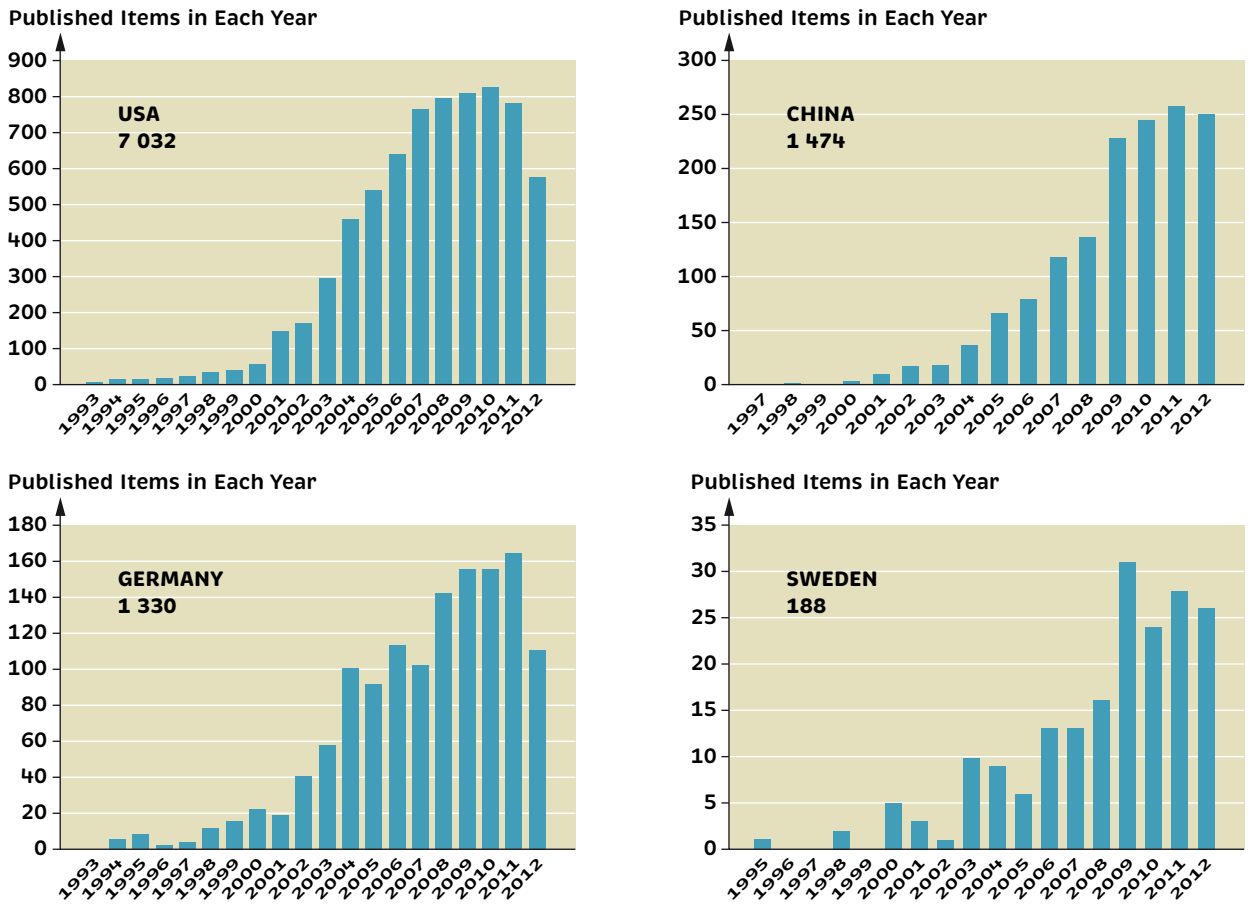


FIGURE 10 Published items in each year for USA, China, Germany, and Sweden. WEB OF SCIENCE 2012.

phene, electronics (Coulomb blockade, single-electron transistor, quantum computing, LEDs), nanocomposite materials, polymer nanofibres, nanocellulose materials, micro- and nanofluidics, thin films and coatings, nanowires, nanorods and nanowhiskers (ZnO, GaAs, InP, Si), drug delivery, lipid membranes, imaging methods (STM, AFM, electron microscopy). Within environmental and health research, it can be mentioned that several nanotechnology oriented research projects are financed by The Swedish Research Council Formas (*www.formas.se*), promoting and supporting basic research and need-driven research in the areas environment, agricultural sciences and spatial planning. Such on-going studies include effects of airborne nanoparticles (e.g. titania, iron oxide, soot, and bioaerosols) from a toxicological as well as an environmental chemistry perspective, but also efforts towards better risk assessment of nanoparticles. Further research in this area related to human health is supported by e.g. FAS (The Swedish Council for Working Life and Social Research; *www.fas.se*).

If one makes a similar search for publications as above regarding "*nano**", but adds search words related to safety and risk and hazard etc., one finds that the relation in publication numbers between Sweden and the whole world is the same, about 1 %. One also finds that the fraction of publications dealing with risk, safe-

TABLE 5 Number of publications divided per region in Sweden.

Region	No. of publications	Remarks
Stockholm	1'858	(of which 1'399 KTH)
Göteborg	1'662	(of which 1'243 Chalmers)
Uppsala	1'524	
Lund	1'467	
Linköping	750	

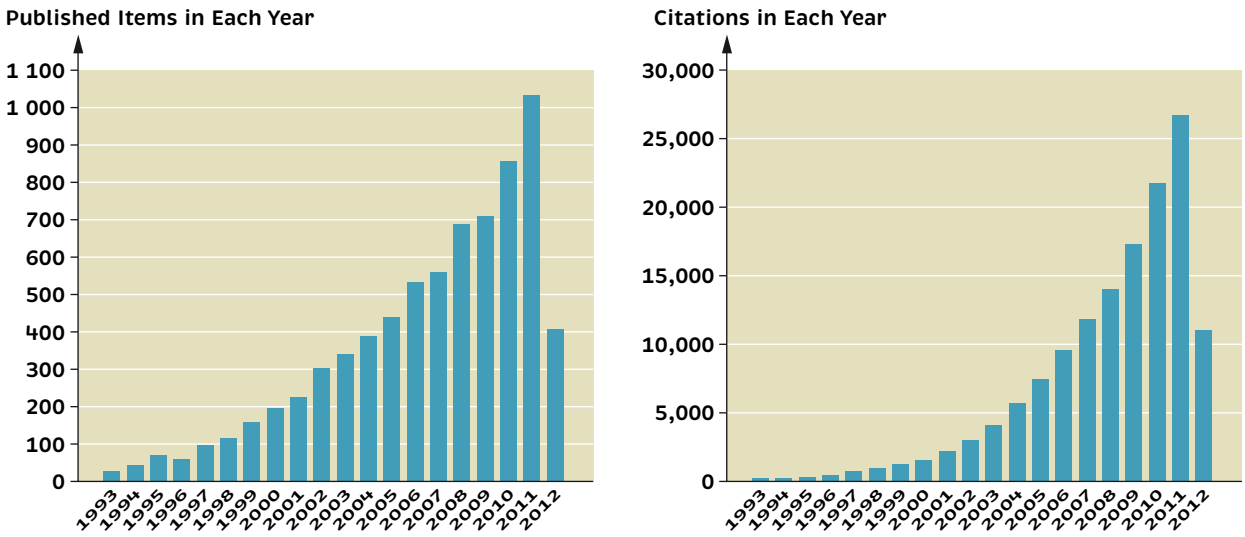


FIGURE 11 Published items and citations related to nanoresearch in Sweden (Search phrase: *"nano*"* NOT *"nanosecond*"* NOT *"nanogram*"*). The average number of citations per publication is 19.
WEB OF SCIENCE 2012.

ty, hazard etc. in the nano-area represents between 7–8 % of the total number of *"nano*"* publications, measured over all years and worldwide. Interestingly, if one searches only for the last 4 years this fraction has increased significantly to nearly 9 % for the whole world and to nearly 12 % for Sweden, the latter indicating a very rapid increase for this area in Sweden.

Under the European framework programs FP6 and FP7 there has been an increasing awareness and ambition to include safety aspects in nanoresearch by the formation of a nanosafety cluster (*http://www.nanosafetycluster.eu*, see also (Schrurs and Lison 2012)). The major aim of the cluster is to facilitate the formation of consensus on nanotoxicology in Europe. Sweden is involved in several of the projects launched within the European nanosafety cluster. The aim of these projects is to develop reference methods and materials for life cycle analysis, exposure, hazard identification, and risk assessment of engineered nanomaterials. More recently there is increased focus on mechanisms of nano-bio interactions.

2.5 Examples of nanomaterials with different functions and their applications

Nanomaterials can be classified in many different ways; function or application, type of material, toxicity etc. Below we have chosen to make a mix of application/function and material type. The reason is that in some cases the nanomaterial type has, or is expected to have, a broad spectrum of applications (e.g. various nanocarbon materials), while in other cases a particular application uses many different nanomaterials (e.g. in heterogeneous catalysis). The presentation here is exemplifying and not intended to be exhaustive. We start by focusing on material types, after which some applications and application areas will be briefly described.

a) Selected examples of nanomaterials

Carbon nanomaterials

The discovery of C_{60} in 1985 by Curl, Kroto and Smalley is often considered as an important milestone in the history of nanotechnology. Given the high stability of carbon nanomaterials as compared to many other nanomaterials, and considering the fact that these materials can be custom-synthesized and functionalized in various ways using organic chemistry approaches, the field of carbon nanochemistry has exploded in the past decades, leading to a large variety of nanocarbons such as fullerenes, nanotubes and graphene. Owing to their extraordinary mechanical, electrical and optical properties, which differ significantly from other forms of carbon, carbon nanomaterials have made their way into various fields, mainly at the

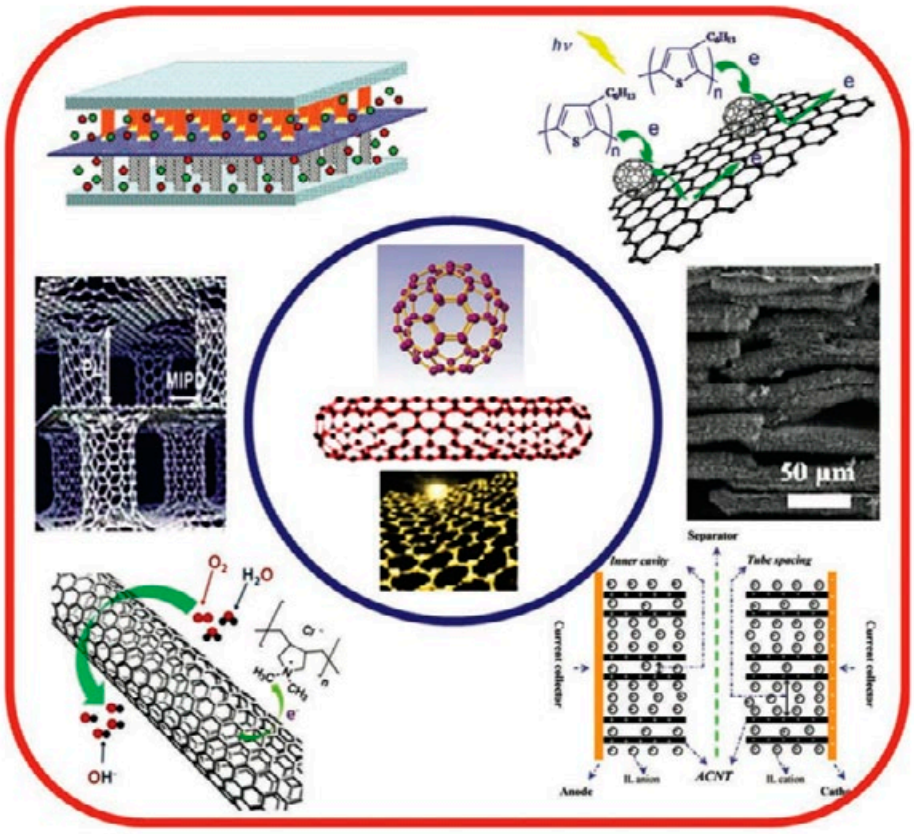


FIGURE 12 Illustrations of how carbon nanomaterials can be used for advanced energy conversion and storage. DAI ET AL. 2012.

research stage. To give a few examples, carbon nanotubes are being researched in the context of nano-electronics, drug delivery and biosensing, and three-dimensional arrays of fullerenes have opened new avenues to design high-surface area catalysts with high photochemical and electrochemical activity. Carbon nanomaterials are today applied to (try to) improve the performance of various sustainable energy conversion and storage technologies, including solar cells, fuel cells, supercapacitors and batteries (Dai et al. 2012). Similar and more applications are currently investigated for the recently discovered graphene (Nobel prize 2010 to Geim and Novoselov).

Silver nanoparticles

The antibacterial action of silver (and copper) is known since more than two thousand years (Chernousova and Epple 2012). Metallic silver has been used in consumer products (including coins and cutlery), and silver salts (like silver nitrate – *lapis infernalis*) have a long tradition in medicine due to their bactericidal properties (Chen and Schluesener 2008; Alexander 2009). Since about 20 years, silver in the form of nanoparticles has been increasingly used for consumer products like textiles, mobile phone coatings, and refrigerator coatings, and also for medical devices like plasters, catheters and surgical instruments (see Figure 9). This leads to a release into the environment, mainly through washing machines and subsequent sewage water treatment plants that amounts to several tons per year in large metropolitan areas (Gottschalk et al. 2009; Wijnhoven et al. 2009; Gottschalk and Nowack 2011).

The synthesis of silver nanoparticles is typically carried out by a bottom-up approach, i.e. by a reduction of silver salts, followed by colloidal stabilization. Alternatively, gas-phase approaches to prepare airborne particles were introduced. In general, these procedures yield silver nanoparticles with different size (from a few nm up to the µm scale), shape (e.g. spheres, rods, cubes, triangles, platelets) and surface properties (from purely metallic to polymer-coated and even biofunctionalized). Consequently, their characterization must involve a number of tech-

niques, among which electron microscopy and colloid-chemistry methods like dynamic light scattering are the most prominent (see below; Chapter 4).

As most nanoparticles, silver nanoparticles are also taken up by many kinds of eukaryotic cells. They end up first in endosomes and later in lysosomes where they are exposed to a low pH. The nanoparticles are releasing silver ions inside the cell and interfere with many biological processes by interacting with proteins, membrane components and nucleic acids. Thus, their toxic action is multifold.

