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NanoSafety – Risk Governance of Manufactured Nanoparticles

Interim Report – Phase II

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- Institute for Technology Assessment and Systems Analysis (ITAS), Karlsruhe
- Danish Board of Technology (DBT), Copenhagen
- Catalan Foundation for Research and Innovation (FCRI), Barcelona
- Fraunhofer Institute for Systems and Innovation Research (ISI), Karlsruhe
- Institute Society Technology (IST), Brussels
- Institute of Technology Assessment (ITA), Vienna
- Rathenau Institute, The Hague
- Technology Centre AS CR, Prague

Contact:
Dr Leonhard Hennen (Co-ordinator)
Institute for Technology Assessment and Systems Analysis; Karlsruhe Institute of Technology
c/o Helmholtz-Gemeinschaft
Ahrstr. 45, D-53175 Bonn
Leonhard.Hennen@kit.edu

Project Description

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The project is being carried out by
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the **Institute of Technology Assessment (ITA), Austrian Academy of Sciences, Vienna**;
as members of ETAG.

Project Leader: *Torsten Fleischer, Institute for Technology Assessment and Systems Analysis (ITAS)*

Authors:

Torsten Fleischer, Jutta Jahnel, Stefanie Seitz (ITAS-KIT), Ulrich Fiedeler, Myrtill Simko (ITA)

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Members of the European Parliament in charge:

Mr. Vittorio Prodi, MEP

STOA staff in charge:

Mr. Theo Karapiperis

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GENERAL INFORMATION

The Nano*Safety* project deals with the governance of the potential environmental, health and safety (EHS) risks of manufactured nanoparticles. Because of the great uncertainties regarding their actual health and environmental effects and numerous methodological challenges to established risk assessment procedures (definitions, toxicology, exposure and hazard assessments, life cycle assessment, analytics, and others), risk appraisal and risk management of manufactured particulate nanomaterials (MPN) are confronted with serious challenges. At the same time, precautionary regulatory action with regard to MPN is demanded by a number of stakeholders and parts of the general public.

Regulation under uncertainty raises fundamental political questions of how lawmakers should regulate risk in the face of such uncertainty. To explore this issue in greater detail, the project focuses on two important perspectives of regulation: Risk management strategies for MPN as discussed or proposed for the EU or its member states, and risk communication problems and needs for EHS risks of MPN.

This interim report concludes phase two of the project.

It is intended to provide an executive overview of the state of research on potential EHS risks of manufactured particulate nanomaterials, including risk assessment for MPN and the limitations it is currently facing. It also discusses the role of definitions in regulatory debates and delivers a cursory synopsis of the relevant definition proposals in policy papers and pieces of legislation in the EU context. Furthermore, a suggestion for a legal definition has been developed. The report gives a brief review of regulatory activities regarding MPN at the European level, discusses advantages and limitation of selected regulatory instruments and presents first ideas for options for parliamentary action.

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EXECUTIVE SUMMARY

The NanoSafety project deals with the state of research of the potential environmental, health and safety (EHS) risks of manufactured particulate nanomaterials (MPN). In addition, it provides an overview of the current regulatory debate and discusses options for an appropriate risk governance framework. In the present Phase II of the project, various issues of risk management of MPNs are explored concerning definitions for the term "nanomaterial", hazard identification, hazard characterization, exposure assessment and existing regulatory measures.

To develop new regulatory approaches for intentionally produced nanomaterials is a demanding task. A number of fundamental questions have accompanied this process, and many of them appear to be still unanswered. On the one hand this is due to a number of still unsolved scientific problems and uncertainties as well as technical challenges. On the other hand this is due to different normative perspectives that the plurality of decision makers and stakeholders involved in the process have (i) on regulation of chemicals and technologies, and (ii) the "right" balance between a responsible development and safe use of nanomaterials. The latter includes the protection of humans and the environment on the one hand and the ability to innovate and socioeconomic interests on the other.

To specify these challenges more precisely, a number of key questions in the regulatory discourse have been identified which will be addressed in the present report.

Characterizing and defining manufactured particulate nanomaterials (MPN)

The first question is whether there is sufficient evidence to consider nanomaterials as being different from bulk, especially in regulatory contexts. It is widely agreed that more knowledge is needed about physical and chemical properties of MPNs to assess potential risks. Nevertheless, there is an ongoing debate which particular parameter(s) are most relevant for this task – in contrast to bulk material where only mass and concentration are considered for hazard and risk assessment. The following characteristics are considered to characterize nanomaterials (in alphabetical order): agglomeration and/or aggregation, chemical composition, crystal structure/ crystallinity, particle size/size distribution, purity, shape, solubility, stability/bio-persistence as well as surface properties, such as area/porosity, charge, chemistry including composition/coatings, defects and reactivity. However, mostly the size, shape and the surface properties of the particles are characterized whereby latter can influence the reactivity of the MPN.

The problem of the scientific characterization of a potential noxa is closely linked to the problem of finding an adequate legal definition for nanomaterials in EU legislatory documents. A number of definitions have been proposed by regulators, scientific committees and standardisation organisations over the last few years. These numerous and sometimes conflicting definitions, generally written from a scientific and not from a legal/regulatory perspective, have led to competing framings and considerable confusion in regulatory debates. One could argue that uncertainties about a sensible definition of nanomaterials – or the lack thereof – might have further complicated the efforts to develop an effective regulatory policy for nanomaterials.

The absence of a commonly adopted definition of nanomaterials gave rise to develop a working definition to be use within the NanoSafety project. Considering that insoluble

nanoparticles and nanoscale carbon allotropes (buckyballs and carbon nanotubes), which are mobile in their immediate environments, are of concerns due to significant EHS implications, one might argue that these two subgroups should be covered by any definition used for regulation that is motivated by the precautionary principle. Thus, we propose – following JRC – to use "particulate nanomaterials" as an umbrella term. Particulate nanomaterials are understood as a single or closely bound ensemble of substances (consisting of atoms and molecules), at least one of which is in the condensed phase and having external dimensions in the nanoscale in at least two dimensions. Nanoscale means the size range between 1 and 100 nm. In addition, we will focus only on "manufactured" ("intentionally produced" or "engineered" could be used synonymously) particulate nanomaterials (MPN) because incidental products of human activities (like industrial, combustion, welding, automobile or diesel) or naturally occurring nanomaterials lie beyond the scope of this report.

Criteria for a legal definition

In the light of the above-mentioned debate, the process towards the development of a harmonised legal/regulatory definition of nanomaterials should be intensified. Four arguments might be helpful to assist this process:

- Legal definitions of nanomaterials have to describe the object of regulation sufficiently precise to be clear to all parties affected by it. They have to consider practices of production and application of nanomaterials as well as to be enforceable by the responsible authorities.
- A legal definition of nanomaterials incorporates not only scientific and technological knowledge (and its respective uncertainties), but also includes the results of policy choices and political decisions. It therefore should be science-based but does not necessarily have to be identical to scientific definition(s) of the same term.
- The breath of the legal definition has to be matched with both the regulated artefact and the regulatory goals. A legal definition of nanomaterials has to take into account that these may occur in nature including in a number of natural products that are consumed by humans, could be incidentally produced as results of various human activities, or can be intentionally manufactured. This situation results in different hazard assessments, diverse exposure scenarios and various starting points for regulatory intervention, depending on the aims of the regulation. Meaningful regulation is limited to human activities; therefore a legal definition of nanomaterials should focus on manufactured nanomaterials.
- A legal definition of nanomaterials based on "new" properties occurring at the nanoscale might be difficult to achieve. Therefore, a size range in which the most size-dependent properties appear could serve as an appropriate, albeit imperfect, heuristic. Although any choice of a size range would be imperfect with respect to certain regulatory goals, since there are no direct, material-independent relations between size and "nanoscale properties", a size range from 1 nm to a value not above 100 nm might cover many configurations of materials that give reasons for regulatory concern. For various reasons, an upper size limit cannot directly be derived from scientific results but would be the result of a balancing of goals and interests and therefore should be subject to political decisions.

Basic regulatory approaches

The second key challenge in the current debates on regulation of nanomaterials originates from a conflict of two different regulatory approaches. One position can be - in a way stylized – summarised as strongly precautionary-oriented, putting nanomaterials under general suspicion because of their new properties and the limited knowledge about their (potential) environmental, health and safety implications. In this approach, nanomaterials are usually defined rather broad and a number of strong measures are proposed to supervise and control the entire life cycle of nanomaterials or products containing nanomaterials or being manufactured using nanotechnologies. Given the considerable broadness of the definitions of nanomaterials and nanotechnologies, a large number of both natural and artificial materials and products as well as various technological processes will be affected by this regulation. Important questions to be discussed in connection with this approach are: Do the regulatory agencies and other affected parties have sufficient resources to implement and enforce this regulation? What are the implications of this approach on existing and future social practices, technological innovation and economic development? Are there mechanisms to "release" nanomaterials from that regulatory regime, assumed they were proven to be "safe"? And how "safe" is safe enough to justify this decision?

Another regulatory approach is closely linked to evidence from toxicological, ecotoxicological and biological research. Its proponents argue that particularly (or solely) those nanomaterials should be regulated that give rise to concerns regarding their EHS implications, either because toxicological research has shown that a hazard exists or because the physico-chemical properties of the nanomaterial allow to predict a certain hazard potential (e.g. when the nanomaterials exist in free form, are known to be insoluble, biopersistent, etc.).

Limitations of the risk assessment of nanomaterials

Both positions – in different ways – have to deal with profound limitations of the risk assessment of nanomaterials. The methodology for the assessment of chemicals risks – including, but not limited to nanomaterials – applied in most countries consists of four parts: hazard identification, hazard assessment (including dose-response relationships), exposure assessment, and risk characterization. Each of these four elements holds a number of limitations that are not easy to overcome.

The majority of nanotoxicological work done contributed to the field of hazard identification, attempting to reveal the toxicity of MPNs in respect its type and characteristics. The current knowledge suggests that inhalation is the main portal of entry of MPNs into the body. Epidemiological studies about MPNs are not available therefore studies of ambient ultrafine particle (< 100 nm) toxicology are taken into consideration to study human adverse health effects by nanoparticles. Various studies showed that inhaled MPN size-dependently deposit in different regions of the lungs. It was demonstrated that to a certain amount MPNs can be removed by clearance mechanisms (especially in bronchia) and/or immune system (especially in alveoli) of the lungs. Thereby, it seems that these mechanisms are less effective by a decreasing particle size. If insoluble particles are deposited in a certain area of the lung they will undergo clearance mechanisms or will be accumulated in particular areas where they even may pass membrane barriers and enter individual cells causing biological or toxicological effects. At high doses, certain MPNs (e.g. fibre like carbon nanotubes or nanosilver particles) led to pathologic conditions and can cause toxic effects.

In general, the assumption that the move to the nanoscale implicates not only novel material properties but also entails novel environmental and health risks was confirmed on a scientific basis. However, the relevance of the data from the various in vivo and in vitro studies is still unclear. Thus, the available data provide a basis for further investigations by providing knowledge about fate and behaviour (ADME-profiles) as well as the toxicity including underlying mechanism – however only for certain MPNs. It was shown that the shape of certain MPNs as well as their purity is important for toxicity, e.g. carbon nanotubes, seem to be more toxic if trace impurities of iron or solvents were present.

Beside, toxicity testing faces some intrinsic limitations; some of them can be overcome in future, others won't. As mentioned above, there is evidence that some manufactured particulate nanomaterials may be hazardous to human health, depending on their characteristics. But it is currently impossible to systematically link reported properties of MPN to the observed effects for effective hazard identification. In addition, it is still under debate what the most relevant endpoints are and how they are linked to systemic effects. Aside from this, one has to keep in mind that for many nanomaterials, no toxicological studies have been performed so far.

So far, only few studies claim to have observed a dose–response relationship for MPN, and even in these cases it is still unclear whether a no-effect threshold can be established. To establish causality between physico-chemical properties of MPN (which are potential access points for measurement, regulation and enforcement) and an observed hazard for hazard characterisation remains a challenging task. This is not at least because of the lack of reliable characterisation of the MPN used in earlier toxicological studies and the fact that related measurement technologies partly still need to be developed.

A problem repeatedly discussed in this context is that so-called "no-effect studies", i.e. nanotoxicological studies that have "failed" to show effects of MPN on various endpoints, to a large extent remain unpublished. The reasons for that are manifold and span from methodological challenges to limited opportunities and incentives for publication due to the scientific system. Then again, no-effects studies are a valuable repository for hazard characterization and its limited accessibility could be seen as a waste of scientific resources. The scientific community as well as funding organisations and regulatory authorities should raise awareness for this problem and develop mechanisms to overcome the mentioned potential shortcomings of the current situation.

Exposure assessment of MPN faces similar problems of data availability. Some 'proof of principle'-studies have tried to assess consumer and environmental exposure to nanomaterials, but assessments considering realistic exposure conditions are still missing. Some institutions have begun to collect exposure data under realistic circumstances, especially at the workplace. But the knowledge necessary for reliable exposure assessments is bounded by technical difficulties in monitoring exposure to MPN in the workplace and other environments, ignorance about the biological and environmental pathways of MPN, missing knowledge about the release of MPN from products over their life cycle, and other factors.

Hence, risk characterization that builds on hazard and exposure assessment is at this time (and most probably in short- and medium-term) not feasible or certainly not scientifically reasonable and only preliminary.

Challenges for risk assessment and risk governance

The situation described above might suggest that the risk assessment methodology as a whole is inadequate to timely inform political decisions regarding the regulation of nanomaterials, at least in the short- to medium-term. In the light of the various knowledge gaps, it would need enormous efforts to perform valid and broadly accepted risk assessments for specified nanomaterials. Whether these materials are considered "reasonably safe" or "of high concern", both claims will remain unproven for many years. Moreover, its role and validity as justifications for regulatory strategies of these claims will be contested. One might even argue that risk assessment methodology in general is not appropriate for complex subjects like nanomaterials.

In the light of the missing scientific evidence regarding EHS risks of MPN, or the absence thereof, the development of a suitable risk characterisation heuristic (mainly based on physico-chemical properties of nanomaterials and plausible exposure scenarios) and its implementation, at least for a transition period, could be supported. First concepts for such heuristics have been proposed, e.g. in Germany and Switzerland, but their usability for regulatory purposes and possible needs for further refinements still need to be discussed.

Regulation under uncertainty raises the fundamental political question of how policy makers should regulate risk in the face of limited scientific evidence. In this context, it is of particular importance that regulations represent not only a restriction for companies, but can also serve as a guideline for strategic decision and legal certainty. Lawmakers on national and European level are dealing already with the implementation of nanospecific aspects in an incremental case by case approach. These activities imply a wide range of provisions and instruments, depending on the application and life cycle stage and different levels of attention and risk assessment. While a nanospecific framework does not exist, the adaption of existing regulations is an ongoing process, concerning the scope and the threshold limits as well as adequate nanospecific assessment procedures. REACH seems to provide a powerful framework to regulate nanomaterials, but there are open gaps and problems. It is currently under discussion, if – and to what extend – MPNs lie within the scope of this regulation. Other policies concerning nanomaterial aspects are mentioned in this project, mainly the regulation on cosmetic products and the currently discussed amendments on the Novel Foods Regulation, the proposal for a Biocidal Products Regulation as well as the Medical Devices Directive. Besides these mandatory provisions, also voluntary measures based on an increased self-responsibility of producers are important. They are somehow temporary actions in between the establishment of a firmer scientific evidence for specific policy decisions. Advantages and problems of voluntary registers and code of conducts are discussed in the light of governance, regulation and control of nanomaterials.

Another question still under debate is whether existing legislation can be – or should be – adapted to MPN or whether a new regulatory framework for nanomaterials should be developed. Most scholars and practitioners in regulatory law as well as most political decision makers prefer a so-called incremental approach. They favour to adapt the existing legal framework to enable nanotechnology regulation and amending it in order to deal with the unintended implications of this technology. This approach has a number of challenges, limitations and potential gaps since existing legislation is not designed to accommodate some specific aspects of nanomaterials or nanotechnologies.

A number of these aspects have been briefly discussed in chapter 3 of this report, they are among others:

- developing a legal definition for nanomaterials;
- integration of nanomaterials into the REACH classifications and procedures, including the development of suitable guidance documents;
- being able to identify and address the relevant adverse effects of the production, use and disposal of nanomaterials and nanoproducts;
- enabling appropriate integration of nanospecific aspects into existing pieces of legislation for sectors, applications, products, or substances;
- covering borderline products (like medical devices or nanomedicinal products) that cross different classic regulatory contexts and for whom regulators have additional uncertainties for the regulatory coverage of emerging nanomaterials risks;
- finding adequate regulatory instruments;
- enforcing compliance with existing and emerging regulation.

These – and other – aspects need to be addressed as soon as possible for the incremental approach to be successful and to go along with a responsible development and use of nanomaterials and nanotechnology.

As mentioned above, some scholars as well as some stakeholders argue that the limitations of the incremental approach are so serious that an entirely new regulatory framework for nanomaterials is needed. But many voices do not further conceptualize this idea. Therefore an exploratory process towards the development of a new regulatory framework for nanomaterials should be encouraged that also tests its feasibility and discusses its advantages and disadvantages compared to the current incremental approach. This discussion could become more urgent since various technology vision documents forecast the development of future-generation nanomaterials, including active nanomaterials with overlapping aspects of information technology, biotechnology and cognitive science. Although these trends are difficult to foresee, regulators will have to monitor these developments and therefore need both the (scientific and budgetary) resources and the regulatory instruments for being able to answer with flexible responses.

1. MANUFACTURED PARTICULATE NANOMATERIALS (MPN) – A WEALTH OF MATERIALS FOR VARIOUS APPLICATIONS

1.1. On nanotechnology and nanomaterials

Nanotechnology is among the most prominent emerging technologies. Although there are different understandings of nanotechnologies in the scientific community, and the definitions that can be found in research policy documents vary, there are some uniting elements: Nanotechnologies comprise a wide range of approaches that concern the study of phenomena and manipulation of materials at atomic, molecular and macromolecular scales[1], where properties differ significantly from those at a larger scale, which may lead to materials, devices and systems with fundamentally new properties and functions. Therefore, nanotechnologies should be considered as an enabling technology, a broad technology platform for a variety of applications in numerous technological fields.

A wealth of applications has been proposed that are enabled by results of nanoscience and nanotechnology development. To many scientists and engineers, nanotechnology manufacturing promises less material and energy consumption and less waste and pollution from production. Nanotechnology is also expected to enable new technological approaches that reduce the environmental footprints of existing technologies in industrialized countries, or that allow developing countries to harness nanotechnology to address some of their most pressing needs.

Nanomaterials and especially nanoparticles are key components of many of those technologies that present a major opportunity for the economic and sustainable development of many countries. A number of nanomaterial-based products are already on the market and many more are known to be under development.

1.2. Nanoparticles and its applications – advantages and challenges

The terminology that defines or describes subjects like nanotechnology, nanomaterials and nanoparticles is used inconsistently in the scientific literature as well as in policy papers and stakeholder communication. Generally speaking, particles with diameters smaller than 100 nanometers are named ultrafine particles or nanoparticles.

Nanoparticles can be made of a vast range of materials. In the laboratory, numerous variants of nanoparticles have been produced from various materials and tested for its physical and chemical properties. From a current commercial applications perspective, the most common nanoparticles are metal oxides, metals, silicates and non-oxide ceramics. They are usually designed and manufactured with properties tailored to meet the needs of specific applications they are going to be used for. Therefore they are often referred to as

[1] A defining element of nanotechnologies and nanomaterials is the so-called nanoscale, which is usually described as the size range between approximately one and 100 nanometres (ISO 2008) or as a feature characterised by dimensions of the order of 100 nm or less (SCENIHR 2007b).

"manufactured" or "engineered" nanoparticles. Products containing engineered nanoparticles include paints, industrial lubricants, advanced tires, cosmetics, sunscreens, coatings for beverage containers, printing inks and nanomedicines.

1.2.1. Properties and applications of nanoparticles

Nanoparticles are attractive from both a commercially and a scientific perspective because they may exhibit completely new or improved properties based on their respective specific characteristics (particle size, size distribution, morphology, phase, etc.), if compared with larger particles or the bulk material they are made of. It can be argued that below a certain size, the physical properties of the material don't just scale down or up, but change (W&W 2005).

With decreasing size of (nano)particles, the ratio of particle surface to particle volume increases. In other words, a given volume (or mass) of a substance has a higher surface in the nanoparticle form than has the same volume (or mass) of the same substance in its bulk form. This property, also described as specific surface area, is relevant for catalytic reactivity and other related properties. Since chemical reactions take place at the surface of a material; the greater the surface for the same volume, the greater the reactivity. A sample of *particles with a high surface area* (like nanoparticles) has a greater number of reaction sites than a sample of particles with low surface area, and thus, results in higher chemical reactivity.

Examples for the application of these characteristics are catalysts where very high surface areas lead to superior catalytic activity compared to conventional catalysts. This property is exploited in noble-metal based catalysts as well as in metal oxide catalysts (e.g. cerium oxide for automotive catalysts). It is also under investigation for the improvement of a number of new energy technologies like fuel cells or rechargeable batteries. In silver nanoparticles, the high specific surface area leads to an increase in surface energy and hence in biological effectiveness which makes them attractive for antimicrobial applications. Nanoparticles are also used as filler material in polymers where the stronger polymer/filler interaction (due to high surface area) results in a more efficient reinforcement at lower loadings, improved material performances and the reduction of materials use. Sheet-like nanoparticles (like silicates), when added to polymers, can create a physical structure that serves as a gas barrier which is a useful feature for a variety of applications including food and chemical packaging.

Optical properties of nanoparticles change according to their size and shape. For example, transparency can be achieved if the nanoparticle size is below the critical wavelength of light. Combining this effect with other properties (like UV- or IR-absorption, conductivity, mechanical strength, etc.), makes nanoparticles (e.g. from metals, silicates or metal oxide ceramics) very suitable for barrier films and coating applications. In addition, interesting optical (light absorbing/filtering) properties can be used for cosmetic applications. Other examples include ceramic nanoparticles used as improved scratch resistance or transparent abrasion/UV-resistant coating. Metal nanoparticles have been used for high-sensitivity sensors and for enhanced imaging in microscopy of biological samples.

Nanoparticles can also be used to improve and tailor *mechanical properties* of composites, depending on the chemistry of the nanoparticle, its aspect ratio, dissemination and interfacial interactions with the matrix as well as on the chemistry of the matrix itself. Depending on these parameters, different effects on mechanical properties of the final composite can be obtained (e.g. high or low stiffness, strength, toughness, etc.) This may lead to various composite materials with tuneable characteristics.

The decrease of the particle size to the nano-range may also result in *improved magnetic properties*. These may be used for new applications in high density media storage and in medical diagnosis and therapy. Metallic nanoparticles (often with core/shell structure) can exhibit super-paramagnetic behaviour and be used for drug delivery (e.g. Ni and Fe), in hyperthermia and as contrast agents for magnetic resonance imaging.

Finally, and perhaps most importantly in the context of this report, also the *biological properties* of nanoparticles may change as a result of the change of their physico-chemical properties. The biokinetics and biological activity of nanoscale particles can differ from bulk material. They depend on many parameters such as particle morphology (size, shape, agglomeration state, and crystallinity), chemistry or surface properties. These properties can be exploited for a number of medical and food applications. These changes of biological properties and their potential consequences for human health and the environment - that are generally anticipated but in detail largely unknown - are the reasons for both public concerns and regulatory activities.

1.2.2. Sources of nanoparticles

Nanoparticles are not a new phenomenon. Many types of nanoparticles occur naturally in matter or the environment. Many biological materials, some of which are also the sources of human food or food ingredients, are naturally nanostructured or contain nanoparticles. Casein micelles, for example, can be considered as nanoparticles. They are the major protein component of milk and responsible for delivering mineral nutrients such as calcium and phosphate to neonates.

Particularly well investigated is the presence of nanoparticles in the atmosphere where their concentration and composition are highly variable both temporally and spatially. Natural emissions from trees and other plants or soil micro flora (volatiles) as well as from soil erosion can dominate in some regions, while particles from sea spray may dominate elsewhere. Also volcanic ash may deliver large quantities of "natural" nanoparticles into the atmosphere. Another group of atmospheric nanoparticles are the incidental products of processes involving industrial, combustion, welding, and transportation activities (Gwinn & Vallyathan 2006). The local concentrations of nanoparticles in the atmosphere are greatly affected by environmental conditions and depend strongly on emission intensities, proximity to sources, and meteorological conditions. In general, the highest number concentrations occur in urban areas while natural sources dominate in rural areas, although anthropogenic sources can be significant there as well (Buseck & Adachi 2008). Figure 1 summarizes the atmospheric abundance of nanoparticles as a function of environment.

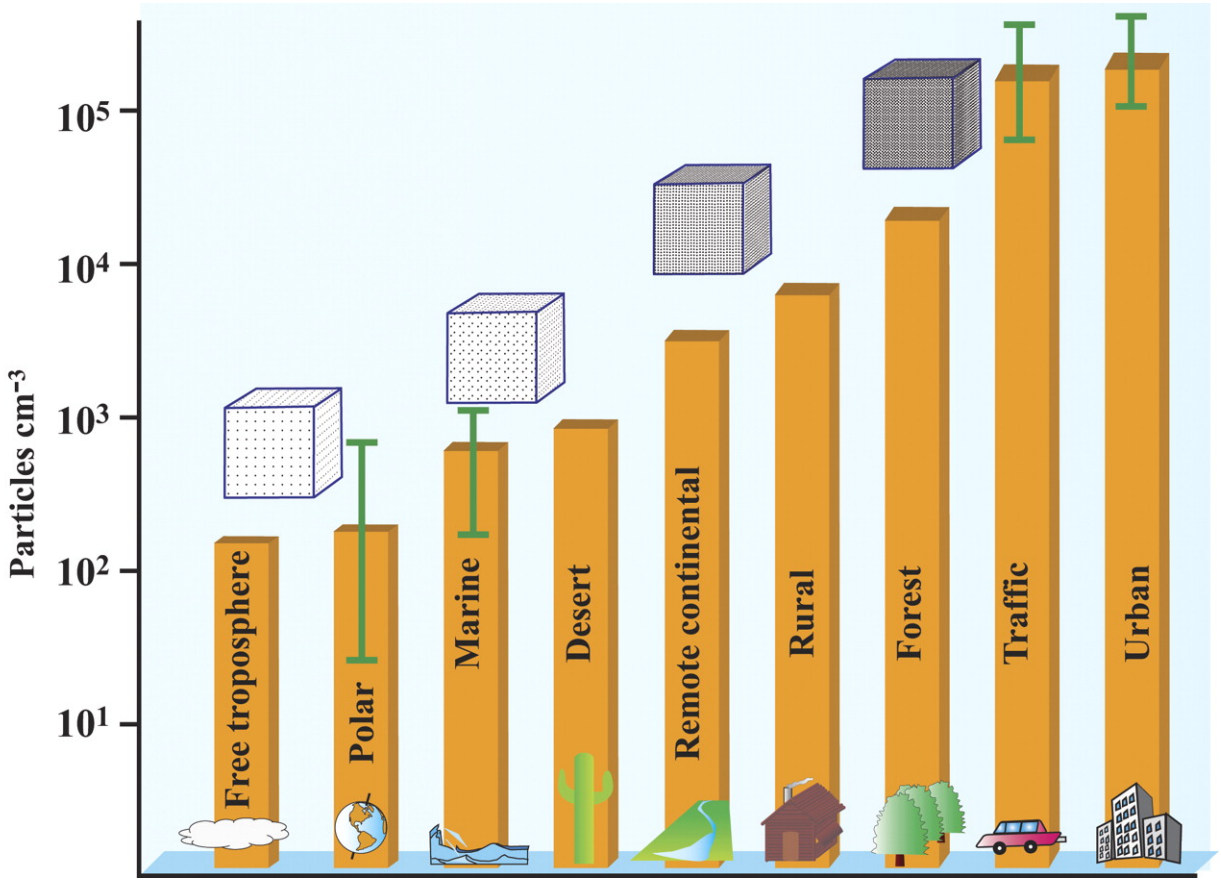

Figure 1: Number concentrations (particles per cubic centimetre) of nanoparticles in the atmosphere in various environments (taken from Buseck & Adachi 2008)

What has changed the general perception of nanoparticles is that science and industry became able to develop and fabricate nanometer-sized particles that are specifically designed and produced to provide novel phenomena, properties and functions at the nanoscale enabling us to measure, control and manipulate matter in order to change those properties and functions (Oberdörster et al. 2007). These intentionally produced nanoparticles can be – and usually are - different from those that already occur in nature. Since manufactured nanoparticles are produced under controlled conditions; in an ideal case, with relatively homogeneous size distribution, higher concentrations of similar manufactured nanoparticles can appear than by naturally occurring nanoparticles.

Manufactured nanoparticles are made using various materials:

Metal oxides are probably the most important nanoparticles in terms of production volumes and recent market usage. Important representatives of this group are titanium dioxide (TiO_2), zinc oxide (ZnO) and silicon dioxide (SiO_2). Other members of this group are cerium oxide nanoparticles, iron oxide nanoparticles and some ceramic nanoparticles.

Metal nanoparticles are also of great scientific and commercial interest since the reduction of the size leads to properties different from those of the bulk metal. A well-known example for that behaviour is that gold, being a non-reactive metal at the macro- and micro-scale, displays catalytic properties when used in the form of nanoparticles.

A number of metals have been produced as nanoparticles. Gold nanoparticles (also known as colloidal gold) are a very popular system for experimentation in materials and biomedical research. They are also tested for therapeutic applications, e.g. as drug carriers. Metal nanoparticles are also used as – or proposed for – applications as catalysts, e.g. in the automotive industry or for environmental remediation.

The metal nanoparticles most used in consumer applications are silver nanoparticles. They can be found in textiles, outdoor equipment, wound dressings, cosmetics, casings of electric and electronic devices, among others. Most of the consumer products containing silver nanoparticles want to capitalize on silver's biocidal properties, its effectiveness in killing a broad spectrum of bacteria and other microorganisms. Known for quite a long time, this approach gained steam because materials engineering methods of manipulating silver were developed so that it could be effectively and cheaply embedded into plastics or grafted onto surfaces.

Some chemical elements can exist in different structural modifications, known as so-called allotropes. Carbon has three common allotropes: diamond, graphite and fullerenes, the latter being nano-objects of special relevance. **Fullerenes** are structures composed entirely of carbon atoms. They may appear in the form of a hollow sphere, an ellipsoid (also called buckyballs) or a hollow tube (called carbon nanotubes). In the strict sense of ISO's definition (cf. Ch 1.3.1, Annex I), neither buckyballs nor carbon nanotubes (CNT) should be considered nanoparticles. But in the related literature as well as in regulatory debates it has become a convention to include them in this category.

Spherical fullerenes, also known as *buckminsterfullerenes* or *buckyballs*, are available in a number of derivatives which stem from the number of carbon atoms used to form the molecule (see Figure 2). The most common spherical fullerene – both in terms of natural occurrence as well as usage as material for commercial application and toxicological research – is C_{60}.

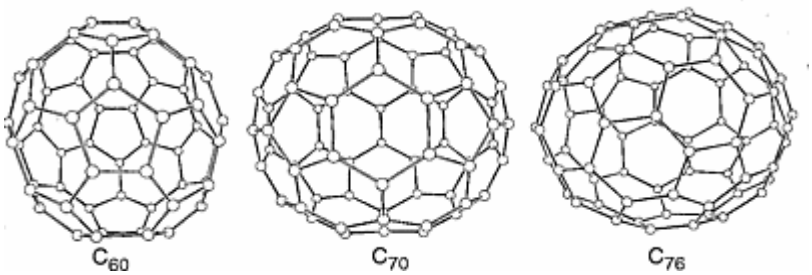

Figure 2: Variations of spherical fullerenes (buckyballs)

Spherical fullerenes for commercial applications are commonly produced in functionalised form. That means that special functional groups – atoms or molecules responsible for specific properties - are added onto the surface of the respective basic molecule. By definition, these groups are key determinants of the physico-chemical properties of the molecule under investigation, and may also influence the biological activity of the molecule,

Carbon nanotubes are hollow nanofibres made of carbon atoms. Their diameter is in the order of a few nanometers, while their length can be up to several millimetres. Due to their exceptional physical and electronic properties (Collins & Avouris 2000), it is expected that carbon nanotubes could contribute to a variety of applications. Thus they are associated with a huge technical and economic potential. They are usually categorized in two families: single walled carbon nanotubes (SWCNT) and multi walled carbon nanotubes (MWCNT).

SWCNT can be described as a one-atom-thick layer of graphite (called graphene) rolled into a seamless cylinder. The way the graphene sheet is "wrapped" is one of the factors determining the physical properties of the nanotube. They are of special interest for electronics applications, as additives for composite materials and as laboratory test systems in solid state physics. Double walled carbon nanotubes (DWCNT) are structures that consist of two SWCNT arranged in a co-axial form. Their morphology and properties are similar to SWCNT but they are better suited for applications where functionalization is required to add new properties to the nanotubes without changing their peculiar mechanical properties.

Multi walled carbon nanotubes (MWCNT) can come in two different forms: as a co-axial assembly of SWCNT of different diameters, nested into each other like in a Russian doll, or as a single sheet of graphene rolled in around itself like a scroll.

Beside their basic structure carbon nanotubes can differ from each other in their length, surface modification (functionalisation, coating) and presence of contaminants. All these factors may impact the physico-chemical properties of CNT and hence also their biological activity.