Silver also acts on bacteria, which is the basis of its use as bactericidal agent. The mechanisms are the same as with cells, but it should be noted that bacteria tend to develop a resistance against silver and therefore can tolerate larger silver concentrations after a few weeks of adaptation. Therefore, a permanent environmental release of silver may lead to widespread selection mechanisms (resistances) among bacteria(Silver 2003).

Gold nanoparticles

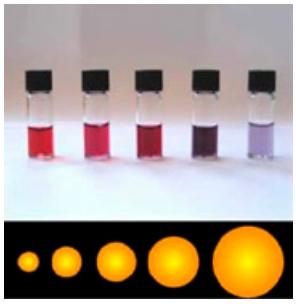


FIGURE 13 The color of a colloidal solution of gold nanoparticles depends on the particle size.

Due to the unique optical, electronic, and molecular-recognition properties of functionalized gold nanoparticles, they are the subject of substantial research. Of all metal nanoparticles, gold is one of, if not the most common. Their use covers electronics, optics, opto-electronics (Atwater and Polman 2010), biomedical diagnostics and therapies (Dykman and Khlebtsov 2012), sensors, catalysts, medical applications and many others, including coloring of glass for thousands of years in different shades of yellow, red, or mauve, depending on the concentration of gold and sizes of the gold particles.

The simplest method to synthesize gold nanoparticles is by the method pioneered by J. Turkevich et al. in the 1950:ies. It involves the reaction of small amounts of hot chlorauric acid with small amounts of sodium citrate solution. The colloidal gold will form because the citrate ions act as both a reducing agent, and a capping agent. This method yields modestly monodisperse spherical gold nanoparticles of around 10–20 nm in diameter suspended in water. The formation of larger particles comes at the cost of monodispersity and shape.

Today the colloidal methods to synthesize gold has gone through a number of refinements with regard to control over shape, size, monodispersity, and coatings. In addition other methods have been developed, e.g., various lithographic ones, which are particularly useful for fabrication of gold particles supported on solid substrates/surfaces.

The interaction between gold nanoparticles and light is determined by the particle environment, size and shape. This is exemplified in Figure 13, where it is shown how the color of gold nanoparticle solutions is strongly dependent of the nanoparticle size, as a result of a localized surface plasmon resonance phenomenon at the particle surface.

This ability of gold (and many other metal nanoparticles) to excite localized plasmons have spurred research and applications in many areas, to utilize this phenomenon in e.g., optoelectronics, optical sensing, capturing of solar light in solar cells and medical therapy.

The broad range of applications under current research with gold nanoparticles, and the change of reactive properties of gold nanoparticles at very small sizes suggest that they should be subject to scrutiny also with regard to safety etc. properties. Furthermore many of the applications mentioned above in the field of plasmonics can be achieved also with silver and other metallic nanoparticles.

Titania nanoparticles

Titania (TiO_2) is one of the "classical" nanoparticulate systems, which are prepared and applied in large scale. As passivating component on titanium metal it is always present in tissue contact when biomedical titanium implants are used, e.g. as total hip endoprosthesis, as surgical screw or nail, or as tooth implants. In this immobile form as passivating layer with a thickness of a few nm, it is clearly biocompatible

and non-toxic. This spontaneous coating of titania *in vivo*, is essentially the same in nature as the above mentioned corona effect –although the composition of the adlayer of course differs widely in different environments.

Titania is used in large quantities as white pigment in many dyes and lacquers, substituting the more toxic lead pigments. As semiconductor, it may convert light into hot electrons (or holes) and an electrical potential difference, which can promote and is used to degrade unwanted compounds, e.g. in waste water by photocatalysis. Titania is generally considered as an unproblematic material, also in the environment. It is also approved as food additive (Wiechers and Musee 2010). Yet another application is in so-called dye sensitized solar cells (DSSC)

Titania occurs in three different polymorphic forms: Rutile, anatase and brookite, with the first two being the most prominent, also as minerals. They have different physical properties, e.g. density and bandgap (semiconducting properties). This must be taken into account when titania is characterized.

As nanoparticle, titania is used, e.g., in sun creams to absorb UV light and also in self-cleaning devices, where UV light leads to electron excitation and subsequent degradation of adsorbed dirt particles (photocatalysis, see more details below under Chapter 2.5.b)). It is generally accepted that titania does not pose problems after ingestion or after application onto healthy skin. This situation is less clear for wounded or inflamed skin.

Like all nanoparticles, titania can be taken up by cells. An adverse reaction is unlikely, given the non-toxic character of titania, however it remains to be proven. This may change under irradiation, which may lead to the creation of reactive radicals even inside cells. If brought into more complex systems like body fluids or surface water, titania may undergo the same agglomeration processes and surface coating by biomolecules as other nanoparticles (Teeguarden et al. 2007).

Other oxide nanoparticles than titania

Current research exploits and develops a large number of other ceramic nanoparticles, of which oxides is the largest subclass, but also nitrides, carbides and many other compounds belong to ceramics. Application areas include fillers in paper (silica SiO_2), catalysts (ceria, zirconia, vanadia,...) and photocatalysts, batteries, solar cells (zinc oxide), mechanical construction materials, cutting tools, corrosion inhibition coatings, to mention just a few. For catalysts, photocatalysts and solar cells there is often a desire to create very large surface area per weight unit, which has lead to the formation of particles, whisker, fibers etc. , which potentially can come loose from their supports

Polymer nanoparticles

By far the largest application area for polymeric nanoparticles, based on publication numbers/literature search, is in the biomedical field, where they are used as therapeutic agents (for example dendrimers and other polymer drug carriers) and also for diagnostics purposes. However, from a volume of use point of view other applications are also important such as using nanoparticles in various polymer composites and as fillers etc.

b) Selected existing or potential application areas based on nanomaterials

Catalysis and photocatalysis: Nanocatalysts for environmental cleaning purposes

Heterogeneous catalysis is an old chemical processing technology, which has been going through several stages and revivals. The first industrial processes were developed at the beginning of the last century between 1900–1910, primarily the Haber-Bosch process for ammonia synthesis from hydrogen and nitrogen, which is a fundamental process behind synthetic nitrogen fertilizers for agriculture. A large number of bulk chemicals are today produced by similar (heterogeneous) catalysis pro-

cesses, e.g., nitric acid, ethylene oxide and methanol. Another extremely important process involving heterogeneous catalysis is catalytic cracking of crude oil, which yields better product patterns in the petrochemical industry than the older thermo-cracking and is responsible for gasoline and diesel fuel production.

A landmark in *environmental catalysis* was the introduction of the catalytic converter in gasoline driven cars, first in California the 1970'ies, which today also includes catalytic cleaning systems for diesel engines, lean combustion engines etc. By this technology harmful emissions (primarily NO_x, CO, hydrocarbons (HC) and soot particles) from cars and trucks have been dramatically reduced. Another example is the so-called selective catalytic reduction (SCR) technique, which is used to reduce NO_x emissions from combustion furnaces and also from diesel driven, heavy-duty vehicles.

Today the attention to catalysis both for environmental applications and for energy technology (fuel production, energy conversions, energy efficiency) is increasing. Searching for *"environment"* and *"catalysis"* or *"environmental"* and *"catalysis"* yields over 4000 publications and *"energy"* and *"catalysis"* yields over 10 000 hits and is accelerating.

The connection between catalysis and nanomaterials is that a large fraction of the catalysts used, e.g., for the applications mentioned above are so called supported catalysts, consisting of very small, i.e. 1 to <100 nm, catalytically active particles supported on a carrier material ("support"). The catalyst nanoparticles are usually deposited via wet chemical methods and then functionalized by subsequent thermo-chemical processing. For example, the support material of a typical car exhaust catalyst is impregnated with Pt and/or Rh precursors (salts), which are then sequentially first oxidized (to remove the salt anions) and then reduced to pure metallic Pt and Rh particles of << 10 nm in size. Many other materials may also be involved in nanoparticle form, like Pd, ceria, zirconia, vanadia. There have been concerns that some of these particles may enter the environment via erosion processes and particulate emissions via the exhaust gases. However, today this is not a main issue – most attention related to particles in the combustion engine area is directed to particulate emissions in the form of soot particles and other particles that originate from the combustion and engine operation processes and produce various types of ash particles (Sappok and Wong 2007; Wirojsakunchai et al. 2007; Florio et al. 2011; Storey et al. 2012).

Photocatalysis is a much newer technology with still very limited commercial use compared to "normal" catalysis. It is, however, a technique receiving very rapidly increasing R&D interest for several reasons, some of which have already been mentioned. The two most important ones are related to (i) photocatalytic cleaning of air and water and (ii) production of fuels from solar light, so called solar fuels. Air/water cleaning combines a (photo)catalyst with light, creating a mechanism where photons are used to excite electrons (or holes) in or very close (nm range) to the catalytic sites, and where activation barriers that would prohibit a normal, thermally driven catalytic reaction are overcome at low temperature thanks to the activation of the desired reaction by the photoexcited electrons/holes. This action can be performed with artificial light or with solar light, the former applied for e.g., indoor air cleaning, the latter explored for solar fuel production. One claimed benefit compared to normal catalysis is (in some cases) cost. Another benefit may be a higher selectivity, i.e. more of the desired reaction product(s) and less of undesired ones. Typical catalysts are TiO_2, by far the most common, and other oxide/semiconductor materials. New materials are continuously explored, included core shell materials, where the bulk of the NPs is of a different material than the surface material.

The solar fuel application was originally dominated by the interest to produce hydrogen from water with the help of solar light, in the same way as described above using hot electrons/holes. The additional difficulty here, compared to just

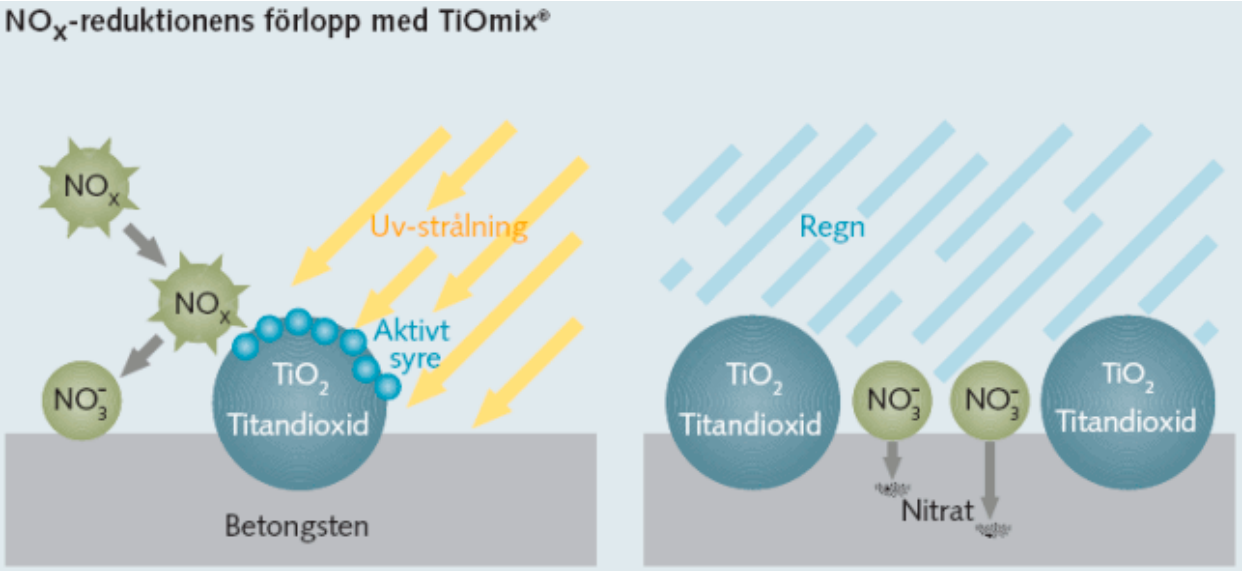


FIGURE 14 Principle for the function of TiOMix, a product to reduce air NO_x.
FROM *www.heidelbergcement.com/se/sv/cementa/produkter/tiomix.htm*

photocatalytic cleaning reactions, is that the solar fuel reactions are always endothermic – the intention is to absorb solar energy and to convert it to and store it as an energy rich fuel. Typical traditional materials are the same as above but many new materials are currently under investigation. A clear change in trend is also that the research aims also at other fuels than hydrogen like alcohols and hydrocarbons, and furthermore that schemes are investigated, which can use captured CO_2 from combustion processes as a raw material in the photocatalytic process towards fuel production.

An example of a product based on the photocatalytic properties of titania is one from the company Cementa. It is called TiOmix ®, and, according to their web site,[2] it can remove or reduce several hazardous compounds (organic, NO_x, ...).

TiOmix can be used for house walls and roofs, tiles, road pavements and other applications. The process is schematically illustrated in Figure 14. UV light from the sun causes excitations in TiO_2 that promote chemical reactions like NO_x removal and/or oxidation of organic molecules. The product has been tested in the field with regard to NO_x removal on sidewalks covered by stone plates into which TiOmix has been incorporated. Field tests were done by Malmö Miljöförvaltning (The Environmental office of the city of Malmö) (Nilsson and Häger 2010). A significant NO_x reduction was observed with NO as test gas. Lab tests had shown larger reductions. In an interview it was pointed out that the current concerns about nanoparticles in the environment is a hampering factor for the market entrance of this product.[3]

Removal of environmental contaminations: Remediation of ground water

Several methods applying nanoparticles are explored today to remedy environmental problems. Among the most well known examples are remediation of contaminated soil and groundwater with nano-scale zero-valent iron and photo-catalysis involving e.g., titania nanoparticles and either artificial or solar light (see previous paragraph). However, the potential environmental risks of nZVI in *in situ* field scale applications are largely unknown at the present and traditional environmental risk assessment approaches are not yet available. This is an example of application of nanomaterials in large scale, where the employment of short and long-term environmental monitoring in and around injection sites, with a focus on transport, persistency, and long-term ecotoxicological effects of nZVI has been recommended in a recent report (Grieger et al. 2010).