1.2.3. Markets for nanoparticles

It is difficult to find reliable market data for nanoparticles and nanoparticles-based products. To the well-known methodological challenges of market analysis add fuzzy definitions of both nanoparticles and nanoproducts, the diversity of potential commercialisation pathways and the complexity of the nanomaterials value chain. Because nanomaterials – like all materials technologies – are enabling technologies, market estimates do not always distinguish clearly enough between the more limited value-added nanomaterials itself and the products that "contain" nanomaterials to enable new functionalities and products (Breggin et al. 2009). A mere summation of market values of individual nanomaterials and components would lead to an undervaluation of the economic relevance of nanomaterials, since its leverage effect would be left unconsidered. On the other hand, to consider the entire product (e.g. of a hard disk drive, a sunscreen or stain-resistant dress-suit) as a nanoproduct and use its simply determinable market value as in indicator would certainly lead to an overvaluation of the economic relevance of nanomaterials.

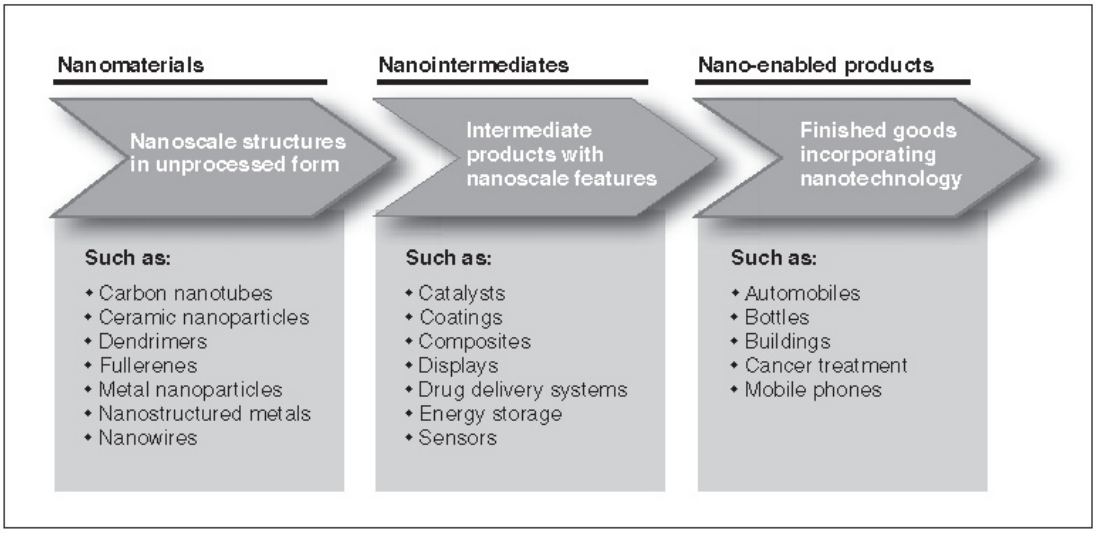

Figure 3: Nanomaterials as enabling technology (GAO 2010)

Notwithstanding these limitations, a market estimates might provide a raw guess of the expectations on the economic impact of nanomaterials. A number of market studies, usually performed by consultancies, have been published over the years. Table 1 summarizes the results of a selection of these studies. The figures should be interpreted with caution. Since the methodologies of data collection and forecasting in these studies are far from transparent, the absolute figures should be read as indicative, not be added up or compared between product segments.

	World Market Volume		
Product group	**Reference Year (Mio USD)**	**Forecast (Mio USD)**	**Source**
nanoparticles used in biomedical, pharmaceutical and cosmetic applications	205 (2007)	685 (2012)	BCC 2007
nanoparticles used in electronic, magnetic, and optoelectronic applications	522 (2007)	1.100 (2012)	BCC 2007
nanoparticles used in energy, catalytic, and structural applications	365 (2007)	1.300 (2012)	BCC 2007
Biomarkers	5600 (2007)	12800 (2012)	BCC 2007
Nanomaterials for nanoelectronics	246 (2005)	1100 (2010)	Sheet 2006
Dendrimers	12 (2005)	42 (2010)	Lux 2007
Electrically conductive polymers	146 (2007)	361 (2013)	BCC 2008
Quantum dots	25 (2008)	700 (2013)	BCC 2008
Nanofibres (without CNT)	48 (2007)	176 (2012)	BCC 2007
Metallic nanopowder (silver etc.)	89 (2005)	770 (2010)	Lux 2007
Carbon Nano Tubes (CNT)	79 (2007)	807 (2011)	BCC 2007
CNT	181 (2006)	1900 (2010)	Electronics ca. 2007
CNT		7720 (2015)	GIA 2010
C60 Fullerenes	3 (2005)	60 (2010)	Lux Research 2007
PVD-materials	1180 (2008)	2200 (2013)	BCC 2005

Table 1: Market estimates for nanomaterials and applications (BMBF 2007, own research)

In an extensive meta analysis of 16 market reports describing global market values for various consumer products containing nanomaterials, the Dutch National Institute for Public Health and the Environment (RIVM) has attempted to assess the market presence of these products and to use this information to gather more insight in the possible exposure of consumers to nanomaterials in consumer products (RIVM 2009). It was shown that the use of nanomaterials in motor vehicles is recently by far market leader, based on estimated market value at present. The authors also estimated that in the near future, the consumer category of electronics and computer will (almost) reach the level of motor vehicles.

The authors of the RIVM study also attempted to estimate the relative contribution of various individual consumer products or its components to the total value of nanomaterials in consumer products. The absolute numbers of the market values of these products were presented in the consulted market reports, but because of the confidentiality of the data and methodological difficulties, only relative numbers are given in the RIVM study. It presents a ranking in categories based on the relative contribution (in %) of the estimated global market value for nanomaterials used in the products (at present and in the near future (2010-2015)). Despite the fact that the information is limited with regard to absolute market volumes, it allows for a good classification of the overall market relevance of various products and is therefore presented in Table 2.

	Present		**Future (2010 – 2015)**
Product group	**RMV category (%)**	**Product group**	**RMV category (%)**
catalytic converters	>50	catalytic converters	40-50
coatings and adhesives	10-20	flat panel display	10-20
hard disk media	1-10	coatings and adhesives	10-20
flat panel display	1-10	hard disk media	1-10
food packaging	1-10	nanotubes - electronics	1-10
automotive components	1-10	food packaging	1-10
UV absorbers in cosmetics	0.1-1	lithium ion batteries	1-10
magnetic recording media	0.1-1	insulation	1-10
insulation	0.1-1	UV absorbers in cosmetics	1-10
photocatalytic coatings	0.1-1	automotive components	1-10
anti-scratch/stick-household products	0.1-1	light emitting diodes	1-10
cladding of optical fibres	0.1-1	sporting goods	1-10
sporting goods	0.1-1	photocatalytic coatings	0.1-1
wire and cable sheathing	0.1-1	transparent electrodes	0.1-1
eyeglass/lens coating	0.1-1	anti-scratch/stick-household products	0.1-1
antimicrobial dressings	0.1-1	wire and cable sheathing	0.1-1
xenon lighting	<0.1	antimicrobial dressings	0.1-1
filtration system	<0.1	magnetic recording media	0.1-1
optical recording media	<0.1	diesel fuel additives	0.1-1

Table 2: Ranking of consumer products containing nanomaterials. The products are ranked based on their relative market value (RMV) of the estimated global market for

nanomaterials in consumer products at present and in the future (2010-2015). (RIVM 2009)

Very popular among scholars of researchers studying the societal and EHS implication of nanotechnology as well as among policy advisers is an inventory of consumer products containing nanomaterials, maintained by the Project on Emerging Nanotechnologies (PEN) at the Woodrow Wilson International Center of Scholars in the U.S. It currently lists over 1,000 nano-enabled products that are on the market in 24 different countries (PEN 2010). Data from this database are frequently used for quantitative analyses and market estimates. But this information should be used with caution. The online inventory of nanotechnology goods basically relies on manufacturers' claims and labels that the product is based on nanotechnology or contains nanomaterials. There is no rigid quality control of these claims. Therefore, one can reasonably assume that there are a number of products which contain nanomaterials or were produced using nanotechnology but which are not included in the data base. At the same time, various products known to contain nanomaterials do not appear in the inventory because the producers or distributors do not label it. Hence, the inventory does not contain the information needed to give a reliable estimate of the full range of current nanotechnology applications. The data is only indicative and might give a glimpse of the wide range and ever-expanding of commercial applications of nanotechnologies in consumer products. The vast majority of these products appears in the cosmetics, clothing, personal care, sporting goods, sunscreens and filtration sectors and are available primarily on the US market, with East Asia and Europe following in second and third place. The materials most frequently mentioned as being contained in products are nanoscale silver, carbon, zinc including zinc oxide, silica, titanium including titanium dioxide, and gold.

1.3. On definitions

The content and scope of a definition of nanomaterials (and nanoparticles) are discussed in many societal spheres, including science, industry and regulatory policy. There seems to be a broad consensus that a generally agreed definition would help to avoid misunderstandings and ensure efficient communication. It is needed, inter alia, for legal acts, manufacturing and trade standards, the analyses and presentation of market data and commercial potentials, for the generation and exchange of scientific data or the assessment of results toxicological studies. At the same time, the attempt to find this general definition appears to be a challenging endeavour.

The nature of, and the demand on, definitions have been debated by scholars from various disciplines since ancient times. It is now widely agreed that there are different kinds of definitions since definitions may serve a variety of functions, and their general character varies with function. This also means that definitions may have different structures, and that the content of a definition of "same" objects may vary according to the purpose of the definition and the context within it is used. In addition, definitions and classifications are not purely describing something but by applying a specific structure to a subject area they are also shaping that area. They are not only descriptive but also constructive (Schmid et

al. 2003). These considerations may also inform the search for definitions of nanomaterials, nanoparticles, nanoobjects or the like.

Nanotechnology it its recent usage is a term coined by science and technology policy (STP). Goals of STP are inter alia to strengthen the scientific and technological bases in order to stimulate innovation, to foster social welfare and economic competiveness, to contribute to a sustainable development and to support other policy areas like public health, energy security or consumer protection. Since *definitions for STP* are especially relevant in early stages of the innovation process, they can be, and presumably have to be, rather open and, in a sense, imprecise. This is also true for "nanotechnology" which is usually defined as the science and technology at the nanoscale, i.e. in the size range between approximately 1 and 100 nanometers. This broad definition of nanotechnology has shaped some definitions of nanomaterials, especially those used in research policy documents and funding programmes, as well as its understanding in the "natural language".

By contrast, *scientific definitions* of terms may differ considerably from their natural language usage. Since scientific methods of investigation, measurement and mutual quality control depend upon sophisticated characterizations of its subjects, scientific definitions have to be precise and unambiguous.

In its comprehensive discussion of the scientific background and foundations of various definitions of nanotechnology (mainly taken from STP documents), a study group at the Europäische Akademie Bad Neuenahr-Ahrweiler has argued that one of the key rationales behind "nanotechnology" is the discovery, understanding, and application of size-depended material properties that have no equivalent in the macroscopic world. Material properties cover magnetic, mechanic, electronic, optical, thermodynamic and thermal features as well as the abilities for self assembly and recognition. The specific-size dependence of these properties becomes evident when they:

- no longer follow classical physical laws but rather are described by quantum mechanical ones;
- are dominated by particular interface effects;
- exhibit properties due to a limited number of constituents, since the usual term "material" refers to an almost infinite number of constituents (e.g. atoms, molecules) displaying an averaged statistical behaviour.

Furthermore, the study group maintains that the size regime usually referred to as the nanoscale "can be used as a good approximation for deciding if a certain technology represents Nanotechnology or not. However, a lateral scale in one or more dimensions is not a physically plausible measure to define Nanotechnology because we can find both effects which are within the interval between 0.1 nm and 100 nm and are not Nanotechnology (…) and effects which occur above 100 nm (or even 1000 nm) but show these 'specific size dependent properties'". As a consequence, a size range should not be part of a nanotechnology (and nanomaterials) definition (Schmid et al. 2003).

The Technical Committee (TC) 229 of the International Organization for Standardization (ISO) has published a draft standard (ISO 2008) that is aiming at providing a list of unambiguous terms and definitions related to nanomaterials (cf. Ch 1.3.1; Annex I). It is

mainly intended to facilitate communications between organizations and individuals in industry and those who interact with them. Although this proposal might be seen as a helpful enterprise for rendering scientific and public communication more precisely and supporting the development of accepted taxonomy of the different classes of nanomaterials, its "nanoscale" definition remains too vague for various purposes.

Legal definitions of technical artefacts in technology regulation have to describe the object of regulation sufficiently precise to be clear to all parties affected by the regulation. They have to consider practices of production and application of the artefacts as well as to be enforceable by the responsible authorities. They are usually science-based but not necessarily identical to scientific definition(s) of the same term. Legal definitions will be shaped by – and in return are shaping – both the artefacts that they intend to describe as well as the contexts in which they are used. A legal definition thus incorporates not only scientific and technological knowledge (and its respective uncertainties), but also includes the results of policy choices and political decisions.

Since it is the aim of this report to assist parliamentary activity with regard to nanomaterials, we will subsequently focus on the discussion of finding an adequate legal definition for nanomaterials.

1.3.1. Excursus: Overview of the most important currently available definitions

Several national and international standardisation bodies, organisations, and authorities have developed a definition for the term "nanomaterial" or "nanoparticle". An extensive and clearly presented overview is given by the Joint Research Centre (JRC 2010) of the European Commission. Annex I summarises the most important European and global definitions in detail, the intentions and goals, the advantages and disadvantages and the resulting problems in a comparative manner. It must be emphasized that each definition will have implications within the context in which it is used. The following organisations are considered:

The Technical Committee TC 229 of the International Organization for Standardisation (ISO) is mainly responsible for standardisation work related to nanotechnologies. The TC 352 of the European Standardization Committee (CEN) also deals with terminology and there is an agreement to systematically propose the ISO documents for adoption as CEN documents. A number of nano-related definitions are published or are being drafted by ISO, whereof the most important are the technical specification CEN ISO/TS 27687 (2008) and the recently published technical report ISO/TR 11360 (2010). Both documents describe a classification system called "Nanomaterial tree" that can be used to categorise nanomaterials with regard to dimensions, shape, chemical nature and properties.

The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) is one of the independent scientific committees of the European Commission which provides advice on issues related to consumer safety, public health and environment. Based on existing definitions, SCENIHR developed a conceptual framework for the description of some basic principles relating to nanotechnologies (SCENIHR 2007b). In addition, SCENIHR

recently proposed a working definition for the term "nanomaterial" on a scientific basis (SCENIHR 2010).

The Organisation for Economic Co-operation and Development (OECD) Working party on Manufactured Nanomaterials (WPMN) published a working document with an elaborate definition for the term "Manufactured nanomaterials" as a guidance for the use of the OECD Database on Research into the Safety of Manufactured Nanomaterials (OECD 2008).

Most importantly in the context of this report, also a number of *legislatory documents of the European Parliament* – either already passed or still in progress – includes definitions of nanomaterials. For example, the regulation for cosmetic products (EC/1223/2009) includes the obligation to label nanomaterials in the list of ingredients. Therefore a definition for the term "nanomaterial" is given in Article 2.1 (k). In the regulation it is also mentioned that the definition shall be adapted to technical and scientific progress.

In the recast of the Novel Foods Regulation the European Parliament proposes to include a definition of "engineered nanomaterial" for the regulation on novel foods. Also this definition shall be adjusted to agreed definitions at international level (European Parliament 2009b). In the recently published report on the proposal for a regulation concerning the placing on the market and use of biocidal products, a legal definition of the term "nanomaterial" was proposed. This definition is the same as given for the term "engineered nanomaterials" in the recast of the novel food regulation (European Parliament 2010b).

	ISO/TC 229 (2008) and CEN	SCENIHR	OECD (2008)
Subject	Rational, hierarchic definition system Classification of nanomaterial concerning the shape	Hierarchy of terminology (SCENIHR 2007b) elaborate proposed working definition of the term "nanomaterial" (SCENIHR 2010)	Working definition for the term "manufactured nanomaterial"
Intention	Technical specification for a future standard to facilitate communications	Framework based on existing terms, on common sense, and on the needs of risk assessment Working definition for the term "nanomaterial" for regulatory purposes	Elaborate additional criterions and possible discriminators for the identification of a nanomaterial concerning physico-chemical properties
Definitions	**Nanoscale:** Size range from approximately 1 nm to 100 nm **Nanomaterial:** Material with any external dimension in the nanoscale or having internal or surface structure in the nanoscale **Nano-object:** Material with one, two or three external dimensions in the nanoscale	**Nanoscale:** A feature characterised by dimensions of the order of 100 nm or less **Nanomaterial:** Any form of a material composed of discrete functional parts, many of which will have one or more dimensions in the nanoscale **Engineered Nanomaterial:** Any form of a material that is deliberately created such that it is composed of discrete functional parts, either internally or at the surface, many of which will have one or more dimensions of the order of 100 nm or less. **Nanoparticle:** A discrete entity which has three dimensions of the order of 100 nm or less	**Nanoscale:** Size range typically between 1 nm to 100 nm **Nanomaterial:** Material which is either a nano-object or is nanostructured **Manufactured nanomaterials:** Nanomaterials intentionally produced to have specific properties or specific composition, a size range typically between 1 nm and 100 nm and material which is either a nano-object (i.e. that is confined in one, two, or three dimensions at the nanoscale) or is nanostructured (i.e. having an internal or surface structure at the nanoscale)
Problems	Definitions differ from actual scientific, public and media used terms (carbon nanotubes are classified as nanofibres and not as nanoparticles, usual designated in toxicological studies)	The terms for nanosheet, nanorod, nanofibre are not consistent with ISO terminology It is not possible to identify a specific size or a specific generic property that is introduced with size for the definition of "nanomaterial". These uncertainties result in an already not enforceable term for regulatory settings (SCENIHR 2010).	The definition is based solely on size because physico-chemical properties even useful for risk assessment can not be translated into a general definition
Support	Helpful for a sophisticated scientific communication and regulatory activity	More relevant for risk assessment purposes, consideration of size, shape and properties, number size distribution, mean size and standard deviation.	Including ISO definitions for a broader application of the term "manufactured nanomaterials"

	Cosmetic products regulation EC/1223/2009	**Recast of the Novel Foods Regulation (European Parliament 2009b)**	**Recast of the Biocidal Product Directive (European Parliament 2010b)**
Subject	Means of the term "nanomaterial" for regulatory purpose	Means of the term "nanomaterial" for regulatory purpose	Means of the term "nanomaterial" for regulatory purpose
Intention	Establishes rules for cosmetic products available on the market, in order to ensure the functioning of the internal market and a high level of protection of human health	Novel foods are subjects of a pre-market control or pre-market notification. Risk management in relation to nanomaterials can be verified by authorities before placing on the market	Active substances of biocidal products are subjected to authorisation in a positive list. Nanomaterials can be used as co-formulants in biocidal products and as active substances as well.
Definitions	**Nanomaterial:** (Article 2.1 (k) Nanomaterials means an insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm Article 2.3: … the Commission shall adjust and adapt point (k) of paragraph 1 to technical and scientific progress and to definitions subsequently agreed at international level …	**Engineered nanomaterial:** (Article 3.2 f) "engineered nanomaterial" means any intentionally produced material that has one or more dimensions of the order of 100 nm or less or is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have size above the order of 100 nm but retain properties that are characteristic to the nanoscale Article 3.3: … the Commission shall adjust and adapt point (c) of paragraph 2 to technical and scientific progress and with definitions subsequently agreed at international level …	**Nanomaterial:** "nanomaterial" means any intentionally produced material that has one or more dimensions of the order of 100 nm or less or is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have size above the order of 100 nm but retain properties that are characteristic to the nanoscale
Problems	The terms solubility and dispersion are used interchangeable thus creating interpretation problems. Persistence is used in a risk assessment context to define chemicals that are retained in the body or in the environment being considered as the opposite of soluble or (bio)degradable. This property may change for each individual NM (SCENIHR (2010)). The possibility is included for a revision of the definition based on scientific and/or international developments	The definition is ambiguous and not clear because several aspects dealing with size have been included (e.g. "of the order of 100 nm or less", "above the order of 100 nm"). The possibility is included for a revision of the definition based on scientific and/or international developments	The same definition for the term "Nanomaterial" and "Engineered Nanomaterial" (see also the Novel Food definition)
Support	Additional properties like "insoluble" or "biopersistent" comprises types of NM with the highest health attention which would have a high priority for risk assessment	The definition combines size and non-specified properties that are characteristic to the nanoscale Adapted from the SCENIHR definition	Adapted from the Novel Food definition

Table 3: An overview of proposals for the definition of nanomaterials

1.3.2. Elements of definitions of nanomaterials

Although there is a great inconsistence regarding the definition of the term "nanomaterial" in detail, the organisations used a characteristic set of criteria and keywords like size scale, shape and additional properties. A summarized overview of the different elements is given in Table 4.

Organisation	Size scale	Size distri-bution	Aggregates, agglomerates included	Properties	Intentionally produced	Also internal structure
ISO-CEN	x					x
SCENIHR	x	x				x
OECD	x					x
EC (Cosmetics)	x			Specific: insoluble, biopersistent	x	x
EU (Recast of Novel Foods regulation)	x		x	Non-specific: nanoscale properties		x
EU (Recast of the Biocidal Product Directive)	x		x	Non-specific: nanoscale properties	x	x

Table 4: Overview of elements in existing definitions of the term nanomaterial

Practically all definitions proposed by international organisations include a *size range* when defining the term "nanomaterial". This aims at distinguishing a nanomaterial from materials in the micrometer range or larger, and from the sizes at the atomic and molecular level. In addition, nanomaterials are defined as being either a nano-object or nanostructured, whereas a nano-object is generally confined in one, two or three dimensions at the nanoscale (see Figure 4). Thus a starting point for the definition is the size of the primary particle.

For the term "nanoscale" specific problems arise, since the lower end of the scale is very close to the atomic scale and the size range of large molecules (e.g. DNA molecules ranges between 0.5 nm and 2 nm, C60-fullerenes have a size range of 0.7 nm).

The European Commission's Joint Research Centre has published a report (JRC 2010) dealing with considerations on a definition of "nanomaterial" for regulatory purposes. In this Reference Report it is proposed, that the upper nanoscale limit should ideally be high enough to capture all types of materials that would need particular attention for regulation. Upper limits which are often used, for example 100 nm, may require qualifiers based on structural features or properties other than size, in order to capture structures of concern with a size larger than 100 nm in the regulation. Establishing a nanoscale size range with rigid limits would be clear and enforceable in a regulatory context (pure downscaling). On the other hand there is no direct relationship between size and novel effects or functions. Therefore, no general size limit can be given for true nanoscale properties. The only feature common to all nanomaterials is the nanoscale (pure downscaling and true nanoscale). For pragmatic reasons the JRC suggested that a lower limit of 1 nm and an upper limit of 100 nm or greater is a reasonable choice. The authors propose to use clear lower and upper limits for a definition, especially with regard to a regulatory purpose. But whether there are additional data for hazard characterization of materials with sizes higher than 100 nm

would be subject to further discussion. Moreover, the discussion should as well take into account size distributions and the non-uniformity of samples.

An important problem of the size range for nanoscaled material is that particles in particulate form may be present as single particles but also as agglomerates and aggregates. ISO/TC 229 (2008) names these particle forms "secondary particles", which may have dimensions beyond the 100 nm size. According to ISO agglomerates and aggregates are considered as nanostructured nanomaterials and the size range for nanoscale is therefore defined as approximately 1nm to 100 nm. SCENIHR suggested that it is important to describe nanomaterials with the mean particle size and the size of the primary particles. When the mean particle size is larger than the size of primary particles this will be an indication of the presence of agglomerates or aggregates (SCENIHR 2010). The state of agglomeration or aggregation may need to be addressed specifically in subsequently developed definition and legislation. In the recast of the novel foods and biocidal products regulations, agglomerates or aggregates were included in the definition of "engineered nanomaterial" and "nanomaterial", respectively.

Besides the size range *additional properties* are used to define nanomaterial. For instance the cosmetics regulation included the properties "biopersistent" and "insoluble" into the definition of the term "nanomaterial". According to SCENIHR it is not possible to identify a specific size or a specific generic property that is introduced with size for the definition of "nanomaterial". These uncertainties result in an already not enforceable term for regulatory settings (SCENIHR 2010). On the other hand for some nanoparticulate materials with a wide range in size distribution the measurement of the surface area may be meaningful to distinguish dry solid nanostructured material like aggregates from non-structured material. The volume specific surface area (VSSA) could be considered as an additional criterion to identify dry solid powders as nanomaterials. The proposed threshold limit is 60 m^2/cm^3 beyond which the material is considered to be nanostructured. However, not all nanomaterials are amenable to VSSA determination.

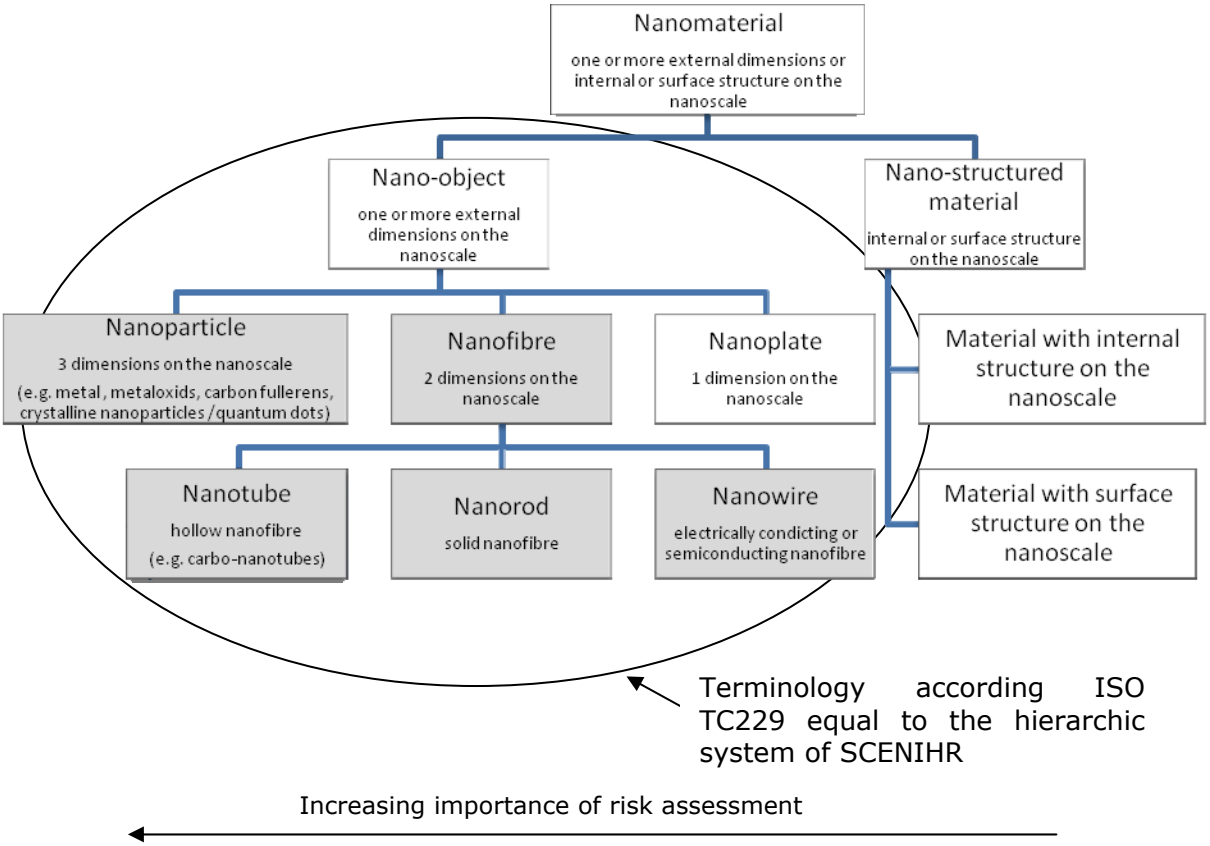

Figure 4: Types of nanomaterial in a hierarchic system, subject of toxicological research according ENRHES (2010) are grey filled. (Material with internal structure on the nanoscale means: e.g. nano-composites, nanoporous membranes, aggregates, agglomerates. Material with surface structure on the nanoscale means: e.g. coatings, functionalised membranes).

1.3.3. The need for a harmonised legal definition

New emerging and innovative technologies like nanotechnology create new challenges for the legislator, if the associated consumer products raise concerns about health and environmental risks. Many nanotechnology applications are based on materials deliberately engineered, for which the term "nanomaterial" is now commonly used. The term generally refers to materials with internal structures and/or external dimensions with a size range between the nanoscale and the micro and macroscopic scales. Definitions of the term "nanomaterial" in its current general understanding are not considered appropriate for scientific as well as regulatory purposes. In fact, different definitions have already been developed, even in European regulations, but some partially conflict and are inconsistent and it is difficult to reach a general consensus.

In its resolution of 24 April 2009, the European Parliament, inter alia questioned whether, in the light of the existing disagreements about the definition of the term "nanomaterial", current Community legislation "covers in principle the relevant risks relating to nanomaterials". Furthermore, it maintained that "nanomaterials should be covered by a multi-faceted, differentiated and adaptive body of law based on the precautionary principle,

the principle of producer responsibility and the polluter-pays principle to ensure the safe production, use and disposal of nanomaterials before the technology is put on the market, while avoiding systematic recourse to general moratoria or undifferentiated treatment of different applications of nanomaterials" and called for "the introduction of a comprehensive science-based definition of nanomaterials in Community legislation as part of nano-specific amendments to relevant horizontal and sectoral legislation" (European Parliament 2009a).

Reacting to these positions, the European Commission's Joint Research Centre (JRC) has published a report (JRC 2010) that reviewed and discussed issues and challenges related to a definition of 'nanomaterial', and intended to provide practical guidance for a definition for regulatory purposes. JRC picks up on the size range vs. size dependent properties discussion described above and argues, in short, that although the size-dependent ("new") properties of nanomaterials are the main reasons for (scientific and regulatory) concerns, a definition based on these properties would not be feasible for a number of reasons:

- Even for typical characteristic nanoscale properties it could be difficult to decide when the property in question is really different from the bulk, i.e. where to establish the boundary between nanoscale and macroscopic properties.
- For a definition of 'nanomaterial' based on specific nanoscale properties, it would be essential to clearly list and precisely describe those properties, their occurrence and the measurement processes to determine them, and to distinguish them from bulk properties.
- A definition based on a comparison to the equivalent bulk material would not be feasible as it assumes that all material exists also in the bulk form which is – according to JRC - not the case, particularly not for more advanced nanomaterials.

The JRC report concludes "that for pragmatic reasons and for the sake of uniqueness, broadness, clarity and enforceability, it is advantageous not to include properties other than size in a basic definition." It also states that a definition of the term "nanomaterial" for regulatory purposes should fulfil additional requirements (JRC 2010):

- A single, comprehensive and "harmonised" definition broadly applicable in EU legislation over and across different regulatory areas (e.g. horizontal and sectoral legislation),
- legally clear and unambiguous, viz. terms such as "of the order of", "approximately" and similar imprecise expressions are avoided,
- enforceable,
- and in line with other approaches worldwide (e.g. ISO, OECD).

1.3.4. Definition for regulatory purposes

What might become obvious from that brief discussion is,

a) that although some of size-dependent properties of nanomaterials and the known and unknown implications of their production, use and disposal on both human health and the environment are the main reasons for political and regulatory concerns, a legal definition based on these properties might be difficult to achieve.
b) that a size range in which the most size-dependent properties appear could serve as an appropriate heuristic.

c) that any choice of a size range as central part of a materials-independent definition for regulatory purposes would be imperfect with respect to certain regulatory goals since there are no direct, material-independent relations between size and "nanoscale properties". Whatever size range would be chosen, some nanomaterials will be subject to legal obligations although there are no indications for adverse effects of their use, and some nanomaterials will lie outside the given size range although there might be reasons for including them in the regulation.
d) that not only the choice of a size range in general, but also the definition of both the lower and the upper limit of the size range are imperfect heuristics. The lower limit, typically given as 1 nm (or, softer, of the order of 1 nm or approximately 1 nm), seems to be hardly controversial since its main purpose is to distinguish nanomaterials from atoms or molecules which should not be regarded as nanomaterials. This is different for the upper size limit. On the one hand, the frequently used upper size limit of 100 nm does not comprise all configurations of materials that give reasons for regulatory concern. Specific nanoscale properties may be found in particles or their aggregates or agglomerates, even if their outer dimensions are beyond 100 nm. One might therefore choose an upper size limit well above 100 nm. On the other hand, in the context of a legal definition for regulatory purposes one should consider that the higher the upper limit is chosen, the larger the number of materials included in the regulation that do not exhibit "nanoscale properties". The specification of the size range in a nanomaterials definition, and especially of its upper limit, therefore should be subject to political decisions.
e) that notwithstanding the actual size range chosen, for reasons of clarity and enforceability, a legal definition should include unambiguous lower and upper size limits. Imprecise attributes like "approximately" or "of the order of" should be avoided.

The authors propose to use clear lower and upper limits for a definition, especially with regard to a regulatory purpose. Furthermore, the state of agglomeration or aggregation needs to be addressed specifically.

According to the report of JRC (2010) it is also likely that certain materials of concern that fall outside a general definition or as a part of nanomaterial with high attention might have to be listed in specific legislation. This is the fact in cosmetic product legislation, where insoluble and biopersistent nanomaterials are of special interest. For regulatory purpose it is possible to specify a general harmonised and broadly applicable definition for the needs of specific implementations.

The authors propose to avoid unclear definitions like in the recast of the novel foods regulation and the possibility for a revision of the definition based on scientific and/or international developments (like in the cosmetics or the novel foods regulation).