2 *http://www.heidelbergcement.com/se/sv/cementa/produkter/tiomix.htm*

3 Private communication with Åsa Nilsson, Project leader R&D, Cementa

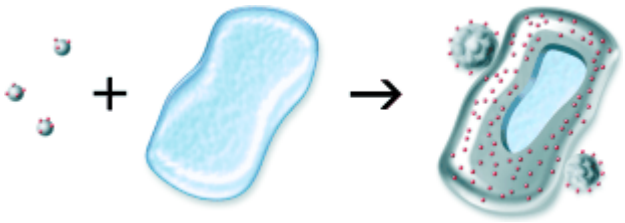


FIGURE 15 Example of coating of living cells with a continuous oxide shells prepared from modified titania nanoparticles (to the left). Release (biodelivery) of encapsulated cells or drugs is possible by dissolution of the titania nanoparticles.
FROM KESSLER ET AL. 2008.

Agriculture: Nanoparticles for release of nutrients, pesticides, and biocontrol organisms

Nanoparticles (especially silica-based materials) are starting to be used in agriculture to achieve slow or retarded release of nutrients and pesticides (Kah et al. 2012). Further micro- and NPs are used as controlled-release agents of various pesticides by large companies and are researched by all the major agrochemical companies. The claimed advantages are a targeted release and a lower pesticide use, but the persistence and mobility of nanopesticides in the environment are yet unknown. There are also potentially attractive applications with respect to bio-encapsulation of microorganisms for release in an agricultural context. One example of such an encapsulation material is titania-based matrices for biocontrol organisms (Groenke et al. 2012), using the same concept as described for cells in Figure 15.

Food: Nanoparticles as food additives and as packaging materials

It is almost unavoidable that engineered nanomaterials at some stage come into contact with food and animal feed. The legislation in place through the efforts of the various European agencies and the FDA in the USA are designed to take into account food additives and other chemicals used in food processing and packaging (FSA 2008, FDA 2012). The regulations in place are guided by the specific chemical properties of each individual component, however the extra properties due to size of the particles, is not accounted for. There is therefore no legislation in place at the moment, which specifically governs acceptable levels of nanoparticles in food and similar consumer products, although the relevant authorities in most countries are currently working towards new rules and regulations.

Nanotechnology applications are foreseen to bring benefits to the food sector, although potentially along with risks (Chaudhry et al. 2010). Nanoparticles may find their way into food in a variety of ways, including:

- Residual particles from food processing steps involving nanoparticles.
- Accidental contamination with nanoparticles from equipment due to wear during processing.
- Addition of nanoparticulate formulations for preservation of flavor and texture enhancement.
- Use of nanoparticles in packaging materials.

Although NPs are not necessarily detrimental it would be wise to have effective methods to monitor levels of nanoparticles in food and to have acceptable limits for nanoparticles (these limits should, of course, be specific for separate compounds).

It may be that nanoparticles find their way into the food chain from sources outside the processing industry. Particles present in nature, either anthropogenic materials inadvertently introduced into the environment or naturally occurring nanoparticles, may be absorbed by plants or microorganisms and through successive ingestion by higher organisms may become bio-concentrated in certain tissues and thereby affecting the organism's metabolism and function. It would be of great

interest to map the occurrence of anthropogenic and natural nanomaterials in the environment and their uptake and transport through the food chain.

Nanomaterials may also have useful properties in food production and processing. As mentioned above, nanoparticles may affect the texture and flavor of food giving greater consumer satisfaction. They may, perhaps be used as a medium for the introduction of specific nutrients in processed foods. Finally there may even be possibilities to utilize the properties of nanoparticles for the controlled release of substances, nutrients and plant protection agents, in an agricultural or horticultural setting. Use in such a context should be accompanied by effective methods to monitor the fate of the particles.

Cosmetics: Nanoparticles as active substances, carriers and formulation aids

Cosmetics is one of the earliest and most intensively developing nanotechnology fields, which was recently reviewed by Strömme et al. (Mihranyan et al. 2012). In fact, more than 13% of registered nanotechnology-based products on the global market in 2009 were classified as products for cosmetic use. New functionalities that nanomaterials introduce as active substances, carriers and/or formulation aids include physical UV shielding, skin whitening, delivery of active ingredients, thickening or enhancement of optical properties. A growing market is represented by nanosilver-containing cosmetics, which are claimed to have an antibacterial effect, e.g. toothpastes, body washes, and hand creams. Notably, even inert metals like gold and platinum are used to promote cosmetics, despite the absence of a biological or antibacterial effect (Chernousova and Epple, in press).

Nanotechnology is also employed in cosmetics packaging (e.g. antibacterial coatings containing nanosilver), air/moisture barriers (e.g. nanoclays) or miniaturized sensors allowing monitoring of conditions during transportation (e.g. temperature and moisture profiles, damage).

Medicine: Nanoparticles as drug carriers and gene transfection vectors

The merging of nanotechnology and medicine is commonly referred to as nanomedicine (Wagner et al. 2008). It is a rapidly expanding field of research including many different applications, such as drug delivery systems, contrast agents for *in vivo* imaging, sensor platforms for *in vitro* diagnostics, as well as medical implants and scaffolds for tissue engineering. The expectations on the field of nanomedicine are high in terms of, *e.g.*, improved therapies and diagnostics, but needs to go hand in hand with proper safety assessments (Nyström and Fadeel 2012). Although not a target for the planned Mistra programme, the nanomedicine area is briefly

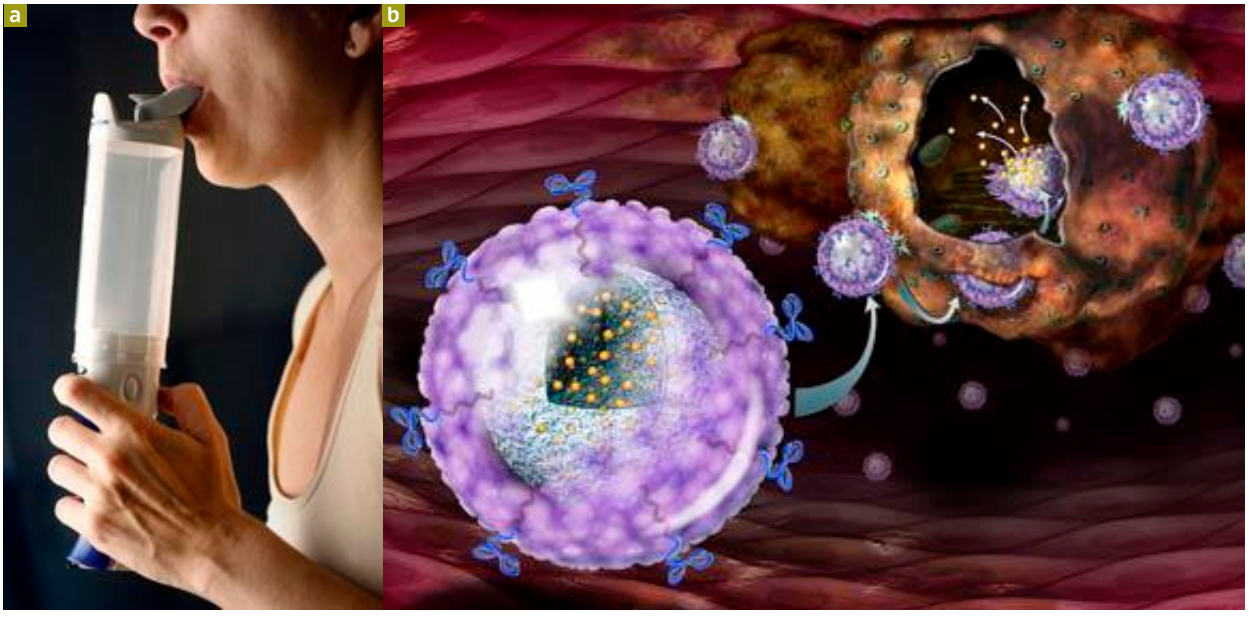


FIGURE 16 There is a rapid development of nanoformulation of drugs, both for alternative routes of administration (exemplified in **(a)** by inhalation of a nanoformulated drug), but perhaps more importantly targeted drug delivery (illustrated in **(b)**, by an antibody-modified nanoparticle targeted to tumour cells for cancer therapy; *http://web.mit.edu/newsoffice/2008/nanoparticles-tt0213.html*).

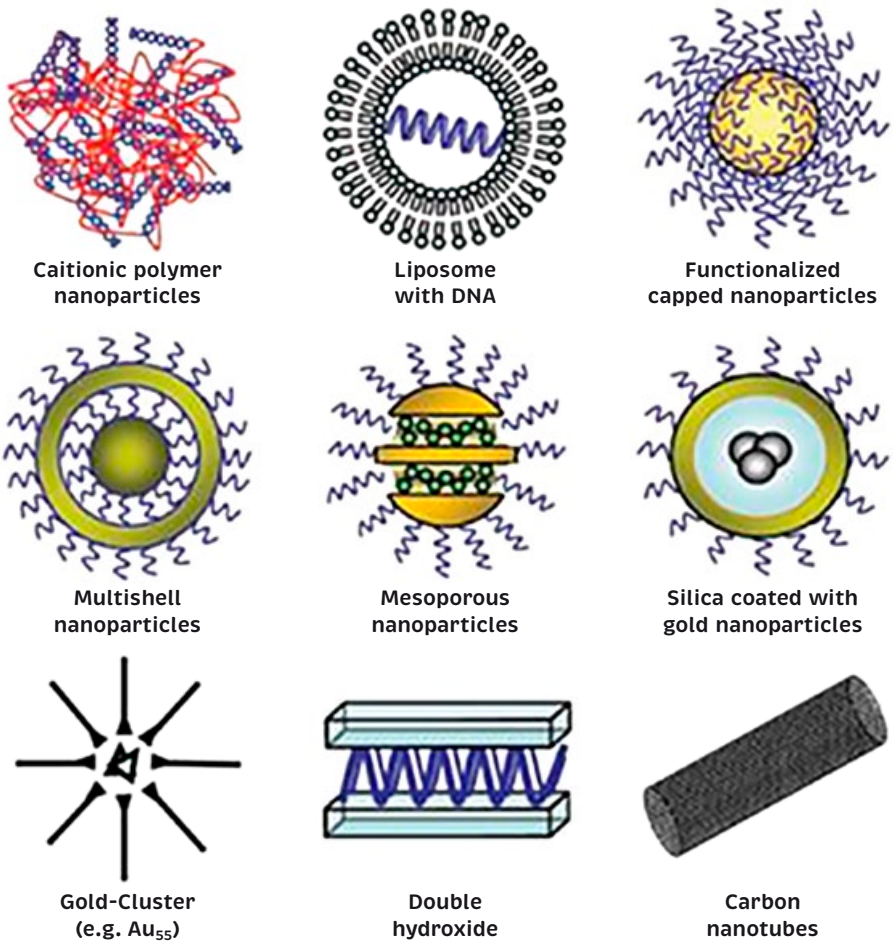


FIGURE 17 Different types of nanoparticles, which can be used for the transfer of nucleic acids into living cells. From Epple et al. SOKOLOVA AND EPPLE 2008.

reviewed here because there are many synergies between nanotechnology for medicine and nanotechnology for the environment and ecosystems.

Intensive research is today directed to design and development of nanosized drug carriers for drug delivery (Figure 16). The hope is that drugs can be used more efficiently, with less negative effects, when properly packaged, such that the drug does not leak (is not released) before it reaches its target tissue. A common targeting idea is to place and expose antibodies on the nanoparticle surface that are specific to receptors on e.g. cancer tumor cells. Release of the drug occurs then either spontaneously or by external activation, e.g. by a local heat pulse. Common drug carrier materials are liposomes and polymer complexes. For example, insulin is often injected in the blood stream complexed with polycationic polymers, designed for slow release of the insulin over a long period of time. Inhalable, nanoparticulate insulin was introduced to the market in 2007, but was withdrawn within less than one year, likely partly due to side effects in some patients.

There are also intense activities around the design of theranostic agents, i.e. agents, which combine diagnostic and therapeutic properties. For example, magnetic nanoparticles can be designed for effective MR imaging and combined with therapeutic hyperthermia of cancer or controlled release of cancer drugs (through the application of an external magnetic field) (Yoo et al. 2011), and gold nanoshell complexes are under development, suitable for both MR imaging and phototherapy (based on plasmonics-derived optical properties) (Bardhan et al. 2011).

Related to this area is also the development of nanoparticle-based transfection agents for cell culture (Figure 17). In a review of this field from 2007, it was shown that various kinds of inorganic nanoparticles mediate gene transfection (Sokolova and Epple 2008). Such agents are not yet in clinical practice, but constitute a very strong research area denoted “gene therapy”.

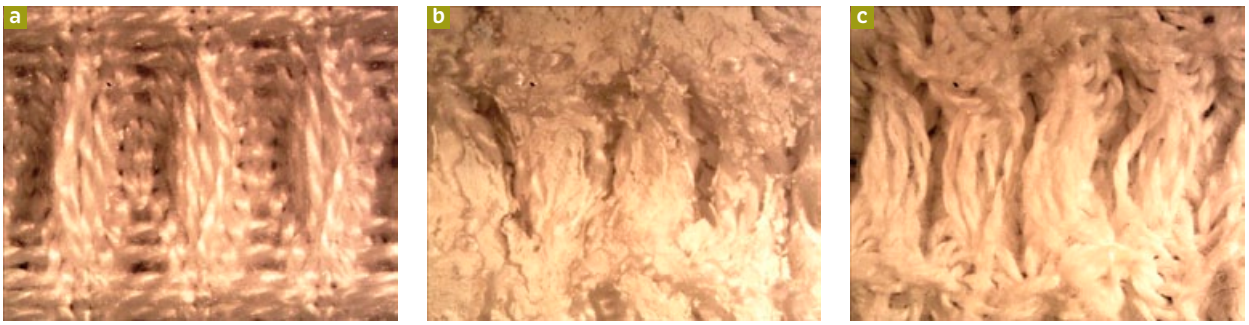


FIGURE 18 The images show three kinds of nanoparticle containing coatings developed at The Swedish School of Textiles, Borås, aiming to develop a textile water purification system based on photocatalysis in nanoparticle form (a textile photocatalytic reactor). In **(a)** the referent fabric directly from the weaving machine is shown. In **(b)** the same kind of fabric has been processed by an industry standard coating with acylate as the binder containing photocatalytic particles. As seen this ends up in a cake-like morphology with an appearance far from the reference. The textile properties are drastically changed resulting in a stiff, rough, dust emitting product. In **(c)** the fabric is instead treated with a sol-gel system. Photocatalytic nanoparticles are formed bottom-up in a true nanosize surface functionalization. By this the textile properties are kept un-changed.
PERSSON AND HELENIUS, IN PREPARATION.

FIGURE 19 Insecticide treated nets last longer when a nano scale formulation of the insecticide pyrethroid is used.
FROM ARTICLE POSTED AT *www.scidev.net*, SEPTEMBER 9TH, 2010 (PHOTO FROM FLICKR/BREAD FOR THE WORLD).

Textiles: nanofibres and composite materials

Finishing of textiles (e.g. the lotus effect finish; "self-cleaning") and fiber manufacturing are areas where nanotechnology has great potential for application. However, many other functions are also envisioned (Coyle et al. 2007).

Nanofibers used in textiles are often electro spun, and nanofiber materials are being developed for (antibacterial) wound care products and medical devices, including implants. Lightweight, electrically conductive fibers (e.g. carbon nanotubes) may be used in textile materials measuring heart activity, or in curtains lighting up in the dark. Nanocrystals as colorants are stable and can, when mixed with dyes, produce a spectrum of colors, which is not attainable by either dyes or pigment. Nanoclays are used to make nanocomposite polymer materials with enhanced mechanical properties.

Use of nanotextiles in filtration and membrane separation are promising areas where nonwoven fabrics composed of electro spun nanofibers are excellent candidates due to their large specific surface area, a high porosity and small pore size in comparison with commercial textiles. An example of the benefits of nanotechnology in an application area such as filtering is shown in Figure 18, illustrating the development of a textile water purification system based on photocatalysis in nanoparticle form.

Nanotextiles are also being used in insecticide treated nets, notably mosquito nets laced with nanoparticles of pyrethroid. Pyrethroid had been combined with nets before, but doing so on the nanoscale means the particles are small enough to cling to the fibres even when washed. These nano-nets can last up to five years – a five-fold improvement on conventional netting (Figure 19).

Electronics: Nanosized components in electronic devices

The electronics industry was partly covered in Chapter 2.2. As pointed out there, most electronic components are firmly attached to their host bulk materials. Therefore, conventional silicon microelectronics, already in the nano-size regime since a decade, is not judged to create any immediate nanosafety or nanorisk concerns, in spite of the fact that the individual electronic components are today at or below 20 nm in size. One exception may be in waste handling of such circuits where, e.g. conductor fragments (Cu, Ag, ...) that are part of the IC circuits, may create nanoparticles that are set free. However this situation may change, if and when the nanoelectronics research results in completely new devices with new materials and production methods, like bottom up self-assembly of new types of electronic components. Such devices may be made of entirely new materials like carbon nanotubes, graphene or even organic/biological molecules (molecular electronics, bioelectronics). If, and in that case when, this is going to happen is impossible to predict.

Sensors: Biochips and detection of chemical compounds in air and water

If we imagine that every transistor on a state-of-the-art IC chip were a chemical sensor for a particular molecule that we wanted to detect, there would in principle be a sensing power to detect tens to hundreds of millions of different chemicals on the area of a stamp. We are still very, very far from that limit in practice, but the thought example/vision illustrates the potential of nano-sensors. DNA chips constitute a conceptual example, which, however, is still in the micrometer range. The creation of DNA chips is one of the great breakthroughs in the medical (and also forensic) area in the last decades. With a DNA chip a very large number of DNA fragments can be tested on an extremely small area. One can imagine how the shrinking of DNA chips and maybe protein chips into the nano-range will extend the impact of biochips both for medical, forensic and other uses. On can also easily see how the concept can be broadened to chemicals, organic or inorganic for analysis of air and water.

Nanosensors aim at exploiting the ability to place extremely many sensing spots or functions on a very small area or in a very small volume. The limitation of nano-sensors development today is a combination of many factors such as design of the specificity of a single sensing spot (low specificity means weak discrimination of one molecule from another), the sensitivity (a too small sensing spot may give rise to too few molecules assembled on that spot and therefore a too small signal to detect), spatial resolution (if sensing spots are crowded too closely together they may disturb each other either during sampling of molecules to be detected or during readout (conventional optical readout is limited to a few hundred nanometer spots). Sometimes cost is also an issue. However, these limits are continuously pushed to better and better performance and it is a pretty safe prediction that sensors based on nanotechnology and nano-materials will be a rapidly growing area, with impact on every area that exploits sensors; industrial production, transport systems, energy systems, agriculture, safety at airports, drug search and anti-terrorism, and not the least environmental control such as car exhausts, city air control, CO_2 levels, water control, general chemicals analysis etc.

Energy: Nanomaterials in solar cells, fuel cell electrodes, and battery electrodes

Energy technology is one of the areas where nanoscience and nanotechnology are expected to have a very large impact. The number of publications is increasing very rapidly (Figure 20).

A list of areas where nanoscience and nanotechnology already have, or are expected to have a large impact, is shown in Table 6. Some of these application areas are further articulated below. Other than catalysis and photo-catalysis, nanomaterials are further expected to influence insulation materials for heat insulation in buildings, (better) materials for electrical transmission lines (lower weight, smaller losses), smart windows for keeping houses warmer or cooler or both, and miniaturized sensors for a variety of energy efficiency and control applications.

TABLE 6 Potential areas where nanotechnology can contribute, or already contributes, to a sustainable energy system

Nanotechnology areas contributing to a sustainable energy system	
Photovoltaics (i.e. solar cells for electricity)	
Hydrogen production & storage	
Gasification of coal and biomass	
Solar thermal energy	
Catalysis	Car and industry emission exhaust cleaning
	Energy efficient industrial processes
	Fuel conversion and use
Electro-catalysis, e.g., fuel cells, batteries	
Thermoelectrics	
CO_2 fixation	
Sensors for energy efficiency and clean emissions	
Smart windows	

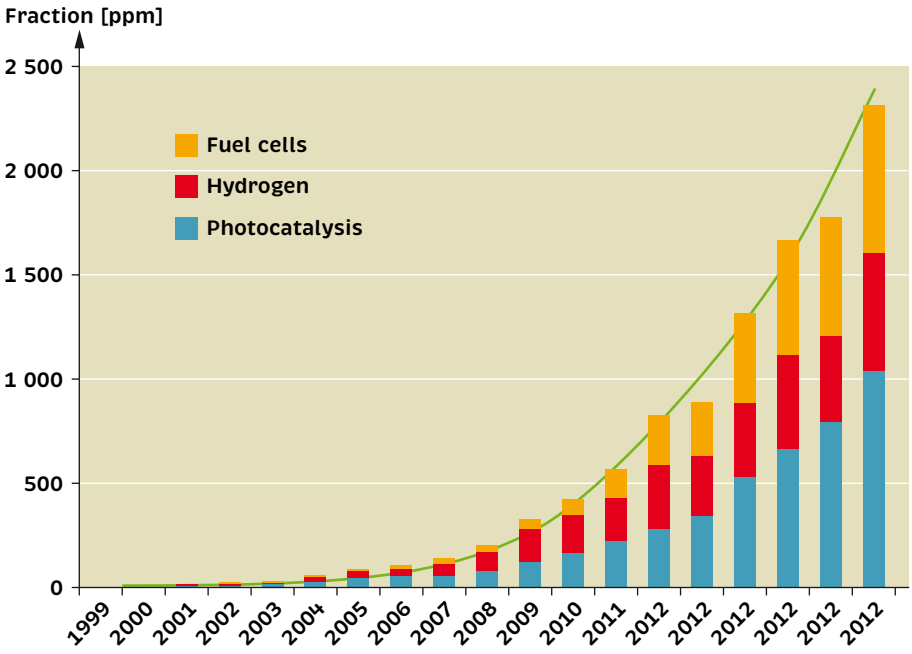


FIGURE 20 "Nano-for-Energy" publication trends. This is an updated version of a similar graph previously published graph (Zäch et al. 2006).
WEB OF SCIENCE, APRIL, 2012.

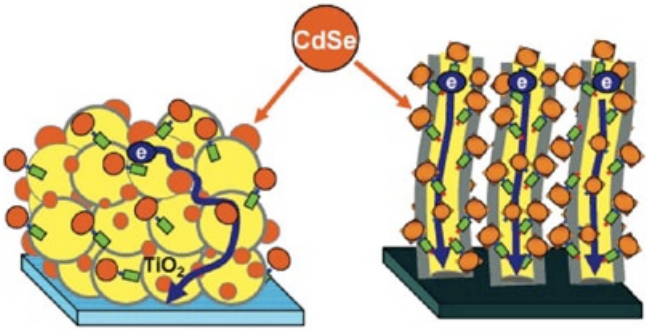


FIGURE 21 Random versus Directed Electron Transport through Support Architectures, **(a)** TiO_2 Particle and **(b)** TiO_2 Nanotube Films Modified with CdSe Quantum Dots. Schematic by Kongkanand et al.
KONGKANAND ET AL. 2008.

The emission of large amounts of greenhouse gases, with CO_2 being the most well known representative, has become a serious environmental concern in that it threatens our planet's climate and ecosystems. The largest source of carbon dioxide emissions is the burning of fossil fuels such as oil, gas and coal to generate energy. Strategies to approach the issue of carbon dioxide emissions include i) to increase energy efficiency, ii) to promote energy production from renewable sources, and iii) to develop strategies for CO_2 management. Nanotechnology is a viable tool for all of these approaches, as illustrated below with three selected examples.

The cost of solar electricity is to a significant extent governed by manufacturing and material costs on the one hand and cell efficiency on the other hand. In order to make solar electricity economically more viable, the former have to be reduced and/or the latter has to be raised. Nanostructures that efficiently absorb light, such as semiconductor nanowires, plasmonically-active metallic nanoparticles or quantum dots (see e.g. Figure 21), can be used to reduce the active layer thickness in semiconductor-based solar cells without compromising the cell's light harvesting capacity. In this way, the consumption of costly materials can be reduced, and the use of flexible substrates and continuous roll processing technologies becomes possible. Both these factors allow for significant cost savings. In the case of organic and dye-sensitized solar cells, where materials costs are much lower than for semiconductor-based solar cells, the main role of nanotechnology is to control the structure of the donor-acceptor interface and to minimize charge transport pathways, respectively, in order to increase current extraction efficiency.

Besides cost issues, its intermittent character and the associated need for energy storage are other factors that have limited the widespread use of solar energy. Nanostructured electrodes have shown great potential to enhance the key parameters of electricity storage in batteries, namely storage capacity, charging/discharging rates and cycle life. At the heart of this enhancement is the high surface-to-volume ratio of nanostructures, which implies reduced ion transport paths, increased robustness towards volume changes and large surface area.

Another way of storing solar energy is to produce chemical fuels (solar fuels) such as hydrogen, where the fuel can be stored and used to generate electricity in a fuel cell when needed. The catalyst required to run this process typically consists of expensive noble metals. Since the involved chemical reactions occur on the catalyst surface, nanostructures with a high specific area are advantageous and allow lowering the cost of fuel cells. Nano-engineered membranes are a promising avenue to the construction of more efficient, lighter and longer lasting fuel cells. All these materials potentially also generate emissions of nanoparticles.

3. Environmental and Health Risks caused by Nanoparticle Emission

Nanoparticles may cause hazards relevant to humans and to ecosystems (Oberdorster et al. 2007). Therefore it is important to map exposure and fate of nanoparticles in the environment, as well as to study nano(eco)toxicology. Decisions taken on the regulation of nanomaterials will probably be based on incomplete datasets. There therefore exists a need for the collection of data to aid the assessment of risks and benefit from the deployment of nanomaterials.

3.1 Nanomaterials in the environment

There have always been naturally occurring nanomaterials in the environment (e.g. minerals, ashes) and in biological systems (e.g. proteins, viruses, pollen). Thus, from an evolutionary perspective, ecosystems and humans have adapted to being exposed to these materials. However, the occurrence and effects of incidentally generated nanoparticles (like diesel emission soot and ash particles) have shown that new health risks may be related to these, perhaps because they are "unknown" to the human body. The anticipated rise in environmental occurrence of manufactured nanomaterials therefore raises the question whether similar (or novel) effects can be anticipated. In the following, a few examples of naturally occurring, common antropogenic nanoparticles, and manufactured nanomaterials in the environment are given.

Naturally occurring nanomaterials: Nanoclays

One example of a commercially important, naturally occurring nanomaterial is nanoclay (Patel et al. 2006; Nalawade et al. 2009; Suresh et al. 2010). Clays have a layered structure, and the particles used are platelets with a few hundred nanometers in width and few tens of nanometers in thickness. The layers of the clay can exfoliate to extremely thin layers (about 1 nm) resulting in a very high surface area material. Hundreds of natural clays are known, and they are used in very large scales as fillers, ion exchangers, sorption materials in water purification etc. Increasing amounts of clays are used as polymer nanocomposites where they are mixed with a variety of polymers (thermoplasts, thermosets, synthetic and biopolymers) or rubber. They can enhance the stiffness at low addition levels and improve barrier and flame-retardant properties. The interface between clay and polymer is an issue and to improve the adhesion either the polymer or the clay needs functionalization ("compatibilization"). Polymer/clay nanocomposites are used in millions of tons as rheological modifiers for paints, inks and greases. Additional commercial applications of clays are emerging in a variety of diverse markets ranging from automotive to packaging.

A synthesis of silicate clays leading to uniform products is very difficult, and the synthetic clay-like layered materials do not contain silicate layers but are layered metal double hydroxides (LDH). Being fully synthetic, they are chemically pure and their properties can be controlled. Emerging applications both for natural silicate clays and synthetic LDHs are found in cosmetics and drug delivery. Clay nanocomposites can be made both with excipients and active agents. The organic, polymeric or biomolecules can bind on the clay platelets and between the single layers. The active agent (drug) -clay interactions allow to modifying the active agent (drug) release and even improve drug dissolution.

Antropogenic nanoparticles in the environment: Combustion produced soot, wear particles, …

The major sources of antropogenic nanoparticles in the environment are combustion processes and emissions from consumer products and goods.

In urban environments, 70 % of airborne fine particles result from combustion and 50 % are due to primary emissions from combustion sources (Xi and Zhong 2006; Dellinger et al. 2008; Lou et al. 2010).