1.3.5. Working definition for the purpose of this report

Current research indicates that, of all possible configurations of nanomaterials, two subgroups are those that are by far the most significant as far as human health and environmental impacts are concerned: Insoluble nanoparticles and nanoscale carbon

allotropes (buckyballs and carbon nanotubes), which are mobile in their immediate environments. One might argue that these two subgroups should be covered by any definition used for regulation that is motivated by EHS concerns.

To use the term "nanoparticles" as an umbrella term for both subgroups mentioned above – which is common practice in natural language as well as among most toxicologists – creates a structural inconsistency with the taxonomy of nanomaterials proposed by ISO and might be misleading in regulatory contexts. Both nanoparticles and buckyballs have three dimensions on the nanoscale while carbon nanotubes can have lengths in the micrometer range and therefore are to be considered as two-dimensional nanoobjects, as nanofibres.

The use of the term "nanomaterials" is not considered appropriate for the further discussion in this report. In its current general understanding as well as in the framing proposed in the ISO document it appears to be far too broad. It covers many materials and structures that have never been subject of EHS concerns, that would never interact with biological systems or that occur naturally and most likely defy any meaningful regulatory access.

We therefore propose – following JRC – to use *"particulate nanomaterials"* as an umbrella term. Particulate nanomaterials are understood as a single or closely bound ensemble of substances (consisting of atoms and molecules), at least one of which is in the condensed phase and having external dimensions in the nanoscale in at least two dimensions. Nanoscale means the size range between 1 and 100 nm.

In addition, we will focus only on "manufactured" ("intentionally produced" or "engineered" could be used synonymously) particulate nanomaterials (MPN). Incidental products of human activities (like industrial, combustion, welding, automobile or diesel) or naturally occurring nanomaterials lie beyond the scope of this report.

2. PROBLEMS OF RISK ASSESSMENT OF ENVIRONMENTAL AND HEALTH RISKS OF MPN UNDER UNCERTAINTY

2.1. Introduction

Manufactured particulate nanomaterials (MPN) are expected to be a major opportunity for the economic and sustainable development of many countries. A number of products containing MPN are already on the market and many more are known to be under development (see chapter 1.2). But some of the properties that make MPN attractive for a number of applications in various branches are precisely the properties that are sources of concern: The physico-chemical properties of MPN are different from those of larger particles. Therefore also the biokinetics and biological activity of nano-scale particles can differ from bulk material which early arouses the concerns that the use of MPNs may bear new risks to human health (Oberdörster et al. 2005).

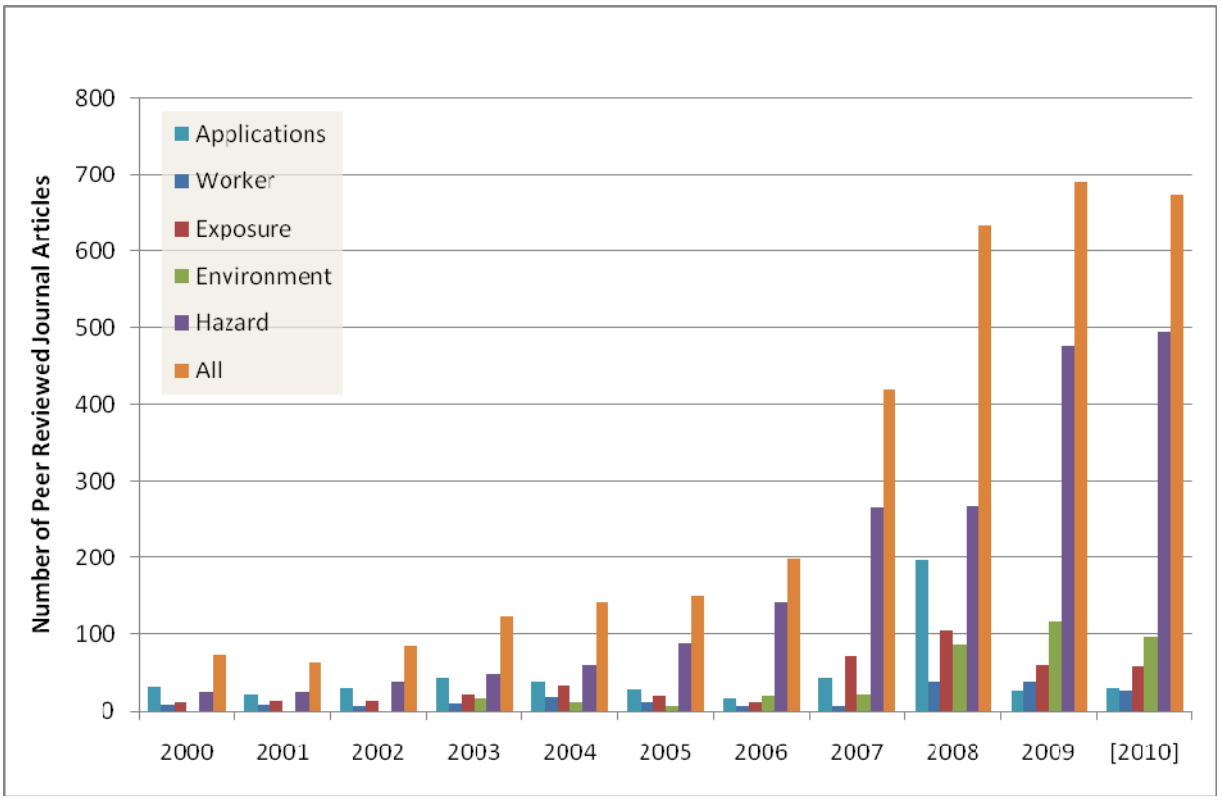

Figure 5: Number of peer reviewed research journal articles on MPNs with a special focus on applications, exposure risks of industrial/research workers, exposure assessment in general, exposure risks of environment or hazard assessment. Data analysis was done using the ICON NanoEHS database (http://icon.rice.edu/report.cfm). Data for 2010 includes the results for the period 01/10-09/10 including the extrapolated data until the end of the year.

The discussions about potential environmental, and health risks of MPNs have triggered a variety of activities on national and multinational level over the last years, mainly focusing on scientific (toxicological, biological, analytical) and regulatory aspects. Research about

biological and toxicological effects of nanoparticles (a.k.a. nanotoxicology) has been massively intensified. Nanotoxicology emerged from the classical toxicology and studies of biological effects of engineered nanomaterials on living organisms and in ecosystems include amelioration of studies leading to prevention of adverse effects (Oberdörster 2010a). Therefore nanotoxicology uses basically the methodology of the classical toxicology in order to determine structure/function and dose relationships between nanoparticles and toxicity. However, there is a consensus about that the classical measures of toxicology are not applicable to nanomaterials and it is under discussion which standard procedures are suitable (Müller et al. 2008, Fadeel & Garcia-Bennett 2010). However, peer-reviewed research on MPNs and their toxicology has grown nearly 600 percent between 2000 and 2007, increasing almost exponentially across the 7-year period (Ostrowski et al. 2009). This trend has continued until 2008, seeming to reach a plateau at present (see Figure 5).

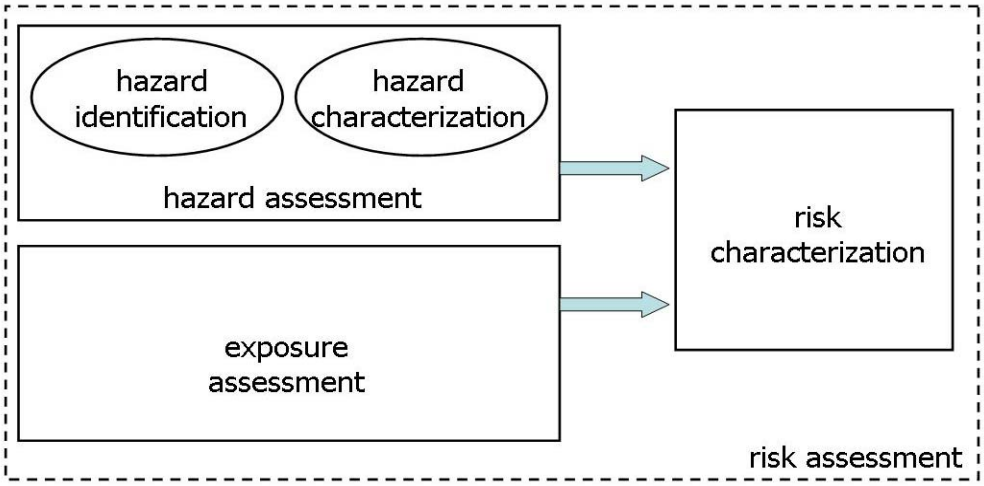

Figure 6: Elements of a chemical risk assessment (developed from OECD, 2003).

Risk assessment is the perquisite for risk management and resembles a process in which the probability of a harmful effect to individuals or populations is quantified. It is often express as the formula "Hazard x Exposure = Risk". Thereby, the risk is defined by two characteristics: (1) the hazard of the material that needs to be identified and characterized and (2) the contact with the hazardous material which is the exposure (Krug et al. 2006). For nanomaterials a proper risk assessment is rather difficult since hazard and exposure assessment is still not clear.

According to the Risk Commission (2003), a scientific risk assessment process primarily deals with consequences of the effects of noxious agents to human health based on four crucial questions.

1. The question of characterization of the hazard potential. What dangers to human health may basically arise from the noxious agent in question?
2. The question of dose-response relationships: What quantitative connections exist between the amounts of a noxious agent used (dose) and the extent of the expected effect?
3. The question of exposure: to what extent is the relevant population group exposed to the noxious agent?

4. The question of the overall estimate of the risk: What is the nature and magnitude of the risk to human health in general, and how accurately can it be estimated? The answer to this fourth question must be arrived at through a critical aggregation of the answers to questions 1 to 3.

A terminology was developed by the OECD refers to a similar conceptual framework (OECD 2003). In OECD's language, a chemical hazard/risk assessment consists of four elements as presented in Figure 6. Thereby, hazard identification corresponds to question 1, hazard characterization to question 2, exposure assessment to question 3 and risk characterization to question 4.[2]

In this chapter, we give an overview of the main findings including current methods and concepts as a systematic review, and the actual thinking and ongoing research on EHS risks of manufactured particulate nanomaterials. Furthermore, an attempt was made to discuss the uncertainties left.

2.2. Principles of nanotoxicology

2.2.1. Techniques of characterization and detection of MPNs

Knowledge about the characteristics of MPNs is important for research and development, but also for risk assessment. Reliable hazard assessment of MPNs requires many highly standardized in vitro and in vivo studies to guarantee the reproducibility and consequently the consistency of the data. Therefore, it is crucial to have accurate information about the tested material. The lack of this information often renders studies unsuitable for hazard and risk assessment (ENRHES 2010).

It is agreed that more knowledge is needed about physical and chemical properties of MPNs than about bulk materials to assess potential risks. Nevertheless, there is an ongoing debate which particular property(s) are most meaningful – in contrast to bulk material where only mass and concentration is considered for hazard and risk assessment. The following characteristics are considered to characterize nanomaterials (in alphabetical order): agglomeration and/or aggregation, chemical composition, crystal structure/ crystallinity, particle size/size distribution, purity, shape, solubility, stability/bio-persistence as well as surface properties, such as area/porosity, charge, chemistry including composition/ coatings, defects and reactivity. However, mostly the size, shape and the surface properties of the particles are characterized whereby latter can influence the reactivity of the MPN. One has to note that to determine the surface reactivity is a rather ambitious intention than a clear parameter, since it is unclear which is the main

[2] The exact definitions provided in the OECD paper are the following (OECD 2003):

Hazard identification: The identification of the type and nature of adverse effects that an agent inherent capacity to cause in an organism, system or (sub) population.

Hazard characterization: The qualitative and, wherever possible, quantitative description of the inherent properties of an agent or situation having the potential to cause adverse effects. This should, where possible, include a dose-response assessment and its attendant uncertainties.

Exposure assessment: Evaluation of the exposure (the concentration or amount of a particular agent that reaches a target organism, system or (sub) population in a specific frequency for a defined duration) of an organism, system or (sub) population to an agent (and its derivatives).

reaction/effect induced by certain MPNs (Card & Magnuson 2009, Oberdörster 2010a, ENRHES 2010).

A variety of different methods and instruments are used to determine the properties of nanomaterials. Most of them were established for non-nanomaterials; others were refined or newly developed for MPNs. High resolution microscopy methods are especially used to analyze shape and aggregation state, while various kinds of spectroscopy and chromatography methods are especially used to analyze chemical composition, purity and surface chemistry. The Tapered Element Oscillating Microbalance is the most applicable method for mass determination, while the Zeta Potential Analysis and the X-ray Diffraction are the only available methods to analyze surface charge and crystal structure, respectively. For the analysis of particle number and size distribution several instruments and techniques are available (e.g. Differential Mobility Analyzer or Dynamic Light Scattering method). To determine the surface area the Brunauer-Emmett-Teller Adsorption Measurement is the most applicable method (Luther 2004, Zuin et al. 2007).

Gathering relevant information for the presents of MPNs in a defined environment (e.g. a working place) by exposure measurements is of high importance for exposure assessment. In theory, the considerable arsenal of methods used for characterization of MPNs listed above is available for detection of MPNs in biological and environmental samples (e.g. water or soil). In practice, it is not that easy because either the instrument has to be at the place of the measurement (online) or samples have to be sent for later measurement in laboratories (offline). Online measurements are favourable because they allow real-time monitoring. But therefore the instruments need to be of a size which is reasonable for transport and it is the usage needs to be as simple as possible to be carried out at any place. For online measurements three types of detection principles are available: (i) light scattering (e.g. photometers, optical particle counters, or condensation particle counter); (ii) light absorption (e.g. aethalometer); (iii) electrical charging (e.g. Diffusion Charging Sensors, Electrical Diffusion Battery, Photoelectric Aerosol Sensor or Scanning Mobility Particle Sizer). These online methods are not very specific[3], but especially light scattering and electrical charging methods are best suited for measuring MPNs in a workplace environment with the limitation for measurement in the gas phase (Marquis et al. 2009). More specific and powerful techniques are the Transmission Electron Microscope Imaging methods, however these are offline methods. Nevertheless, they can also be used for the detection of MPNs in liquid phases.

2.2.2. Exposure

Exposure to a toxic substance during a certain period of time is usually measured by intensity (concentration, radiation, etc.) and duration. Control and prevention of exposure can effectively remove the risk of the toxic agent. It has to be pointed out that without exposure no risk is present (ENRHES 2010). However, there are several exposure scenarios to MPNs to be considered: (i) occupational exposure to workers, (ii) exposure to consumers by nanomaterial-containing products or medical applications in a controlled manner and (iii)

[3] Optical sizing instruments are usually "blind" for small particles (i.e. <0.3 µm) while electrical sizing instruments are usually not suitable for larger particles (i.e. >0.5µm) (M. Fierz at the IVSS Colloquium Lucerne, 2010).

in an unintended way, e.g. by different kind of contaminations including environmental pollution or accidental release from consumer products or productions processes (ENRHES 2010). The majority of studies which aimed to quantify exposure conditions was performed in occupational settings, like production activities, handling and/or downstream processing, and was focused mainly on inhalation exposure. Studies showed some evidence of elevated exposure of airborne MPNs which were not necessarily correlated with activities at the workplace. However, in some cases the elevated exposures were due to absent, malfunctioning or disabled safety and control systems. By good manufacturing practice (occupational hygiene) and maintenance of individual and collective safety systems an effective protection of workers is possible to perform (ENRHES 2010). The use of respirators and other filters appear to be effective to collect nanoparticles from the air (Mostofi et al. 2010). However, exposure scenarios outside working places (consumer and environment) are not studied yet; only two modelling studies aimed to predict environmental and consumer exposure (Boxall et al. 2007, Mueller & Nowack 2008). Recently, the Dutch RIVM attempts to gather exposure information by using commercial market reports and expert consultations in order to identify product categories with a high priority for future exposure studies, like sunscreens and other cosmetic products, as well as coatings and adhesives (do-it-yourself products; RIVM 2009).

2.2.3. Methods for toxicity testing

To evaluate the potential hazards of toxic substances (noxae), different methods can be used: (a) cell-free and cellular in vitro assays, (b) in vivo studies and (c) human and epidemiological studies. The impact of these studies is different: epidemiological studies are considered to be much more valuable than in vitro assays. A further technique which is currently under development is the use of in silico models by applying tools of systems biology in order to predict the toxicity of new MPNs and intends to replace animal experiments in future (Maynard et al. 2006, Xia et al. 2010).

In vitro studies investigate toxicological, mechanistic and other relevant effects, providing evidence for the development of diseases, and having a wide variety of biological endpoints. In vitro assays can be used for hazard identification, whereas the risk assessment aspect is limited. For example, cell-free in vitro assays include the assessment of the inherent capacity of MPNs to induce the release of reactive oxygen species (ROS) in a liquid medium (see Figure 7). The rationale is that the ROS generating potential of MPNs correlates with the in vivo reactivity and thus with the toxicity of MPNs. Also the chemical reactivity, solubility and behaviour in simulated body fluids are tested. In cellular in vitro assays, mostly cell lines are used to study the effects of MPNs, but also primary cells and/or co-cultivated cells (more than one cell type) as well as organ-cultures seem to be more and more established. Depending on the study objective different endpoints can be examined.