Soot particles may be formed in all combustion reactions, not only in diesel engines, but also from gasoline, alcohol, wood, coal and waste combustion. The main origin of soot is incomplete combustion of the fuel that is combusted. In addition to soot, which essentially is like amorphous carbon black, but often also containing hydrocarbons to various extents (see below), the combustion produces two types of nanoparticles: one with around 1 nm and the other of 10 nm size. Soot itself has a typical particle size of 100 μm, but it consists of much smaller nanosized spherules with diameters 10–80 nm. These spherules attach to each other and form complicated chains of particles, often with fractal appearance. Both the chemical composition of the soot particles (e.g. the amount of incorporated hydrocarbons and impurities) and the size and shape, depend strongly on the fuel and on the combustion process (oxygen fuel ratio, temperature, pressure,). For example, oxygen rich and high temperature combustion produces almost no soot, while low temperature, fuel rich combustion produces much soot. The most common metrics used to describe particle toxicity are surface area, sulfate and carbon content and occurrence of polycyclic aromatic hydrocarbons (PAHs), but they cannot fully explain the observed health impacts. Combustion product nanoparticles may contain metals, different organic carbon compounds and they can generate oxidative stress in exposed organisms. Soot in and from diesel combustion engines has been quite extensively studied. In model studies the formation of soot in the fuel-rich part of a flame has been explored in detail, as a result of incomplete combustion, and chemical mechanisms via polycyclic aromatic hydrocarbon compounds have been identified.

One very important part of air-born pollution is formed by tire wear particles (Wik et al. 2009; Kreider et al. 2010). The estimated annual emissions are in order of tens to hundreds of million kilograms in every country. Another way to quantify the emission is grams per meter of road per year, the number being ca. 140 g. Ecotoxicology, including risk assessments of tire wear particles, has been studied taking in account aquatic toxicity, terrestrial toxicity, and health effects. The physical and chemical characterization of wear particles has been only insufficiently studied.

In addition to tire wear particles there are substantial emissions from asphalt surfaces especially in countries, which allow the use of studded winter tires. The tire wear particles have immediate effects on road runoffs, receiving waters and air. The particles can accumulate in sediments and some bioavailability studies have shown they can also be found in living organisms.

In Sweden, VTI (The Swedish National Road and Transport Research Institute) has made several studies of wear particles related to road traffic.

Regarding traffic related nanoparticles connected to wear of materials, there are two main questions addressed:

1. Are nanoparticles, which are used to improve properties of materials in tires, road pavements, etc., emitted to the environment as nanoparticles?
2. Are nanoparticles formed from wearing processes, primarily from tires or road pavements? The involved materials may be bulk or nanomaterials.

To investigate the occurrence of nanoparticle emission from traffic related wear mechanisms, both laboratory and field tests have been used. *Brake wear* has been studied using dynamometers(Sanders et al. 2003; Beddows and Harrison 2008; Iijima et al. 2008) as well as in test rigs such as pin-on-disc machines. In field tests particle measurements using inlets close to the expected source, e.g. wheels or brakes have been performed (Hussein et al. 2008; Pirjola et al. 2010; Mathissen et al. 2011). Particle formation from the tire/road interface has been studied at VTI using a circular road simulator, where tires are run around a circular track while particle emissions are measured in the simulator hall(Gustafsson et al. 2009). Laboratory tests have also been made in vertical drum equipment at BASt (Kreider et al. 2010), where a test rig with a wheel is placed inside a rotating drum.

For detection of nanoparticle emissions, size distribution devices are useful. Several equipment using different techniques are used. Nanoparticles from wear processes might well be partly volatile, making detection and sampling non-trivial.

Nanomaterials are used in tires, e.g. silica and carbon black. During normal driving conditions, low or no emissions of nanoparticles from ordinary summer tires are detected, while in cornering and situations with high slip noticeable emission of particles peaking at 30–60 nm are present (Mathissen et al. 2011). It is not clear though, whether or not these particles originate in nanomaterial added to the tire or if the formation (wear) process itself is responsible for the size range.

Brake wear, both from cars and trains, tend to generate generally smaller particles than other traffic related wear processes (Abbasi et al. 2011). Mathissen et al. (2011) showed that at full braking a nucleation mode at about 6 nm is formed as well as a coarser mode at 30–60 nm.

In controlled tests, using a road simulator at VTI, nanoparticle emission has been proven to be connected to the presence of studs in studded tires (Gustafsson et al. 2009). These particles have a number peak at about 30–50 nm. The origin is likely to be stud/tire rubber, stud/pavement rock or stud/bitumen. So far, no chemical analysis has been made to identify the particle source.

Also in railroad environments, nanoparticle emissions have been detected. At the railroad tunnel stations below Arlanda airport, certain electrical train sets were found to be connected to emissions of nanoparticles, while other train sets were not (Gustafsson et al. 2012). The process of formation is unknown, even though spark formation from the pantograph contact is suggested.

In an ongoing research project run by VTI together with Stockholm University, the Royal Institute of Technology and Lund University, sources of particles, including nanoparticles are studied in a road and a railroad tunnel. The aim is to identify the sources and find ways to mitigate emissions. In the road tunnel, a certain task will be to identify the stud related nanoparticles found in laboratory tests.

Manufactured nanoparticles in the environment

The increasing use and production of manufactured nanoparticles will inevitably lead to environmental exposure from multiple potential sources. These sources include spills during production and transport, production wastes (liquid, solid, airborne), and release from products during the use, re-use, and end disposal. In terms of exposure to the aquatic environment, the widespread and diverse use of products containing manufactured nanoparticles subsequently leads to a focus on

municipal wastewaters streams, including direct discharges of storm water, combined sewage overflows, and ineffective removal of engineered nanoparticles at sewage treatment plants, as well as potential leaching of engineered nanoparticles from municipal solid waste landfills (Gottschalk and Nowack 2011; Nowack et al. 2012). Studies are now emerging showing the release of engineered nanoparticles incorporated in different types of commercially available products, e.g. textiles and paints (Benn and Westerhoff 2008; Kaegi et al. 2010). While techniques exist for air sampling and analysis, serious technical limitations remain for monitoring in soil, water, and sediments with regards to sampling procedures, sample preparation, and analytical-chemical detection.

The increased use of silver nanoparticles in consumer products is an important example of an expected increased occurrence of manufactured nanoparticles in the environment. Silver nanoparticles are used in consumer products as different as socks, underwear, air sanitizers, and food supplements (Luoma 2008). For textile uses, a release into the aquatic environment is likely as well documented in the literature (see e.g. (Benn and Westerhoff 2008; Geranio et al. 2009; Impellitteri et al. 2009)). Due to lack of monitoring data – and the afore-mentioned technical obstacle related hereto – modeling of environmental concentrations has been carried out. These models show that silver nanoparticles may be transported to waste water treatment plants upon release from textiles. Here the silver will be primarily incorporated in sludge (Blaser et al. 2008; Gottschalk et al. 2009), however this is dependent on the treatment efficiencies and the configuration of the treatment plant. Therefore, a release of silver nanoparticles to surface water bodies cannot be ruled out. Silver, as nanoparticles or as dissolved silver, is very toxic towards aquatic organisms ranging from bacteria and algae, over crustaceans to fish (Fabrega et al. 2011). Depending on the waste management options chosen for disposal of wastewater treatment sludge, silver may also be released to agricultural fields. This may not only have effects on the terrestrial ecosystems by may also result in leaching of silver to surface and groundwater.

3.2 Exposure models for nanomaterials in the environment

It has been found that transport, transformation and uptake in the environment are more complex for nanomaterials than for substances present in a molecular or ionically dissolved form, and new tools to understand and appreciate the exposure are urgently needed. However, existing experience and knowledge of how colloidal material (humus, proteins, peptides, inorganic colloids, etc.) occurs in nature might be applicable also for intentionally produced nanoparticles (Klaine et al. 2008).

Nanoparticles released into the environment may form aggregates and agglomerates that behave differently from the free nanoparticle, to a greater or lesser extent. The degree of aggregation and agglomeration depends on the type of nanoparticle (importantly its surface properties), its concentration and its properties in combination with the environmental conditions (Arvidsson et al. 2011; Quik et al. 2011).

Knowledge of various nanomaterials, fate and transformation in the environment is necessary to estimate the exposure levels and thus the risks a use of nanomaterials may cause. In Sweden, the Swedish Chemicals Agency (KemI) has called for a development of dispersion models for nanomaterials in order to make estimates of the exposure situation for risk assessment of various substances and materials (KemI 2008). This is also an intense area of risk research and models to describe the fate and distribution of nanomaterials are under development, many

of which apply principles used for chemical fate modelling and material flow modelling (Mueller and Nowack 2008; Gottschalk et al. 2009; Gottschalk et al. 2010; Praetorius et al. 2012).[4]

The attempts to model dispersions etc. have often been made on the basis of present knowledge to make a conservative estimate about the concentrations in the environment. Thus, calculations are based on simplified assumptions about nanomaterial applications, their emission and behavior in the environment, but the model approaches anyway provides valuable "order-of-magnitude" information for environmental exposure assessments.

3.3 Potential beneficial and adverse effects on human health

Most nanoparticles may be taken up by cells. Sometimes this has adverse effects on the cells but there are also high expectations on nanomaterials as future, improved drug carriers. Notably, the uptake of nanoparticles by cells may occur intentionally (area of nanomedicine) or unintentionally (area of nanotoxicology), and lead to successful treatment of disease or cause disease.

Classical examples of diseases caused by nanoparticle exposure

It is well established that nanomaterials may sometimes have adverse effects on human health. One well-known example is carbon dust in the form of micron- and nanosized particles (Teeguarden et al. 2007). The earliest reports of coal miner's black lung date to 1831, and since that time, a large number of clinical and epidemiological studies have documented the existence of coal workers' pneumoconiosis. Also, diesel trucks and buses have spewed large amounts of soot into the air, where fine particulates can cause respiratory and heart problems. While large progress has been made to reduce the emission of particulate matter from diesel engines and to protect coal and laboratory workers from exposure to carbon nanomaterials, further studies are needed in order to guarantee their safe handling and use, not the least considering the raising importance of coal as an energy source.

Improved treatment of diseases by nanodrugs

As already mentioned above (see Chapter 2.5b), there are intense on-going research activities in the nanotechnology field, including e.g. the development of targeted nanodrugs, towards more efficient treatment of disease. The tuning of the biological effects of these novel materials is a balance between adverse and beneficial effects, where early toxicology testing is important to avoid investing to much resources in concepts which will eventually fail due to safety reasons.

Nanotoxicology

Following upon the knowledge build-up around material properties of different classes of nanomaterials (natural, antropogenic, engineered), the new field of nanotoxicology aims to understand how the physical form and chemical composition of nanomaterials interact synergistically to determine toxicology (see e.g. (Krug and Wick 2011; Maynard et al. 2011)). Importantly, it has been suggested that dose, biokinetics, and the significance of physicochemical properties are areas which are important in understanding nanomaterial toxicity compared with that of macroscale materials and/or constituent chemicals (Oberdorster 2010). With respect to dose, it has been discussed in the literature whether mass concentration alone is a relevant measure for nanomaterials, or whether number concentration

4 See also KemI report carried out by Gothenburg University and Chalmers soon to be published including a comparison of different exposure models for nanomaterial and discussing implications to develop such models.

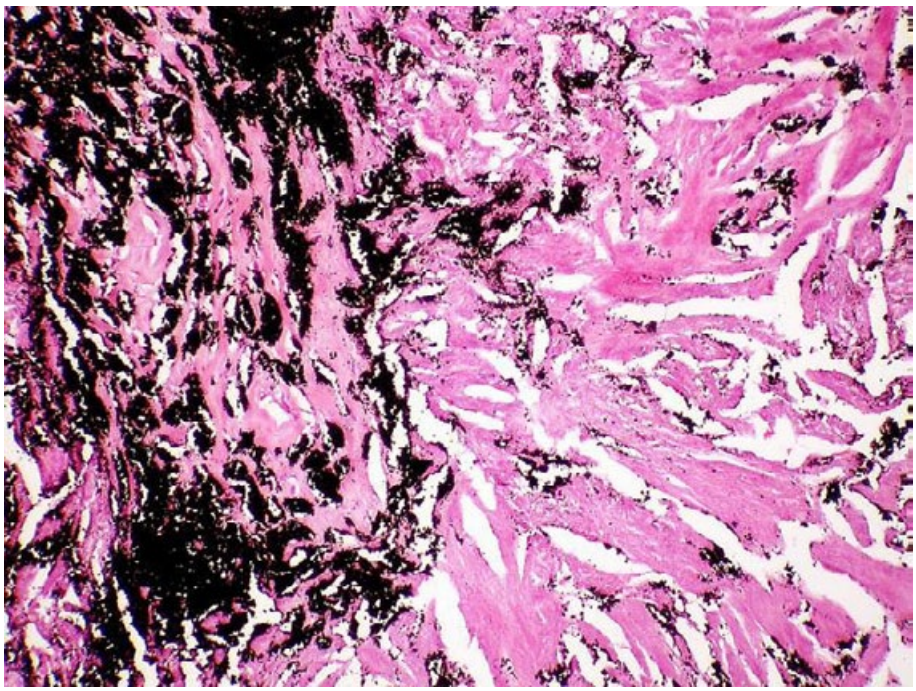


FIGURE 22 Coal workers pneumoconiosis – Collageneous fibrosis due to silica inhalation and black pigmentation due to carbon inhalation.

or surface area is a more sensible measure. Furthermore, dosimetry needs to be developed (see further Chapter 4). Another challenge is the tendency of nanoparticles to aggregate and agglomerate, which becomes important, e.g., where transport between organs, across cell barriers, or along neuronal pathways is mediated by size. Furthermore, particle shape has been indicated to be a key parameter in determining biological impact, where fiber-like morphologies have been suggested to particularly potent.

In order to learn about the effects of nanoparticles on human health it is important to perform toxicokinetic studies, addressing, e.g., nanoparticle interactions with biological barriers in vitro, as well as absorption, distribution, metabolism and excretion data in animal studies. Due to their unique properties, nanomaterials may be taken up and distributed in the body differently than bulk materials or dissolved ions. Notably, nanoparticles have a tendency to translocate from primary deposition sites to secondary organs. For example, once they are in the airways, nanoparticles can be distributed to other parts of the body, and nanomaterials have been shown to be transported across the epithelium out from the lung (Kendall and Holgate 2012). In another example, it is shown how nanoparticles reach the brain via the sensory nerve or by crossing of the blood-brain barrier (Oberdorster et al. 2009). Nanoparticles may also cross various membranes in the cells, and appear to enter cells both by passing through cell membranes and via endocytosis (Greulich et al. 2011; Canton and Battaglia 2012). Some nanomaterials have for instance been found in the nucleus and/or the mitochondria, which means that the distribution may be very different for nanomaterials compared to other materials. This may be of significance for the toxicity of nanomaterials (Nel et al. 2006).