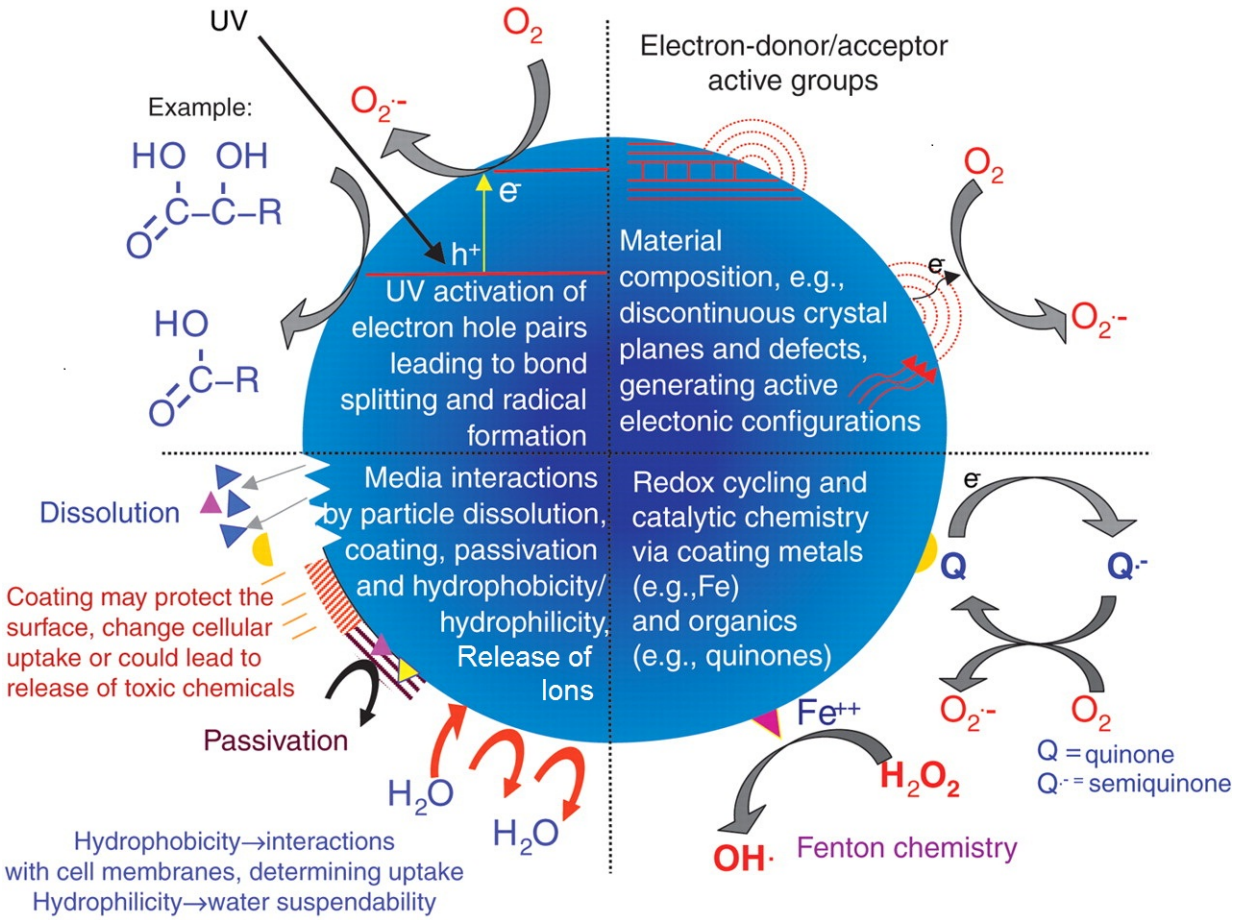

Figure 7. Possible mechanisms by which MPNs interact with biological tissue. Examples illustrate the importance of material composition, electronic structure, bonded surface species (e.g., metal-containing), surface coatings (active or passive), and solubility, including the contribution of surface species and coatings and interactions with other environmental factors, e.g. UV activation (modified from Nel et al. 2006, Xia et al. 2009).

In vivo (animal) studies provide information about effects on a whole living organism displaying the full repertoire of body structures and functions, such as nervous system, endocrine system and immune responses and are powerful for health risks assessment. These studies are usually conducted on laboratory animals, often rodents (rats and mice), that are exposed to the MPNs in highly controlled conditions to test inter alia (i) the acute and/or chronic toxicity, (ii) carcinogenicity/genotoxicity to various target organs, (iii) toxic effects on the reproductive system and/or on the development of the offspring. However, the extrapolation of the data to humans includes in certain cases difficulties also because of the inter- and intra-species variation.

In general, epidemiological studies show the occurrence and distribution of diseases in populations allowing scientists to learn about the causes of disease, which finally may lead to preventive measures. Human studies are usually observational and therefore vulnerable to bias and confounding. Unfortunately, no epidemiologic study for MPNs is available beside the studies dealing with ultra fine particles.

2.2.4. Dosimetry

Dosimetry is the calculation of the particular dose that reaches a certain target tissue/organ or the body. The dose is defined by the total amount of an administered substance over a time period, its uptake or absorption by an organism, organ, or tissue. For dose calculation in nanotoxicology it is problematic to use the mass as an indicative like in classic toxicology, since the surface area of nanomaterials is much larger in relation to the mass than for the corresponding bulk material. At present there is no consensus which metric is the most favourable among the physico-chemical properties of MPNs. It is suggested that the surface area as a measure of reactivity and therefore for potential toxicity should be taken into consideration and "activity per unit surface area" has been mentioned as well (Oberdörster 2010b). Another metric for dose calculation is the so called biopersistence of the material which is a measure of the time period when a material is present within a biological system. Thus, a number of information is needed to calculate the dose for in vitro and/or in vivo studies.

2.2.5. Portals of entry and biokinetics

The first step of hazard identification is to identify the portal(s) of entry of a toxic substance into the body. MPNs can enter the human body by inhalation, ingestion or via the skin pores but also by parenteral administration like injection for medical purposes. Among these uptake routes, the lung appears to be the most important portal of entry followed by the gastrointestinal tract. The penetration of the intact skin can be excluded as it has been demonstrated by in vivo studies. However, one has to note that translocation to the dermis in damaged skin is not to exclude and thus, at present under investigation. Furthermore, to a small amount (1-2 percent of the translocated MPNs) uptake by sensory nerve endings in the upper and lower respiratory tract has also been shown (Oberdörster et al. 2009, Geiser & Kreyling 2010). The uptake in the gastrointestinal tract was not demonstrated yet, but since MPNs can cross epithelial and endothelial barriers and can be translocated via afferent and efferent pathways, their uptake cannot be fully excluded. Studies with different kind of nanoparticles showed that translocation rates and amounts are very low (between 1-3 percent; Elder & Oberdörster 2006, Elder et al. 2006). However, if MPNs enters the body, they will be either eliminated by different mechanisms (e.g. by macrophages) – in dependency of size – or can be distributed via the blood circulation and in some cases by the lymphatic system. Intracellular uptake and distribution of MPNs followed by the interference with different signal transduction pathways and the induction of cellular effect has been shown in many studies (ENRHES 2010). Up to now little is known about the metabolism of MPNs. It was suggested that organic/carbon-containing MPNs will be metabolized while inorganic wont. However, the chemical stability appears to be the determinant of persistence for some classes of MPNs, e.g. metal MPNs where leakage of ions may appear (ENRHES 2010). It was shown that if nanomaterials are within biological media (e.g. body fluids of the respiratory or the gastro-intestinal tract, the blood or extra/intracellular fluids but also cell culture media) a so called "corona" is covering the MPNs composed of proteins and/or lipids which is adsorbing on the surface by biophysical/chemical mechanisms. Analysis of such protein corona formation in plasma showed the existence of an inner "hard corona" with stable and very slow exchange of proteins, whereas the outer weakly interacting protein layer is rapidly exchanging with free

proteins (Walczyk et al. 2010). This corona changes the physico-chemical properties of the MPNs and determines the distribution across barriers in the target tissue/cell. About the excretion or elimination of MPNs very little is known as well. A small number of studies showed that MPNs can be eliminated by (i) faces, (ii) urine, depending on size, charge and metabolization and (iii) immune relevant cells (e.g. macrophages; Gormley & Ghandehari 2009).

Another crucial issue in performing hazard identification is the knowledge of the biokinetics of a certain MPN. Therefore one compiles the so-called ADME-profile which stands for Absorption, Distribution, Metabolism, and Excretion, describing the disposition of the nanomaterials within the organism (see Figure 8).

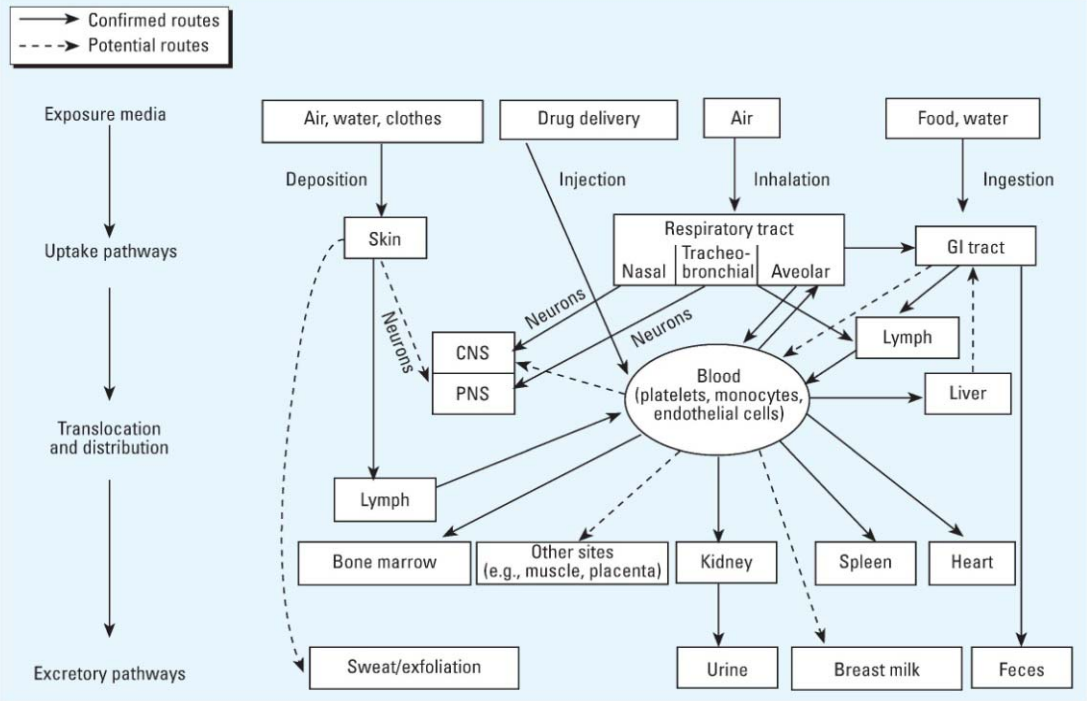

Figure 8: Biokinetics of MPNs. Although many uptake and translocation routes have been demonstrated, others still are hypothetical and need to be investigated. Translocation rates are largely unknown, as are accumulation and retention in critical target sites and their underlying mechanisms. These, as well as potential adverse effects, largely depend on physico-chemical characteristics of the surface and core of MPNs. Both qualitative and quantitative changes in MPN biokinetics in a diseased or a compromised organism also need to be considered. CNS, central nervous system; PNS, peripheral nervous system. (Taken from Oberdörster et al. 2005.)

2.3. Health and environmental risks of MPNs

2.3.1. State of the art in risks to human by MPNs

The current knowledge about exposure to MPNs suggests that inhalation is the main portal of entry of MPNs into the body. Epidemiological studies about MPNs are not available

therefore studies of ambient ultrafine particle (< 100 nm) toxicology are taken into consideration to study human adverse health effects by nanoparticles. Various studies showed that inhaled nanoparticles and carbon nanotubes size-dependently deposits in different regions of the lungs (see Figure 9). Different studies have shown that 90% of the smaller particles (1 nm) are deposited in the nasopharyngeal (upper airways) and the rest in the tracheobronchial (lower airways) region. Particles in the range of 1-5 nm deposit in nasopharyngeal, tracheobronchial and in the alveolar region, whereas 20 nm particles deposit to around 50% in the alveolar region (ICRP 1994).

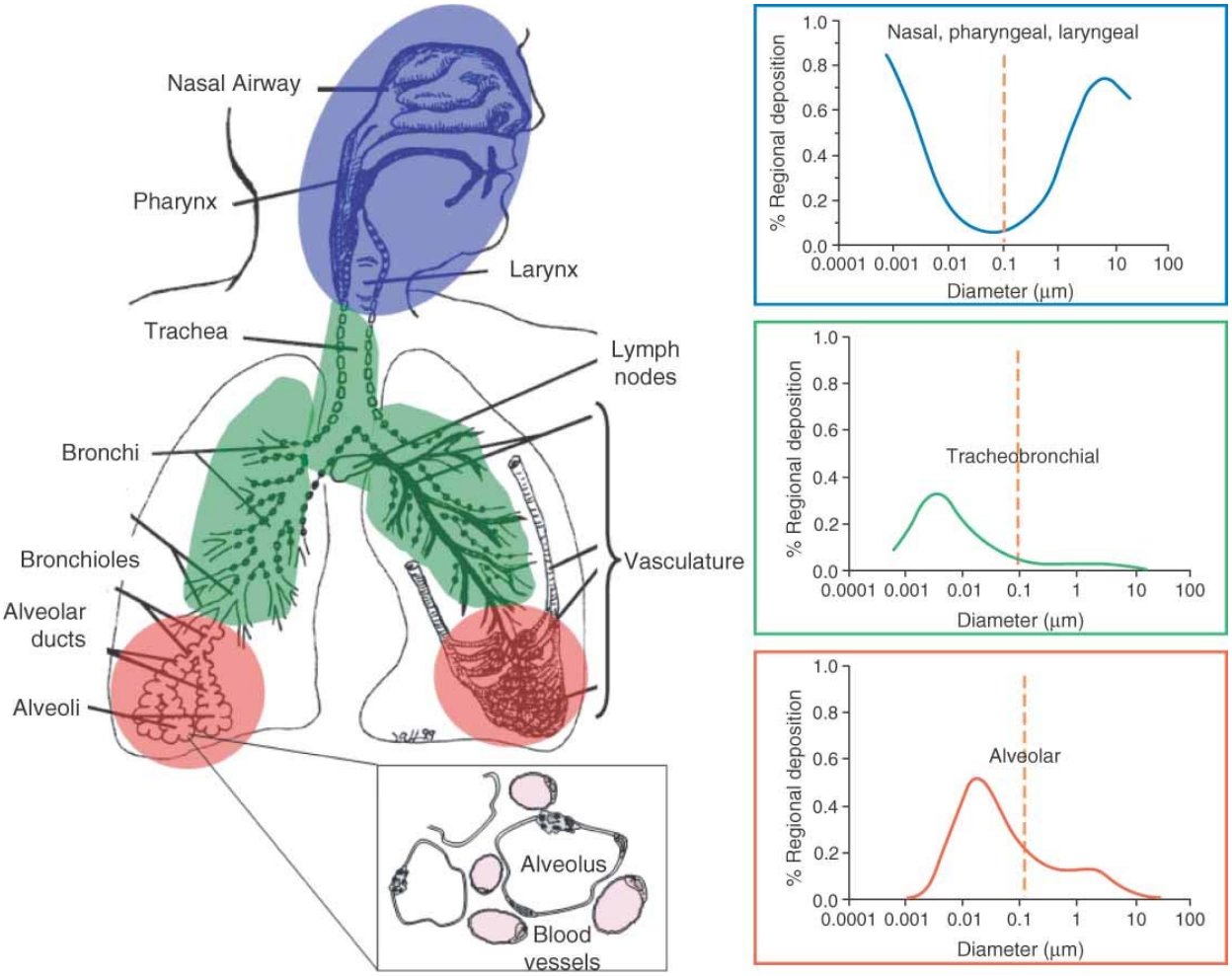

Figure 9. Deposition of particles in the respiratory tract as a function of their size with inset illustrating the proximity of the air spaces (alveoli) to the vasculature (in pink) (Taken from Elder et al. 2009).