It should be emphasized that the biokinetics of nanoparticles is influenced by the local biological environment over time, where the "corona" of biomolecules coating the particles is important for the biological fate of the nanoparticles (Cedervall et al. 2007; Monopoli et al. 2012).

Future sophisticated nanomaterials will ask for development of more advanced test methods and systems-based approaches to allow assessment of toxicity and potential risks (Maynard et al. 2011). This development is unlikely to keep pace with the accelerating development of novel materials, and there will be a knowledge gap between the materials being produced and their safe use. This challenge is suggested to be met by high-throughput toxicological screening (Nel et al. 2012).

3.4 Nanoecotoxicology

There are limited ecotoxicological studies on nanomaterials available, but the ones available show that effects occur in the test systems. Yet, it seems difficult to draw any firm conclusions about whether intentionally produced nanomaterials in general could pose a greater threat to the environment than intentionally produced substances in general. Increased knowledge of uptake mechanisms for different nanomaterials and additional toxicity testing procedures are strongly required, both with regard to various nanomaterials and regarding different test organisms (Stone et al. 2010).[5]

Especially, for environmental organisms issues of bioaccumulation is of very high importance (Baun et al. 2009). However the knowledge on uptake, distribution and elimination is very limited and thus uptake mechanisms and further distribution in different organisms are important research areas as is increased knowledge on bioaccumulation (Stone et al. 2010; Mikkelsen et al. 2011).

In order to interpret results from ecotoxicological tests on nanomaterials so that they can be used in risk assessments, it is important to develop standardized methods to have control over what the test organisms are actually exposed to, what they receive and what affects them (see further Chapter 4).

5 *http://ihcp.jrc.ec.europa.eu/whats-new/enhres-final-report* (viewed 19 November, 2012)

4. Experimental Methods to study Nanoparticles

When studying nanoparticles it is of importance to measure and indicate the concentration/dose (e.g., based on total particle surface or their weight, so-called dosimetry) in various tests (e.g. cytotoxicity (Teeguarden et al. 2007)). This is more difficult for nanoparticles compared to most molecules, and there is not yet consensus within the scientific community on reference materials or methods to use (Krug and Wick 2011). Therefore, on the initiative of OECD, development of methods for nanoparticle characterization and effect studies is underway in the Working Party on Manufactured Nanomaterials (WPMN).

The WPMN has undertaken to determine for each of the included nanomaterials (Table 7) about 60 pre-decided endpoints (OECD 2010). The selected endpoints belong to the following areas;

- nanomaterial information/identification (9 endpoints),
- physical-chemical properties and material characterization (17 endpoints),
- environmental fate (15 endpoints),
- environmental toxicology (6 endpoints)
- mammalian toxicology (9 endpoints)
- material safety (3 endpoints)

The OECD view is that in most instances, existing test methods and assessment approaches can be used, although, e.g., methods of sample preparation and dosi-

TABLE 7 The manufactured nanomaterials selected by WPMN. The table of nanomaterials should be viewed as a "snapshot in time" as materials could be added or removed depending on the current use and production of nanomaterials. OECD 2010.

Manufactured nanomaterials under study by the OECD
Fullerenes (C_{60})
Single-walled carbon nanotubes
Multi-walled carbon nanotubes
Silver nanoparticles
Iron nanoparticles
Titanium dioxide
Aluminum dioxide
Cerium oxide
Zinc oxide
Silicon dioxide
Dendrimers
Nanoclays
Gold nanoparticles

metry for safety testing may need to be adapted. Thus, OECD continues to review all existing methodologies to identify and implement the necessary changes for their application to nanomaterials. This basic view does of course not rule out that new methods might need to be developed for specific situations, where existing methods may not suffice even after adaption.

4.1 Nanoparticle interaction and "effect" studies

The interaction of nanoparticles with (bio-)molecules is of obvious importance and experimentally accessible to some degree. For instance, people have now started to analyse the amount and nature of proteins, which are adsorbed onto the surface of nanoparticles after immersion into body fluids like blood (Monopoli et al. 2011; Lesniak et al. 2012). This process is closely related to the concept of corona formation, i.e., adsorbed layers of molecules on the surfaces of nanoparticles. It remains elusive, however, which parameters control the adsorption of molecules onto the surface of a nanoparticle, when this adsorption is reversible or irreversible, if/when adsorbed molecules are replaced by other ones at a later stage of exposure and whether adsorbed molecules are in some equilibrium between the state of adsorption and dissolution. Yet another question regarding proteins is if they adsorb in their native state, or denature partly or totally, with very different functionalities as a result.

To address these points (see also Table 8), new experimental techniques or adaptation of existing ones are necessary, and theoretical studies would complement these results. To understand the interaction of complex molecules with nanoparticles in complex media is one key to assess their effect onto the environment and people's health. These questions are difficult to address and require new/adapted methods (both experimental and theoretical) (Montes-Burgos et al. 2010; Krug and Wick 2011; Stark 2011).

4.2 Collection of nanomaterial samples from the environment

In general, it is difficult to collect nanoparticles from complex media like body fluids or surface water or wastewater. The nanoparticles are typically present in a low concentration, and they are mixed with other types of micro- and nanoparticles, coated with (bio-)molecules, agglomerated with other types of particles etc. Therefore, the simple approach of centrifugation or filtration does not work because it leads to a mixture of solid or semi-solid material from which the nanoparticles

TABLE 8 Examples of endpoints for testing of nanomaterials suggested by OECD/WPMN. OECD 2010.

Endpoints for environmental fate	Endpoints for environmental toxicology	Endpoints for mammalian toxicology
Dispersion stability in water	Effects on pelagic species (short term/long term)	Pharmacokinetics/Toxicokinetics (ADME)
Identification and further testing of degradation product(s)	Effects on sediment species (short term/long term)	Acute toxicity
Abiotic Degradability and Fate	Effects on soil species (short term/long term)	Repeated dose toxicity
Adsorption-Desorption	Effects on terrestrial species	Chronic toxicity
Adsorption to soil or sediment	Effects on microorganisms	Reproductive toxicity
Bioaccumulation potential	Effects on activated sludge at WWTP	Developmental toxicity
		Genetic toxicity
		Experience with human exposure

have to be isolated. Notably, centrifugation and filtration are difficult for small, dispersed nanoparticles due to the slow or non-existing sedimentation and the need for nanofilters, which tend to get clogged by other particles. For most of the size range of interest Brownian motion of particles dominate over gravitation force, inhibiting sedimentation. Therefore, there is an urgent need to develop separation techniques to quantitatively isolate and analyse representative samples of nanoparticles from complex fluid systems (Teeguarden et al. 2007; Krug and Wick 2011). In this respect both airborne nanoparticles, nanoparticles dispersed in water-based media, and nanoparticles dispersed in a solid matrix (like soil) have to be considered.

4.3 Characterisation/analysis

The characterisation of nanoparticles even in clean systems is a challenge in itself, and methodology towards this end is being developed. The need for integrated analytical techniques in the area of food and consumer products was recently discussed, and it was concluded that the analytical difficulties have their origin not only in the sample preparation but also in the actual characterisation (Stamm et al. 2012). These are generic issues also relevant in the environmental context.

The difficulties related to the characterization of nanoparticles, even in pure form, arise from the many properties of nanoparticles, which may all influence their behaviour in the environment, including their biological properties. A full characterization of these properties is a demanding task cost and time wise. These properties are mainly (see also Figure 23):

- chemical composition
- surface composition (may differ from the former)
- particle size
- particle shape
- surface functionalization
- surface charge (zeta potential)
- crystallinity
- polymorphic phase(s)
- state of agglomeration

Note 1: These properties combined with the environment where the NPs are, in turn determine the composition of the so-called corona layer, that is the composition of the adlayer of molecules that may be adsorbed on the NP surface from the environment.

Note 2: Several of the above properties are interrelated and not independent quantities. This also raises the question of suitable reference materials to calibrate the existing and yet to be developed analytical methods.

Note 3: In the list above we have not included certain properties, which are important in the context of the fate of the nanoparticles. These are e.g. stability towards dissolution in different media (pH, salinity,...) temperature stability, corrosion properties, affinity of different inorganic and organic molecules to the nanoparticles (corona effects), catalytic effects on the environment etc.

A variety of experimental techniques are typically necessary for a full characterization. We must distinguish between techniques that can be applied to dispersed nanoparticles (e.g. dynamic light scattering, optical spectroscopy, ultracentrifugation, nanoparticle tracking analysis) and methods which can only be applied to isolated (typically dried) nanoparticles (for size and shape mainly scanning and transmission electron microscopy (TEM, SEM) and scanning probe microscopies; for chemical composition, e.g., EELS and EDX in TEM/SEM instruments, and surface analytical methods like SIMS, AES, XPS). The drying may cause artefacts, e.g. wrong conclusions about the state of agglomeration. It must also be stressed that it is difficult and presently almost impossible to distinguish between a large particle

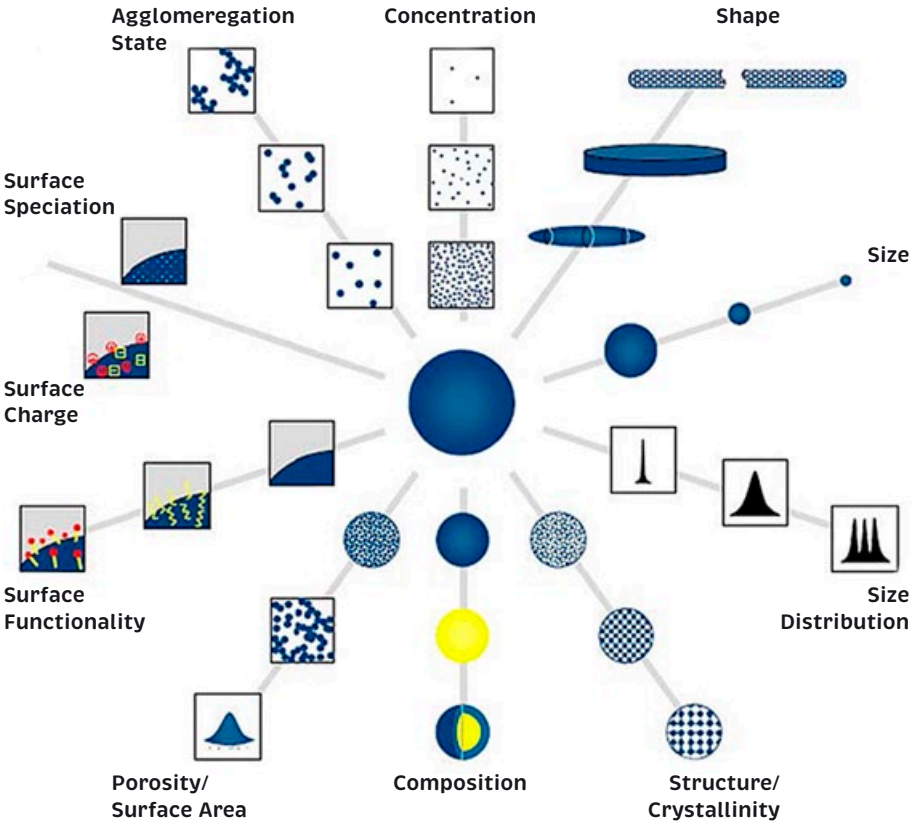


FIGURE 23 A schematic view of relevant physical-chemical descriptors for fate and toxicity studies.
HASSELLÖV AND KAEGI 2009.

and an agglomerate of smaller particles. Furthermore, analytical methods usually have a range of particle sizes in which they are applicable, and therefore heterogeneous samples containing particles from the nm scale over the µm scale to the mm scale cannot be analysed by one method alone.

It must be noted that many of these characterization techniques are typically applied right after synthesis in pure solvents, typically in water. It is well accepted now that the state of nanoparticles changes if they are brought into contact with complex media like body fluids (like saliva or blood) or surface/sewage water which contains a multitude of ions and dissolved organic matter. For examples, proteins in solution are almost always adsorbing on fresh surfaces. Under these conditions, the particle surface is thus typically coated with a mono- or multilayer of organic material, e.g. proteins or humic acids, creating a so-called corona "skin" on the particles. The particles therefore develop new and different surface properties, compared to the original ones, which is likely to influence both their uptake paths and their effects on biological systems. Agglomeration may also be induced by higher ionic strength (salt concentration) in the dispersant medium (Krug and Wick 2011; Chernousova and Epple 2012).

Care must therefore be taken when these methods are applied as they can lead to different results, e.g. for the average particle size or chemical reactivity or biological effects. It is therefore recommended to use more than one method for characterization. The development of new or, when possible, adaption of existing *in situ*-methods, which permit to analyse nanoparticles in complex environments is strongly desired (Nel et al. 2009; Montes-Burgos et al. 2010; Monopoli et al. 2011).

4.4 Synthesis and availability of model nanoparticles

The synthesis of nanoparticles is generally carried out either "top-down" or "bottom-up". Well-defined nanoparticles with a narrow size distribution and a low

degree of agglomeration are typically obtained by bottom-up syntheses (Goesmann and Feldmann 2010), e.g. by the reduction of metal salts in the presence of surface-capping agents to obtain metallic nanoparticles. Notably, the synthesis parameters must be well controlled to obtain well-defined nanoparticles. It is also important to develop methods to scale-up syntheses from the mL scale to the L scale or m^3 scale, taking the volume of the dispersions as a measure. Some synthetic procedures, e.g. for metallic nanoparticles, are notoriously poorly reproducible when monodisperse assemblies of non-spherical particles shall be prepared. Here, a detailed understanding of the basis processes of chemical reaction, nucleation and growth is needed. Especially important would be contributions from theoreticians to simulate these processes, which are quite difficult to assess experimentally. Generally the availability of well-characterized sets of model NPs is highly desirable both for calibration/evaluation of characterization methods, for development of test methods for studies of NP effects, and for laboratory experiments and controlled field tests. Without such availability comparisons between studies from different laboratories are hampered and as is the establishment of reliable experimental data basis, in turn slowing down regulation processes.

5. Ethical, Legal, and Safety (ELSA) Aspects

5.1 Ethical aspects of nanotechnology

The borderline between ethical aspects of nanotechnology and safety, risk, hazard and other aspects has of course a broad grey zone. For example, to not pay attention to the latter would clearly be unethical. On the other hand ethical aspects have other dimensions with their own agenda. Another important question for ethics and nanotechnology is if there are specifically new ethical questions related to this area or if it is "business as usual" in the sense that the ethical questions are the same as for all technologies with a broad (potential) impact on society. In any case the development of nanotechnology has led to questions that need to be dealt with using ethical decision-making to make sure that the technology is used for the common good. Examples of questions, which should be considered, are how potential dangers can be minimized (e.g. weaponry development and uses) and how to create and enforce global laws to ensure a sustainable development.

5.2 Chemicals regulations to secure safe handling of nanomaterials

Appropriate rules are needed to ensure that risks to health and the environment associated with nanomaterials can be avoided. Besides the legislation for cosmetic products there are no EU-wide rules specifically regulating nanomaterials. No individual country has yet devised any legislation governing nanomaterials besides a number of initiatives for national mandatory reporting systems. This means that nano-based products and processes in most cases are subject to the same requirements as apply to larger scale particles and materials.

This situation needs to be improved and several initiatives have been taken on an international level, as well as on a European level, to systematize the studies of effects of nanoparticles included in commercial products, and to suggest proper actions to reduce risks with these materials. The concept of the OECD-WPMN project is that testing of a certain set of nanomaterials can derive much valuable information regarding the safety of nanomaterials in general and help establishing assessment methods. In this way, the understanding of what intrinsic properties of the nanomaterials that affects the human health and the environment, and how to develop test methods may be significantly increased, as well as of how an appropriate regulatory system should be formulated.

Industrial chemicals legislation

In order to understand and anticipate how regulations may be developed for the relatively young area of NM and NPs, it is beneficial to look at existing rules and regulation for chemicals in general. As was evident from the bibliometric analy-

sis above, publications in the area of nano-safety etc., have developed significantly only during the last decade and the area is therefore immature and the knowledge about safety aspects is fragmented. It is furthermore likely that many aspects of a regulatory system for nano-materials will borrow its structure and organization from the more mature area of chemicals in general. Therefore a rather extensive review of the latter is given below, with comments on NM and NPs when possible and relevant.

EU rules on industrial chemicals are found in two extensive EU regulations: REACH Registration, Evaluation, Authorization and Restriction of Chemicals) and CLP (Classification, Labeling and Packaging of substances and mixtures).

CLP is an EU regulation which includes rules on how chemicals should be classified with respect to hazards, how hazardous chemicals should be labeled with symbols (pictograms) and other information to users and how the packaging of dangerous substances should be designed. Manufacturers placing a chemical on the market are responsible for compliance with these requirements. Classification is based on a global standard GHS (Globally Harmonized System of Classification and Labelling of Chemiclas), developed within the UN.

Classification is concerned with physical hazards as well as hazards to human health and the environment. There are detailed rules for how classification of substances will be carried out and how mixtures containing hazardous substances should be classified. The classification is important for several reasons. It forms the basis for information given by packaging labeling and safety data sheets so that users may gain knowledge of potential risks. But it also has great significance for the application of a variety of other instruments, where the classification determines the requirements of users. Examples are the EU rules on the classification of waste, the rules relating to measures against accidents in the chemical industry (the so called Seveso directive) and the requirements for registration in REACH. A very important principle is that the classification is based on intrinsic properties and not on risk assessment. This means that information on hazardous properties will be provided regardless of the intended use of the substance or mixture and if any risks will be associated with a particular use. Further, the fact that the classifi-

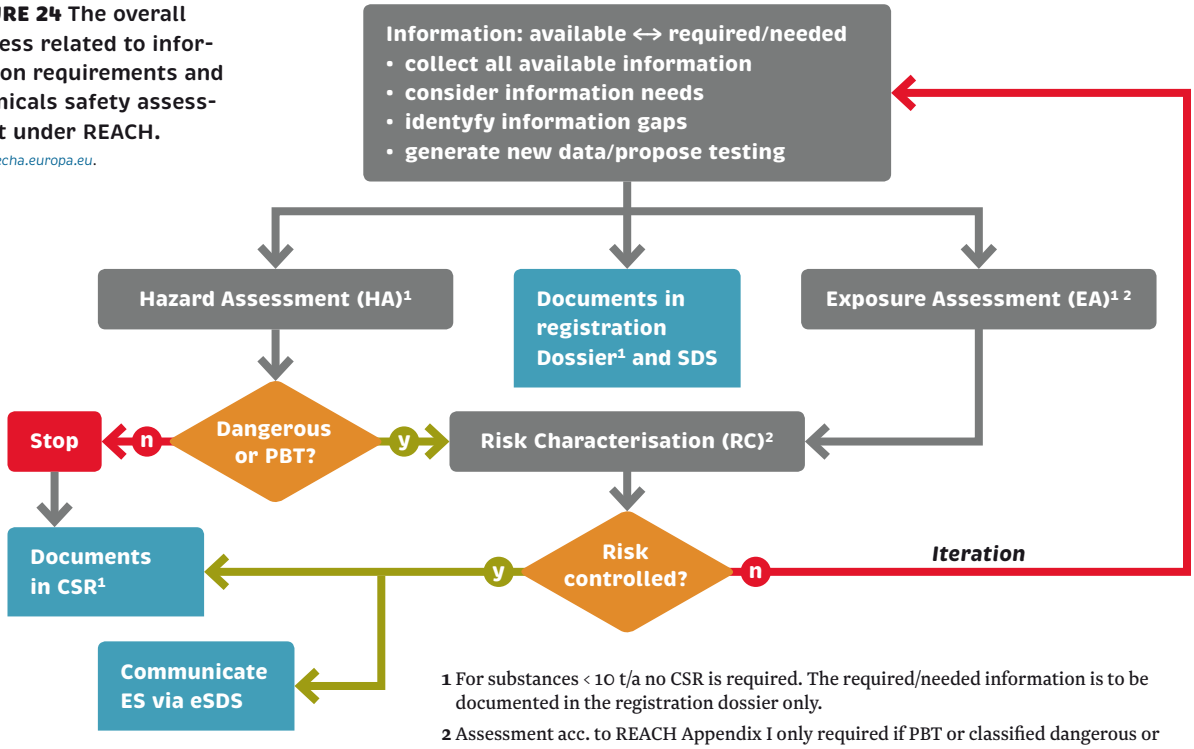


FIGURE 24 The overall process related to information requirements and chemicals safety assessment under REACH.
FROM *echa.europa.eu*.

1 For substances < 10 t/a no CSR is required. The required/needed information is to be documented in the registration dossier only.

2 Assessment acc. to REACH Appendix I only required if PBT or classified dangerous or exposure based waiving (Apendix XI).

cation is based on intrinsic properties also means that it can be the basis for many actions in succession laws.

To determine whether a substance or a mixture entails physical hazards in the CLP there are requirements on manufacturers, importers or downstream users to perform new tests, unless there already exists adequate and reliable information, which is sufficient for the assessment. As for health hazard and environmental hazard, there is no requirement in the CLP to develop the necessary knowledge in the form of test results to make the proper classification. Those aspects may be based on existing knowledge, which is often inadequate.

REACH is an EU regulation, which brings together several former EU rules in one act. The Regulation also contains several important new elements and the establishment of a central Chemicals Agency in Helsinki.

Figure 24 above presents an overview of the overall process of collecting and assessing existing information on the intrinsic properties of a substance, including identification of needs to generate new data. It also describes the process of chemical safety assessment additionally required for substances produced/imported in amounts of more than 10t per year.

The main elements of REACH can be summarized as follows:

- *Registration:* Manufacturers and importers must register substances handled in quantities in excess of 1 ton per year. Data (test results) should be included in the registration, as well as a chemical risk assessment for each of the uses recommended by the registrant for substances set out on the market in more than 10 tons per year. The chemical safety report includes exposure scenarios with more or less detailed conditions for the handling of hazardous chemicals that must be followed.
- *Information requirements:* There are requirements to provide safety data sheets to professional users of chemicals, a requirement, which supplements the labeling under the CLP Regulation and incorporates exposure scenarios. There is also a limited obligation to provide information on particular hazardous substances in articles.
- *Downstream users*, who are not manufacturers or importers, but using a substance in their activities, may sometimes be required to make their own chemical safety report.
- *Evaluation of dossiers* will be done both to ensure that the submitted records are accurate, and in some cases also in the form of a detailed evaluation of substances found on a specific priority list.
- *Applications for authorization* to be made of substances that have special environmental or human health hazards. Such substances are placed on a candidate list and gradually transferred to the list in Annex XIV with a timetable for the authorization applications.
- *Restrictions* i.e. bans or other restrictions for specific substances and specified uses. Annex XVII contains 60 entries that lay down rules on restrictions for substances and includes a long list of particularly hazardous chemicals (CMRs) that may only be marketed to professional users.

Pesticides legislations

EU rules for pesticides are found in the legislations for plant protection products and for biocidal products. Pesticides are defined as a chemical or biological product that is intended to prevent or deter animals, plants or microorganisms, from causing damage or detriment to human health or damage to property. Biocidal products are intended to prevent or control animals, plants or microorganisms, including viruses, causing harm or inconvenience to human health or damage to property.

Plant protection products are mainly used to protect plants and plant products in agriculture, forestry and horticulture from attacks by fungi, pests and competing plants.

The *Biocides Directive* (Council Directive 98/8/EC) regulates the placement of biocidal products on the market. The Biocidal Products Directive is intended to harmonize the internal market for biocidal products in the EU and ensure a high level of protection for humans, animals and the environment. A biocidal product must therefore be authorized to be placed on the market. To enable a biocidal product to be authorized under the Biocidal Products Directive, the active substances contained in the product must be included in one of the positive lists of the Biocidal Products Directive. For possible inclusion in the positive list, Member States evaluate the active substances and their risks for health and the environment and vote thereafter whether the substance is to be included in the lists of active substances which may be used in biocidal products. Following the evaluation of an active substance, a biocidal product containing an active substance can be authorized for placing on the market only if the substance is included in Annex I i.e. the product is accepted for marketing only if the risks to health and the environment are deemed acceptable.

In current legislation on biocides the opportunity to identify nanomaterials as additives in the biocidal product is limited. The Biocidal Products Directive requires only qualitative and quantitative information on the composition of the active substance. However, there is no requirement to characterize an additive on particle size so hence there is a risk that a substance at the nanoscale is not discovered within the approval process for biological products, unless it is declared by the registrant.

The Biocidal Products Regulation EU (No.) 528/2012 shall be applied from 1 September 2013 and has specific requirements regarding nanomaterials that go much further than the Biocidal Products Directive. These requirements generally apply not only to the substance that causes the biocidal effect but also to co-formulants in the products.

Rules on the conditions and procedures for the authorization of plant protection products must be applied by the Member States and are laid down in the *Plant Protection Products Regulation* (Regulation (EC) No 1107/2009). Regulation (EC) No 1107/2009 is new and replaces the former Directive 91/414/EEC. The purpose of this Regulation is to ensure a high level of protection of both human and animal health and the environment and at the same time to safeguard the competitiveness of Community agriculture. Particular attention should be paid to the protection of vulnerable groups of the population, including pregnant women, infants and children. *The precautionary principle should be applied and this regulation should ensure that industry demonstrates that substances or products produced or placed on the market do not have any harmful effect on human or animal health or any unacceptable effects on the environment.* Substances should only be included in plant protection products where it has been demonstrated that they present a clear benefit for plant production and they are not expected to have any harmful effect on human or animal health or any unacceptable effects on the environment. In order to achieve the same level of protection in all Member States, the decision on acceptability or non-acceptability of such substances should be taken at Community level on the basis of harmonized criteria. Such rules should provide that plant protection products should not be put on the market or used unless they have been officially authorized and have entered a Community positive list of authorized active substances.

In addition to active substances a new feature of the regulation is that certain substances, which affect the mechanism of action of the active substance should be approved. These are known as safeners and synergists.

The rules and their applicability to nanomaterials

The EU Commission is of the opinion that existing chemicals legislation covers nanomaterials, even though their applicability for nanomaterial is also questioned. This is an opinion, which also Sweden and other Member States support, i.e. existing chemicals legislation to large extent covers also nanomaterials, but there is also a need for changes/modifications. While the commission is planning to take care of this in Annexes and guidance to the legislation, Sweden is of the opinion that there is a need for a change in the articles of REACH, or alternatively in a nanospecific regulation in order to achieve safe handling and use of nanomaterials. Critical issues that are discussed are e.g. substance identification, tonnage levels, information requirements and test methods

In October 2011 an EU Commission Recommendation on the definition of nanomaterials (see Chapter 2.1) was established (EC 2011). The idea is that the recommendation, which is comprehensive, will be adapted as a whole or in parts to different legislations. An agreed definition is a starting point and a prerequisite for regulation or other measures to enable a good evaluation of the risks posed by nanomaterials to the environment and health.

Over time it has become obvious that REACH and CLP as they are written today are not fully applicable to nanomaterials. In order to secure safe handling of nanomaterials and to avoid negative effects on health and the environment it would therefore be necessary to review and revise the legislations. Rules need to be amended so that they can deal effectively with any risks associated with nanomaterials.

Within REACH and CLP, there are a number of issues, where the need for guidance or modified or new regulations for nanomaterials exists. Such issues include substance identification, the tonnage system, testing methods, chemical safety and risk reduction measures, and information in the supply chain.

In the regulation of classification and labeling it is important to understand whether current criteria, which are often directly linked to outcomes from the testing methods, are applicable to nanomaterials. In addition, the applicability of the current cut-offs and concentration thresholds for classification of nanomaterials needs to be reviewed especially as dosimetry and sample preparation for toxicity testing seems to be different for nanomaterials and for bulk materials.

A feature shared by the pesticides legislation and the REACH and CLP regulations is that health and environmental hazard testing and also physical-chemical properties should be done with the help of internationally accepted guidelines or equivalent for testing of chemicals. It is highly important that the test methods used to gather information on substances in REACH and other chemicals legislations works and is applicable to all substances covered by the legislations, i.e. also for nanomaterials.

At present it is not fully clear whether such testing methods in their current form are directly applicable to nanomaterials or if they need to be modified or if new testing methods must be developed. It is likely that the characterization will be dominated by existing (maybe modified and/or adapted) methods, but the need for entirely new methdodology for specific cases cannot be excluded). (See also comment above under 3.2, last paragraph). Much work on evaluation of the applicability of testing methods on nanomaterials is underway especially in the Working Party on Manufactured Nanomaterials in the OECD (OECD/WPMN) (see Chapter 4). Further, guidance on dosimetry and sample preparation for testing of nanomaterials has been developed by WPMN.