It was demonstrated that to a certain amount MPNs can be removed by clearance mechanisms (especially in bronchia) and/or immune system (especially in alveoli) of the lungs. Thereby, it seems that these mechanisms are less effective by a decreasing particle size. If particles are deposited in a certain area of the lung or body MPNs will be either dissolved and/or metabolized, undergoing clearance mechanisms, or insoluble particles will be enriched in particular areas or even in individual cells causing biological or toxicological effects (Schmid et al. 2009, Geiser & Kreyling 2010). Rigid CNTs longer than 15 µm (needle like) induce fibre like pathology since macrophages are not able to uptake these structures (Poland et al. 2008, Bai et al. 2010, Pacurari et al. 2010). Further, biopersistent MPNs are

deposited within the lung for an unknown period (Borm et al. 2006). Patients with bronchitis or asthma seem to react stronger to CNTs than healthy persons (Frampton et al. 2004). However, MPNs can trigger inflammation within the lungs due to various mechanisms, e.g. via the action with macrophages resulting in the production of ROS (Geiser & Kreyling 2010). This was shown inter alia for nano-sized polystyrene, TiO_2, Au and Zr (Geiser et al. 2005). ROS production is linked to oxidative stress (e.g. lipid and protein oxidation) but also for inducing different intra and extra cellular signal cascades, e.g. recruiting of immune cells (see Figure 10; Elder et al. 2000). In vivo studies showed that to a certain amount of the retained MPNs can be translocated to the blood system (passing the air-blood tissue barrier) but also to other organs (Nemmar et al. 2001, Nemmar et al. 2002, Oberdörster et al. 2002). The question is whether these particles can be enriched in a specific site and are causing health effects. It is known that certain MPNs are enriching in liver, spleen, and kidneys. Some studies reported that MPNs are reaching the heart and even the blood-brain-barrier is penetrable for specific nanoparticles (Semmler et al. 2004, Oberdörster et al. 2005, Bhaskar et al. 2010). Particles were identified in placenta or testis as well (Braydich-Stolle et al. 2010, Chu et al. 2010). The question remains about the dose of particles: Is this amount (dose) of particles hazardous? And how long do the particles remaining within the body? The translocation rate of deposited MPNs from the lung to the blood circulation and then to other organs seems not to exceed 5 percent (Kreyling et al. 2009, Oberdörster 2010a). However the corona formation can change the translocation rate and possibly increase the hazardous effects.

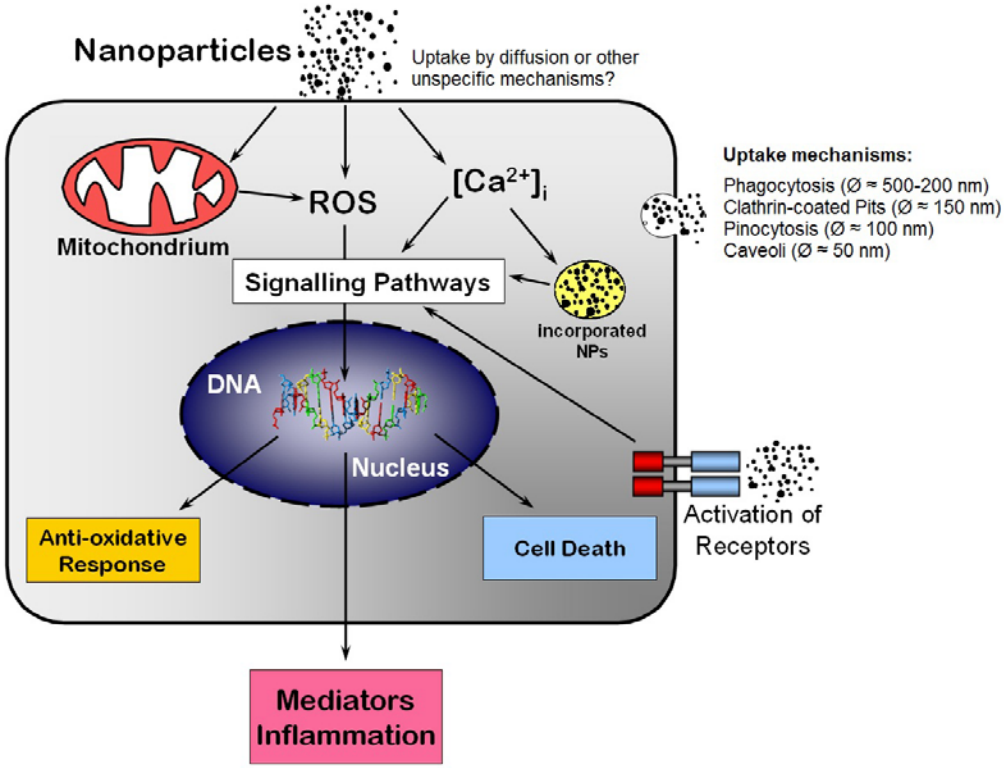

Figure 10. Model of the effects of MPNs on cells (modified from Donaldson & Stone 2003, Krug et al. 2006)[4]

[4] Available at http://www.nanopartikel.info/files/content/dana/Wissensbasis/Titandioxid/invitro_modell_en.jpg

MPNs can enter the cells by active or passive mechanisms and cause cellular effects like genotoxic damage or interacting with other cell components leading to cell death or other effects (see Figure 10; Elder et al. 2000, Roller & Pott 2006). Several studies investigated almost the whole spectrum of biological endpoints by using different cell system and nanomaterials with different outcome. However, the majority of the published in vitro studies conforms the toxic effects of MPNs. Very few data are available showing dose-dependent analyses. In general, in vitro studies are showing the potency of toxicity and the hazard of the material.

The skin is the largest organ of the human body being the best barrier to the environment. Since sunscreens and other cosmetics contain nanoTiO_2 and nanoZnO the question arises, if MPNs can penetrate the skin and reach the blood system. According to the present knowledge MPNs are not penetrating the healthy skin (Choksi et al. 2010) although they reach the hair follicles (Lademann et al. 1999, Lademann et al. 2006). However, it has been shown that quantum dots (nanoparticulate semiconductor crystals) penetrate the human skin (Ryman-Rasmussen et al. 2006) but the biological relevance of this is not clear. Also it is not clear, if nano silver on the skin is influencing the skin flora (Kulthong et al. 2010). In addition, there is an indication that damaged skin (sunburn, chronic skin diseases, or wounds) may be a port for entry in the blood system (Rouse et al. 2007, Borm et al. 2006, Kiss et al. 2008).

There are very few data available about uptake of MPNs via the gastrointestinal tract (GIT) since in occupational setting oral uptake is not considered. However, the GIT can be a site of exposure to MPNs after ingestion of food containing MPNs (in food supplements or contaminations), swallowing the sputum after inhalation or clearance of MPNs and other kind of uptake. The GIT is a reabsorbing organ with a large and permeable surface. It was shown that MPNs (e.g. polystyrol particles) can cross the intestinal wall which is dependent on the physico-chemical properties (Volkheimer 1974, Kanapilly & Diel 1980, Kreyling et al. 2002).

The most recent data collection and evaluation is the ENRHES report (2010) which is a comprehensive and critical scientific review of the health and environmental safety of fullerenes, carbon nanotubes, metal and metal oxide nanomaterials. The authors came up with the following conclusions:

- The toxicity of fullerenes is influenced by chemical structure, surface modifications and preparation procedure, and involves an oxidant-driven response.
- An increasing number of CNTs walls, functionalisation and reduced metallic impurities may suggest reduced toxicity, although there are of course other factors to consider. However, the physico-chemical properties that eliciting oxidative stress and inflammation leading to cytotoxicity and disease is still unknown.
- The toxicity of metal nanoparticles is reliant on internalization and their oxidative nature driving inflammatory, genotoxic and cytotoxic events. Thereby it appears that the ion-release effect is involved in the observed toxicity.
- In the case of metal oxides, it has been demonstrated that its toxicity is of inflammogenic, oxidative, and genotoxic nature. Thereby, the explicit conditions during

toxicity testing (e.g. exposure methods, dose, cell or species used or light conditions) have a strong influence on the outcome.

2.3.2. State of the art in environmental risks of MPNs

Studying ecotoxic effects, environmental conditions have to be either simulated at the laboratory level or real life conditions have to be investigated within the environment. Since MPNs are hard to measure and almost untraceable within the environment real life investigations cannot be performed. Therefore, so called marker organisms are used to test ecotoxic effects under laboratory conditions. These aquatic organisms are often vulnerable to noxes and can be used to measure different biological endpoints. Factors that characterize ecotoxicity are similar to those that are identified for human toxicity, like biopersistence, chemical or biological reactivity, chemical composition and especially surface functionalisation. Little is known about the influence of the environment on the MPNs, since for example the metal speciation may change due to changed redox-conditions or salt content. Also the degradability and the accumulation of MPNs can change the biological effectiveness of the MPNs; therefore information is fundamental to determine the environmental hazardousness of MPNs. In general, since only a few ecotoxicological studies are available, it is not possible to draw any common conclusion on the ecotoxicological effects by MPNs. Also no clear pattern on species sensitivity, suitability as a model organism for nano-ecotoxicity testing or relevance of endpoints is seen (ENRHES, 2010). However, there is evidence for potential adverse effects of MPNs in the environment. For example, it seems that MPNs are passing through the food chain from smaller to larger organisms (Zhu et al 2010b). Within the food chain MPNs can potentially harm aquatic organisms like fishes and invertebrates and, already at low concentrations, microbes, earthworms and (crop) plants (Handy et al. 2008a, Handy et al. 2008b, Ferry et al. 2009, Boxall et al. 2007, Scott-Fordsmand et al. 2008, Lin et al. 2009). Since MPNs have been shown to be capable to harm microbes, it is discussed that MPNs can have an impact on functional ecosystems which is dependent on an intact micro flora (Cimitile 2009). Much attention has been drawn on aquatic ecosystems. All investigated groups of manufactured nanoparticles (fullerenes, CNTs, metal and metal oxide nanoparticles) have shown to be toxic to aquatic organisms such as zebrafish (Zhu et al. 2009a, Bar-Ilan et al. 2009), daphnia (Zhu et al. 2009b, Zhu et al. 2010a), algae (Aruoja et al. 2009, Hall et al. 2009), invertebrates (Canesi et al. 2010, Baun et al. 2008), and rainbow trout (Farkas et al. 2010).

There is an ongoing controversial discussion whether MPNs are responsible for the observed effects or rather the toxicity testing methods including the used chemicals (e.g. solvents) are inducing them. For example, C60-solvent interactions and solvent degradation products may increase the C60 ecotoxicity. Metal and metal oxide nanoparticles, especially silver and copper nanoparticles showing toxic effects in high doses, seem to release continuously ions reaching toxic levels in small areas (e.g. cell). Moreover, some studies point out that these MPNs are not degradable and therefore of high concern. It has to be noticed that the behaviour of the MPNs within the environment is highly complex, since it can be influenced by several factors like changes in pH, temperature, UV-radiation, the presence of other reactive substances, etc. (Handy et al. 2008a, Handy et al. 2008b, ENRHES 2010).

2.3.3. Limitations and difficulties of risk assessment

The major disadvantage in many methods used for characterization and detection of MPNs is that the equipment is developed for research use, requiring large, expensive and immobile instruments, extensive sample preparation and often laborious conditions (e.g. ultra-high vacuum) as well as highly trained personal. These circumstances (i) increase the errors in quantity and quality analysis especially since sampling techniques are often inadequate, (ii) prevent in situ (within the living cell/organism) analysis, and (iii) the sample might be not representative and representing just a snapshot of a particle concentration at a certain location. Moreover, analyses of MPNs in complex media can induce changes in physico-chemical properties of the MPNs which are often different from pure or neutral media used in research and development (SCENIHR 2006, Tiede et al. 2008, ENRHES 2010). Unfortunately, none of the available techniques is capable to provide all necessary information about the properties of a certain MPN. Further, biological samples are often limited in size and thus only to a small degree of the different properties can be determined. And most available characterization techniques destruct the material itself; therefore samples cannot be analyzed twice or by more than one technique. Another limitation of the available methods is the incapability to distinguish between naturally occurring (e.g. minerals, protein complexes, combustion products, etc.), unintentionally produced nanoparticles (e.g. soot, diesel or welding fumes), and MPNs. To differentiate between background contamination and MPNs electron microscopically methods are needed. Thus, the development of new techniques and instruments to assess exposure of MPNs in air, water, soil and biological probes are required. New techniques should be able to deal with complex samples, minimizing sample alterations, avoiding artefacts and providing as much information as possible. Moreover, new instruments should be inexpensive, portable and equipped with smart sensors that for example can combine information on various aspects of exposure and hazard (Maynard et al. 2006, Tiede et al. 2008). The development of such techniques and instruments is quite time costly but already present in ongoing research (see for example Amodeo et al. 2008, Zhu et al. 2010c).

Many exposure related studies are published on occupational scenarios while much fewer studies are published on environmental and consumer exposure. Thus, the available studies are useful in mapping the "exposure landscape"; however, a clear numerical estimation of exposure is still impossible. The authors of the ENRHES report (2010) claim for more data on occupational, consumer and environmental exposure as well as for relevant information about both acute and chronic exposures to support effective risk assessment.

Research is usually hypothesis based activity whereby experiments are highly specifically designed for individual studies and thus not necessarily for the purpose of risk assessment. Hence, results are often not comparable since the used conditions are differing from study to study (e.g. different cell types/animals, testing conditions, handling, etc). Furthermore, studies are often performed without standardized techniques (e.g. guidelines) and therefore the reproducibility of results is often not possible. Additionally, experiments are often performed without positive and/or negative controls and never in a blinded manner. Whereby it is a matter of fact that latter can unintentionally influence the results. There is an ongoing debate on high dose in vitro or in vivo studies. There are various arguments for

high dose studies, e.g. that they are valuable for hazard identification, proof of principle and are applicable for high throughput assays (Oberdörster 2010b). However, these studies are little contributing for risk assessment. In ecotoxicological studies it is difficult to simulate real environmental scenarios, since the dose is quite unknown, and the extrapolation of data very limited. Another important difficulty is the missing definition or concept for dose/concentration of MPNs. Surface functionalisation which are detected in most real-life applications of MPNs (e.g. titanium dioxide in sunscreens should be functionalized to reduce photocatalytic activity) are not addressed by many studies. As mentioned above, the use of solvents in case of non-dispersing nanoparticles (e.g. fullerenes) in aqueous media is problematic due to various reasons, e.g. it may produce testing artefacts (Henry et al. 2007). However, these facts are well known within the scientific community and addressed in many publications. Thus, the quantity of publications which can be used for risk assessment is continuously increasing. Nevertheless, intrinsic limitations of the present toxicity tests (e.g. extrapolation of in vivo studies to humans or knowledge gaps in general) will not be solved in a short term and thus needs more research and further development. To speed up this process an international coordination of research activities is needed, as it has been addressed by the OECD. The OECD is already active in initiatives on standardization and harmonization by the Working Party on Manufactured MPNs (WPMN) and also the International Alliance for Nano-EHS Harmonization (IANH). The OECD program, for example, includes the gathering of all available information (published and ongoing research), the identification of knowledge gaps (the coverage of research themes), and testing a representative set of MPNs (14 MPNs for 61 endpoints) along with the development of guidance on sample preparation and dosimetry for the testing of MPNs. In addition, the publication of the so called no-effect studies is to recommend, since these information is necessary for the ongoing research.

2.4. Conclusions

One of the central challenges of risk assessment is the large and rapidly growing number of manufactured particulate nanomaterials to be tested for biological activity along with the limited human financial and time resources. To assess the risk of MPNs, two components have to be identified: hazard and exposure. Regarding hazard it is possible to make some general statements that represent current sound knowledge: The assumption that the move to the nanoscale implicates not only novel material properties but also entails novel environmental and health risks was confirmed on a scientific basis. It seem to be clear, that certain MPNs (e.g. fibre like carbon nanotubes or nanosilver particles) induce at high doses pathologic conditions and can cause toxic effects. The various in vivo and in vitro studies have shown that several types of MPNs cause multiple types of biological effects, even though the relevance of these data is unclear. Thus, the available data provide a basis for further investigations by providing knowledge about fate and behaviour (ADME-profiles) as well as the toxicity including underlying mechanism, however only for certain MPNs. It was shown that the shape of certain MPNs as well as their purity is important for toxicity, e.g. carbon nanotubes seem to be more toxic if trace impurities of iron or solvents were present.

However, there are intrinsic limitations of detection and toxicity testing methods and very little knowledge is available about the exposure to NPMs; summarizing these limitations in brief:

a) Information about acute (high) or chronic (low) exposure of the general public to MPNs are not available. Also data about occupational exposure is insufficient.
b) Lack of appropriate instruments to detect MPNs in gas and liquid phase being appropriate for on-line measurements of multiple MPN properties.
c) Toxicity is determined by a variety of MPN properties (size, shape, surface, etc.) therefore case by case studies are necessary. Plus, it is not clear which metric is the most meaningful for toxicity.
d) A vast number of in vivo and in vitro studies have been published showing that certain MPNs are causing several types of biological effects; however, the biological relevance is unclear. This limits our ability to characterise hazards adequately.
e) Dose-dependent studies (dose-response correlations) using good controls and reproducible standardised experiments are missing.

The missing exposure data prevent risk assessment of MPNs since this requires two components namely hazard AND exposure.