Areas where there is a need for increased or extra information for nanomaterials as compared to bulk materials are for example:

- It is likely that existing test methods for materials and chemicals characterization, as well as effects on health and the environment, are applicable also for

nanomaterials, either as they are or after some adaptions. However, it is not excluded that new methods may need to be developed as well in some areas.

- Identified areas of concern are e.g.: Test methods should be available for physical and physical-chemical properties that can provide extended information on size, shape and surface area and on the characteristics connected with the large area/small mass ratio.
- Proper information on the toxicokinetics of nanomaterials is needed, as understanding about this is very limited. The unique properties of nanomaterials and their transformations in different environments (corona effects etc.) are likely to influence their reactivity, uptake, distribution, metabolism and excretion as compared to bulk materials.
- Expansion of existing testing approaches for inhalation is needed, since most exposure to nanomaterials are via inhalation and cell damage in the lung tissue observed after exposure to nanomaterials need to be investigated more.
- Environmental exposure and aquatic toxicity are areas identified as problematic due to difficulties with water solubility of nanomaterials.

A product type where regulation of nanomaterials should be considered is biocidal products. These products undergo extensive risk assessment with regard to the active substance that produces the control effect. On the other hand, the additives in the products are not assessed in the same way. It seems therefore reasonable to supplement the rules on biocides with requirements that nanomaterials in the additives must be identified by the applicant for authorisation.

An EU common mandatory reporting system for nanomaterials

Functioning reporting systems are needed to learn, which products contain nanomaterials and where they are dispersed in the society. There is a need to know which nanomaterials currently are on the market and what they are used for. There are, for example, an increasing number of products containing nanomaterials designed for consumers use on the market such as cosmetics, household appliances, textiles, food contact materials, products for children and Do-It-Yourself products, but there is no reliable information about the actual exposure of nanomaterials from consumers' products.

The traceability of nanomaterials in the society needs to be improved to secure safe handling of nanomaterials and also in case of emergency (cf. "early warnings – late lessons"). Concerning nanomaterials information gaps could arise in REACH. A first review made by ECHA on dossiers submitted from importers and manufacturers indicates deficiencies in the information on where nanomaterials are used. There can also be significant time lags in the registration of low-tonnage, "phase-in" substances under REACH. Further, the so called "use descriptor system" in REACH seems not to be comprehensive enough to give sufficient information on where nanomaterials are used.

A number of European Member States have earlier laid down voluntary national reporting systems, which to date have not been successful. Instead, there are requests for mandatory reporting system. Also an EU-wide voluntary system was created ("Nanomaterials on the market"). However, this reporting system was not very effective. At the time being there are several countries, including the Netherlands, Belgium, France, Italy and Denmark, which have adopted or is planning the establishment of national reporting systems striving towards an EU-wide system. Other countries, like for example the United Kingdom have tried a voluntary reporting system with no success. The United Kingdom now supports a mandatory reporting system at the EU level. Also Germany supports an EU-common reporting mandatory system.

Like the European Commission the US EPA (in its Nanoscale Materials Stewardship Program; NMSP), the UK Defra (Department for Environment, Food & Rural Affairs and the Australian NICNAS (the National Industrial Chemicals Notification and Assessment Scheme) have constructed voluntary system for collecting information about the use of nanomaterials with respect to details of materials, quantities and uses.

Considering that the area of safety etc. of nanomaterials is primarily not a national problem but an EU common (or global) one, a reporting system should be created at the Community level. The Swedish Chemicals Agency (KemI) therefore advocates the introduction of an EU-wide mandatory reporting system for nanomaterials and that the information requirements of such a system should be established through a stepwise process, where the basic requirements are limited and concern, for example, chemical identity, size, usage and volume. For the nanomaterials, one may need information on substances, mixtures and articles. A common reporting system on nanomaterials in products in the EU can be linked naturally to work on development of the REACH Regulation.

6. Areas of Specific Interest for Mistra and Proposed Areas for Research in a Mistra Program

Based on the above review of nanotechnology and its hazard, risk and safety aspects, a list of potential areas of interest for Mistra has been identified. We first give the *full list* and then discuss which of these topics that we recommend should be omitted, and finally arrive at a *prioritized list*. In this work attention has been given to what Mistra's main mission is, what is done elsewhere, in other programs funded by other sources, and also to the ambition to have a program with some synergies between topics. *Omission of some topics* is based on several criteria; the topic may e.g., fall outside the central realm of Mistra's activities and/or it may be subject to much larger efforts with funding from other sources. *The choice of prioritized areas* has been guided by a combination of what Mistra's main mission is and by identifying areas where we judge that there is both an urgent need for research and a possibility to make an impact with the allocated funding and Swedish research resources.

6.1 List of potential topics

The long list of identified, potential topics is:

(i) **Mapping** of all the NMs/NPs that exist and are likely to appear and compilation of databases about their occurrence, uses, *exposure potentials, transport routes and uptake paths*.

(ii) **Exposure and hazard assessment** in a life cycle perspective.

(iii) **Field studies:** Methods and procedures to study NM/NP *fate* and their *effects on the environment and ecosystems*.

(iv) **Laboratory studies**, including *method development*, *model systems*, *corona effects*, *toxicokinetics and dosimetry*, to evaluate the effects of NM and NPs on organisms.

(v) **Employing and developing** experimental *analytical methods to characterize* NM and NPs in laboratory test systems and in environmental samples.

(vi) **Methods for collection** of *representative samples* of NPs from various environments (work environment, ecosystems, organisms, body fluids, tissues), in order to analyze types and occurrence.

(vii) **Methods to synthesize** representative model systems of NM and NPs.

(viii) **Methods to remove NM/NP** from air and water.

(ix) Health effects.

(x) Studies of the *perception of and attitudes to nanotechnology* and safety/risk aspects including analysis of appropriate *risk analysis* procedures.

(xi) Society organization of assessment and handling of safety/risk aspects, including decision-making and surveillance and regulations/laws.

(xii) Applying nanotechnology to *solve environmental problems*.

Topics deemed to merit lower priority

A research program of the type that Mistra is considering to launch cannot cover all these aspects – it would mean spreading the allocated resources far too thinly. The Mistra program should be based on a selected set of items from the list (i)-(xii) above.

(ix) Human health/medicine: Based on the observation that the largest volume of ongoing research globally is related to human health aspects – and considering Mistra's main mission – we suggest to exclude this aspect, except that the program, when appropriate, should take advantage of existing knowledge in this area (effects as well as methods). For example, this area and its research results, provide invaluable databases, laboratory model systems, methods and other input for several of the prioritized items below. Along with this area goes also veterinary medicine, which is thus excluded.

Topic (xi) - Society organization of assessment and handling of safety/risk aspects, including decision-making and surveillance and regulations/laws. This topic is currently subject to a recent government initiated study and investigation (E Forsberg) with a report expected in the fall of 2013, i.e., before the current program's projects will start. Therefore, although an extremely important topic, it is judged unnecessary and untimely to initiate research projects in this area, where no results will be available until well after the governmental report is already finished. We note however, that results from the actual Mistra program on nanotechnology, if decided by the Board, are likely to provide valuable input to whatever measures that are decided based on the governmental investigation.

Energy technology (essentially under xii): It is easy to argue that a variety of energy technology R&D qualifies under "Applying nanotechnology to *solve environmental problems*". As described earlier, nanotechnology has enormous potential to contribute to a sustainable energy system and the long-term transition from fossil dependence to CO_2 free and sustainable energy supply and use. This applies to all stages along the chain Primary energy supply (e.g. solar and wind) → transmission (e.g. HVDC power lines, pipelines for solar fuels) → storage (e.g. solar fuels, batteries, heat and cold storage) → end use (e.g. energy efficiency and saving, smart windows, buildings). However, so much is invested in other programs with the aim to develop sustainable and energy efficient systems, by exploiting nanotechnology, that we judge that the impact of the present program will be incremental if this area is included – it is a high priority area generally, but it needs its own focused program(s)., and is therefore omitted.

Additional comments on topics (i)–(xii)

(i) Mapping of all the NMs/NPs that exist and are likely to appear and creating a database about their occurrence, uses, exposures, transport ways and uptake paths.

The study of transport/spreading ways, uptake paths (microorganisms) and exposures to the environment etc. are included in the program. Simply establishing databasis, although very important in general, is not a prioritized area of research in this program and not included.

(ii) **Risk assessment in a life cycle perspective.**

Following the life span for different NM and NM, with special focus on implications for the environment and ecosystem are included.

(iii) **Field studies: Methods and procedures to study NM/NP effects on the environment and ecosystems.**

This topic, focusing on "effect studies" is included.

(iv) **Laboratory studies, including method development, model systems, corona effects, toxicokinetics and dosimetry, to evaluate the effects of NM and NPs on organisms.**

This area is included in the program. Laboratory studies are a necessary "up-stream" complement to the field studies (iii) and are a prioritized area. Together with (iii) they should and will constitute a hierarchical system, similar to the evaluation system for drugs or risk assessment for other chemicals; at the very basic level they include e.g., theoretical calculations of model nanoparticles and their effects on very simple systems, then at the next level very simple in vitro experimental studies on simple organisms/cells or even on subcellular components, then more complex systems, still in vitro, of colonies/cultures of cells/microorganisms, towards in vivo animal/organism studies etc. toward mimics of ecosystems in the laboratory. A sequence of such studies, of increasing complexity, creates a necessary link to (iii). The area includes both *model systems* as such (e.g. particles and organisms), studies of *effects* on these model systems, and development of the *experimental methods* to perform them

(v) **Employing and developing analytical methods to characterize NM and NPs.**

(vi) **Methods for collection of representative samples of NPs in various environments (work environment, ecosystems, organisms, ...), in order to analyze types and occurrence.**

These two areas are included in the program. Experimental methods to analyze and characterize NM/NP and to collect representative samples from the environment (air, water, soil, ...) are vital to a overall risk assessment system. If the particles cannot be characterized, considering the large variations in size, shape, aspect ratio, composition, corona shells etc., one cannot study and establish effects of these properties, and then meaningful regulations become impossible or at least very difficult. The same argument applies to collection of representative samples; it is vital to know the true distribution of types, chemistries, sizes, shapes etc. from a particular environment, in order to study their individual and collective (e.g., synergetic) effects, which in turn is central for regulations.

(vii) **Methods to synthesize representative model systems of NPs.**

This area is not included in spite of the fact that it is as important as (v) and (vi) above – without the ability to produce well defined model particles and NM, it will be extremely difficult to establish their individual effects as functions of size, shape, aspect ratio, composition, corona shells, etc., and even more difficult to establish cooperative effects of two or more kinds of NPs. However, synthetic work on nanoparticles is a large activity worldwide today, and in addition very time consuming, so the area is not recommended as a prioritized area in the Mistra program. We judge that collaborations are possible to establish with laboratories focused on synthetic work to get access to existing and "in pipe-line" NPs.

(viii) Methods to remove NM/NP from air and water.

This area is included in the program. Such methods will be essential for development of nanotechnology and for the safety – risk work. What is meant here is different from the methodology mentioned under (vi) above, which is small-scale collection of nanoparticles in order to collect representative samples in order to analyze them. Here we mean instead large-scale methods to remove all NP/NM that are judged to constitute a risk, e.g., from process gases or liquids and from wastewater or soil etc.

(ix) Health effects.

This area is omitted – see above.

(x) Studies of the perception of and attitudes to nanotechnology and safety/risk aspects including analysis of appropriate risk analysis procedures

This is included. The questions regarding perception and attitudes of both the general public, industry and the public sector are complex and also important for the development and acceptance of nanotechnology and for proper risk management. Communication between other areas of society and the R&D sector can promote the acceptance and rate of impact of nanotechnology and vice versa. Furthermore, a focus on evaluating the appropriateness of existing and suggested frameworks for risk analysis would be of high importance before incremental approaches are fully implemented. These issues are considered as important complements to the more technical aspects of the program and are included in the program.

(xi) Society organization of assessment and handling of safety/risk aspects, including decision-making and surveillance and regulations/laws.

This area is omitted – see above

(xii) Applying nanotechnology to solve environmental problems.

As described above there are many opportunities for nanotechnology to also solve or reduce environmental problems not connected with nanotechnology. Typical aforementioned examples are (nano)-catalytic removal of exhaust gases from cars and industries, photo-catalytic cleaning of air and water, nanotechnology based miniaturized sensors for surveillance of chemicals and air quality etc. Another area is CO_2 capture by using nanotechnology based adsorbents. The list can be extended. This area is included in the program.

6.2 Prioritized topics

Based on the analysis above it is suggested that the call for proposals for the potential Mistra-Nanotechnology program is particularly focused on

1. **Methods to collect and characterize** nanoparticles from relevant environments (e.g., water, air, soil, tissues, organisms) and their spreading paths and exposures etc. and risk assessment using a life cycle perspective.
2. **Laboratory studies,** including method development, model systems spanning a range from basic ones to more field-like ones, corona effects and dosimetry, toxicokinetics.
3. **Field studies:** Studies of the effects of NM/NP on ecosystems (field studies, epidemiological studies, toxicokinetics,) with emphasis on understanding the underlying principles, i.e. studies beyond dose-effect relationships or just generation of toxicity data.

4. **Social science aspects of nano-risk perception** and appropriateness of risk analysis frameworks.

5. **Applying nanotechnology** to solve environmental problems.

The following boundary conditions have been taken into account in the process of identifying relevant areas of research for a possible future research programme in the area of nanotechnology:

- The programme must comply with Mistra's mission, goals and objectives.
- The programme must extend the Swedish knowledge base and have a long-term benefit for Swedish industry.
- The programme must be cross disciplinary and include social sciences.
- The programme must be sufficiently focused to have a clear programme identity, to reach a critical mass and to allow for synergies within the programme.
- The programme must be complementary to other already funded or announced (national) programs, and it should stimulate interaction with these programmes.
- There must be a sufficient number of actors who can execute the programme.
- The programme should have a competitive edge in relation to the international research frontier in the programme area

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Nanotechnology is a relatively new and massively expanding area, which is expected to have a huge impact on society. The market potential of nanotechnology-based products is estimated to be more than 250 billion dollars, and is expected to grow by more than an order of magnitude within the coming decade (see e.g. report by Roco et al.). There is thus ample room for new, innovative ideas to be realized. An investment in nanotechnology-based innovations, which contribute to a sustainable development, coupled with surveys regarding decision-making processes and consumer attitude towards nanotechnology would fill several purposes.

MISTRA
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