Another aspect of the recent development in nanotoxicology is those leading toxicologists propose a critical view on conceptions of earlier work based on high dose studies along with the assumption of high translocation rates.[5] Similarly, one should note that certain MPNs have also beneficial properties. Though, a study even suggested that C60 fullerenes might prevent toxicity by being antioxidants. It is thus hardly surprising that an increasing number of medical applications of MPNs exist.

Addressing further developmental needs to overcome the present hindrance of risk assessment we identified the following:

- Further research activity is needed especially in assessing the exposure of the general public and the environment. Therefore, novel instruments and techniques need to be developed or existing ones need to be refined to meet requirements (i) to detect MPNs in complex and small samples especially in biological setting, (ii) to allow discrimination of naturally occurring/background nanoparticles and MPNs, (iii) inexpensive, (iv) portable, and (v) allow measurement of multiple properties at the same time.
- The standardization of methods is needed including (i) reliable and validated procedures for characterization and measurement of dose and exposure, (ii) a broad characterization of the used MPN, and (iii) the use of an agreed dose units which can be used in hazard and exposure assessments.
- Until now, most of the experiments conducted are not standardised since academic research does not primarily aim to produce data for risk assessment purposes. Hence, one should think of implementation of rewards for or even mandatory usage of harmonization tools into e.g. financial support of research. A standardised format for

[5] For instance, G. Oberdörster stated at the NanoAgri Conference 2010: "Under […] realistic conditions, many engineered nanoparticles are unlikely to induce adverse effects, although still largely unknown are effects of chronic, low level exposures."

reporting the results of toxicological studies focusing on physicochemical characterization might be helpful.

- Moreover, an (inter)national coordination of research and development activities (e.g. Road map, master plan) along with the above mentioned standardization of methods would be beneficial in respect to expedite the progress and increase comparability for risk assessment. This should be accompanied with significantly increased.
- The publication of no-effect studies is important and recommended.
- In this context the proposal to create a third-party body, similar to the Cochrane model[6] but comprised of stakeholders from all groups, to review and provide authoritative interpretations of research in nanotoxicology is very interesting. As well as the one to develop a multidisciplinary community of practice and information-sharing forum for researchers and all interested stakeholders (Balbus et al. 2007).
- Further one should promote the multidisciplinary training of young scientist in the nanotechnology field.

[6] The Cochrane Collaboration is an international, independent not-for-profit organisation that was established in 1993. It produces and disseminates systematic reviews (Cochrane Reviews) of healthcare interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions. It aims to provide accurate, up-to-date information about the effects of health care worldwide for an evidence-based medicine (www.cochrane.org).

3. MEASURES FOR NANOMATERIALS RISK MANAGEMENT IN THE EU

3.1. Current parliamentary regulation practices and parliamentary activities

3.1.1. General (pre)-regulatory activities of European institutions

The major trends in European regulation of nanotechnologies are set at the EU level. The rule-setting and decision-making powers in the EU are shared between the European Commission, the Council of the European Union and the European Parliament. All three institutions are involved in creating laws and regulations that are relevant for nanomaterials and its application.

The European Commission develops proposals for policies, regulations and other legal acts, which must be agreed by the Council, representing the Member States, and involving the Parliament in a complex form of interaction. The main legal and regulatory instruments of the EU are Regulations (binding legal acts that are directly applicable in each Member State), Directives (binding policy objectives for Member States that still leave room for Member States in designing implementation), Decisions (legally binding for specific contexts, but not generally applicable to all Member States), Recommendations and Opinions (non-binding but may prepare legislation in Member States), Communications (preliminary documents that may be followed by proposals for legislation) (Breggin et al. 2009).

The Commission is divided into various Directorates General (DG) that prepare proposals for regulations. The Commission's Interservice Group on Nanotechnology supported the implementation of measures in an action plan for nanosciences and nanotechnologies in Europe for 2005-2009 (CEC 2005). In the recently published second implementation report, the Commission acknowledged that an essential element of its integrated, safe and responsible approach is to integrate health, safety and environmental aspects in the development of nanotechnology (CEC 2009a). Nanotechnology products must therefore comply with consumer, worker and environmental protection. The Commission believes that these products will only be accepted if regulations adequately address the new challenges from the technologies.

The European Commission's review of regulatory aspects of nanomaterials, which is published along with a Staff Working Document (CEC 2008a), evaluates relevant regulations with regard to their coverage of health, safety and environmental aspects of nanomaterials. It was concluded that the existing regulatory framework covers in principle the potential risks of nanomaterials. Current legislation has mainly to be improved and may have to be modified in the light of new information becoming available.

European Parliament discussed the Commissions' Communication on "Regulatory Aspects of Nanomaterials" and adopted a resolution in response in April 2009 (European Parliament 2009a). In this response, the Parliament does not agree with the Commission's conclusions as quoted above. Given the lack of appropriate data and assessment methods, the

Parliament states that regulatory change is necessary to address risks in relation to nanomaterials in an appropriate way. The Parliament calls, inter alia, for a review of all relevant legislation, to promote the adoption of a harmonized definition of nanomaterials and to adapt the relevant European legislative framework accordingly. Precise revisions are demanded, especially concerning REACH and worker protection legislation. The Parliament's opinion also includes a number of specific requests to the Commission, related to certain aspects of regulation, labelling, ethics, the involvement of stakeholders, fact-finding, research and coordination.

The Commission was asked to present a new report on regulatory aspects in 2011, paying particular attention to a number of points raised by the European Parliament and the European Economic and Social Committee. The Commission also intends to present information on types and uses of nanomaterials, including safety aspects, in 2011 (CEC 2009a).

Besides these more general activities, Parliament, Commission and Council have started additional political and legislatory initiatives, including proposals for and passing of legal acts that address various specific aspects of nanomaterials regulation. It is the aim of the following paragraphs to present a brief overview of these activities.

The work of the EU's executive and legislatory branches on the regulatory aspects of nanomaterials (and nanotechnologies) is supported by a number of institutions. The EU has created specific regulatory agencies that interact and coordinate the work of national agencies. The main relevant agencies with respect to nanotechnology and nanomaterial are:

- the European Chemicals Agency (ECHA): responsible for managing the Registration, Evaluation, Authorization, and Restriction of Chemical Substances Regulation (EC/ 1907/2006 - REACH) as well as the Classification, Labelling, and Packaging (CLP) Regulation (EC/1272/2008)
- the European Food Safety Authority (EFSA): provides scientific advice and risk assessment on food and feed safety, nutrition, animal welfare and plant protection.
- the European Medicines Agency (EMEA): carries out scientific evaluation of medicinal products.

Both EFSA (with respect to food and feed) and the EMEA (with respect to medicinal products) have also published opinions on the specific aspects on the safety assessment of nanomaterials.

In addition, several scientific committees have dealt with these issues. The Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), both managed by DG Health and Consumers, have formulated opinions on nanotechnology EHS risks. These opinions followed the Commission's request for advice on specific risk assessment issues. The SCENIHR focused mainly on the appropriateness of existing risk assessment methodologies, while the SCCS addressed the safety of nanomaterials in cosmetic products (Breggin et al. 2009).

3.1.2. Chemicals regulation

New European chemicals regulation has recently been adopted with a new over-arching Regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH EC/1907/2006). REACH explicitly states that it is based on the precautionary principle. One of the aims of this regulation is that manufacturers, importers and users have to ensure that the substances brought on the European market do not adversely affect human health or the environment. REACH applies a "no data, no market" principle to the commercialization of substances on their own, in preparations or in articles. This means that industry must provide data (technical dossiers) and, in many cases, a chemical safety report in order to register its chemical substances in a *Registration process*. The specific information requirements vary according to the tonnage at which a substance is manufactured and its potential toxicity (see Table 5). The chemical safety report includes a safety assessment for the use of the substance on its own and its use in a preparation or article at all stages of the life-cycle of the substance. However, the chemical safety report does not need to consider human health risks from end uses of a chemical substance in products which are covered by other regulations (e.g. food contact material or cosmetic products, see also chapter 3.1.3). After registration, the European Chemicals Agency ECHA performs dossier evaluations or substance evaluations in an *Evaluation process*. Substances of very high concern may be subject to an *Authorization process*. Producers or importers of such substances must apply for authorization for each use of the substance. Finally, REACH implements the opportunity of a *Restriction process*, which means that the use of the substance could either subjected to conditions or prohibited.

In addition, the new Regulation on Classification, Labelling and Packaging (CLP) of substances which came into force in January 2009 (EC/1272/2008) contains rules on classification, labelling and packaging of substances and mixtures, including nanomaterials, independent of their production volume. REACH and CLP play a critical role in addressing and regulating EHS risks of nanomaterials, because many of these substances enter the market as chemical substances for the use in a variety of products.

To facilitate the implementation of REACH and CLP concerning nanomaterials, the EU is conducting REACH Implementation Plans on Nanomaterials (RIP-oNs) in order to develop guidance documents. In addition, the REACH Competent Authorities created in March 2008 a subgroup on nanomaterials (Competent Authorities Subgroup on Nanomaterials - CASG Nano). CASG Nano provides details on the preparation of registration dossiers and on general information and testing requirements. The subgroup has established a work programme up to 2012, based on the implementation deadlines under REACH.

A question of great relevance for CASG Nano is whether nanomaterials, which are not explicitly mentioned in the regulation, are covered from a legal point of view by the "substance" definition in REACH. REACH defines substance as "a chemical element and its compounds in the natural state or obtained by any manufacturing process[7]". The CASG Nano report of December 2008 states that "the question needs to be clarified in which

[7] The full definition in the regulation is: "(Substance) means a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition."

cases a nanomaterial is to be considered as a separate substance and in which cases it should be considered as a particular form of a bulk substance" (CEC 2008d). This is important because for legal considerations of substances an unmistakable identification and a nomenclature of nanomaterials are needed. The situation is most difficult in cases where a substance is marketed both in its nanoscale and in its bulk form(s).

Even though it seems to be a word play, it may have considerable consequences which are illustrated by the following example: Annex IV of REACH lists substances with sufficient information to be considered as causing minimum risk due to their intrinsic properties. Carbon and graphite were recently removed from this Annex by the regulation EG/987/2008, because the criteria used for this classification also included carbon nanomaterials. As mentioned in chapter 2, some of these nanoscale carbon forms are associated with potential hazards to human health and the environment.

Another point in the discussion, linked to problem discussed above, is the categorization of a substance within the REACH system. REACH distinguishes between phase-in substances and non-phase-in substances. Simply put: A phase-in substance is a substance ("existing chemical") that has been listed in EINECS or the NLP list and/or manufactured in the EC, but never actually been placed on the market during the last 15 years. A non phase-in substance is a completely new substance that has neither been used nor registered in the market before the entry of force of REACH. This categorization has various consequences for the registration process within REACH.

Phase-in substances need to be registered by different dates:

- substances supplied at ≥1000 tonnes per year; substances classified as *Very Toxic to aquatic organisms* or that may cause long-term adverse effects in the aquatic environment (R50/53) at ≥ 100 tonnes per year and substances classified as *Carcinogenic*, *Mutagenic* or *Toxic to Reproduction* (Category 1 and 2) at ≥1 tonnes per year by 1 Dec 2010,
- substances supplied at 100 to 1000 tonnes per year by 1 June 2013
- substances supplied at 1 to 100 tonnes per year by 1 June 2018

Non-phase-in substances manufactured or imported at over one ton per year can only be placed on the market after an (immediate) registration with the European Chemical Agency (ECHA).

Chemicals produced in volumes less than 1 tonne/year are excluded from REACH regulation due to low quantities produced.

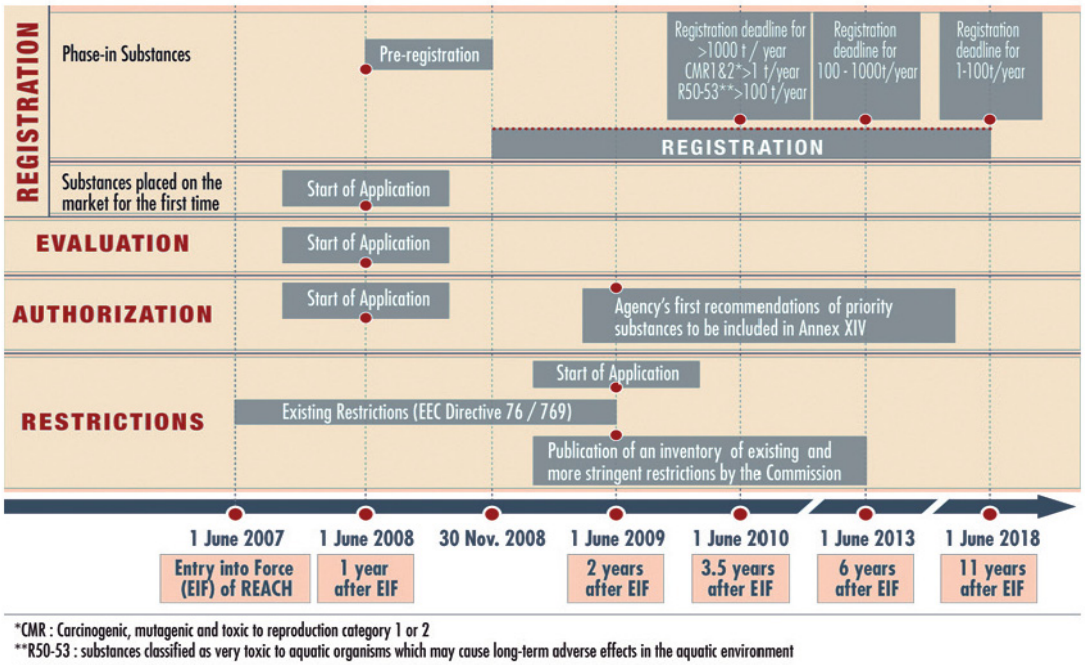

Figure 11: Timeline of REACH Procedures (CRTE Luxembourg)

This situation has led to concerns that nanomaterials categorised as phase-in substances, which are expected to be brought on the market in small quantities, will undergo a systematic risk assessment not before 2018 or not at all.

A further discussion refers to the quantitative threshold (annual supply volume) that serves as a trigger for the information depth in the REACH process. The REACH regulation requires that a technical dossier must be submitted by the registrant to ECHA at the time of registration. The technical dossier shall contain data on the substances and information on the risk management measures, e.g. on the identity of the substance, on manufacture and use(s), guidance on safe use and summaries of studies on physicochemical, toxicological and ecotoxicological properties. For the latter, REACH requires the provision of all information that is relevant and available to the registrant and defines a minimum dataset of information on physicochemical and toxicological properties, including results of different standard testing procedures, depending on the annual supply volume. Table 5 shows exemplary the human toxicity requirements depending on the annual supply volume. Similar lists exist for the physicochemical and ecotoxicological data.

	Annual supply volume (tons per year)			
	≥ 1	≥ 10	≥ 100	≥ 1000
Skin irritation / Skin corrosion		✓	✓	✓
Eye irritation		✓	✓	✓
Skin sensitisation	✓	✓	✓	✓
Mutagenicity		✓	✓	✓
Acute toxicity	✓*	✓	✓	✓
Repeated dose toxicity (28 days)		✓	✓	✓
Repeated dose toxicity (90 days)		✓**	✓	✓
Reproductive toxicity		✓	✓	✓
Developmental toxicity			✓	✓
Two generation toxicity study			✓	✓
Toxicokinetics		✓*	✓	✓
Carcinogenic study				✓

* … with exemptions, ** … case-by-case

Table 5: Standard testing re human toxicology under REACH.

There is concern that the lower requirements for low-quantity chemicals – regardless of whether they are considered as existing or as new substances - may not provide sufficient information to adequately evaluate and assess nanomaterials risks. This is of particular importance because REACH will be an important first-step method gathering relevant data to inform the risk assessment process throughout the life-cycle of nanomaterials. Any gaps within information coverage become important issues in the regulatory context.

The CASG Nano recognized that the principle and approaches to risk assessment do not yet address specific properties of substances at nanoscale and "will need further adjustments to be able to fully assess the information related to substances at the nanoscale/nanoform, to assess their behaviour and effects on humans and the environment, and to develop relevant exposure scenarios and risk management measures". It further recognized that current test guidelines may need to be modified for the determination of specific hazards associated with substances at the nanoscale (CEC 2008d). This is most important for the transfer of a chemical safety report which is only provided for substances and preparations of very high concern. Thus considerable uncertainties remain for the transfer of information in the supply chain of nanoproducts.

A further problem under discussion is whether nanomaterials should be either registered together with its bulk "counterparts" in a common registration process, or whether the substance in its nanoscale form(s) should be regarded as a "stand alone" substance and thus is subjected to a separate REACH process. The rationale behind this proposal includes different aspects: If a nanomaterial generally is considered as a new substance, it would have to be registered separately and automatically be subject to the new chemicals regulation, including the entire REACH process steps. It would have to be registered before being put on the market, and the information requirements to be provided in the technical dossier at the time of registration would apply with the consequence of postponing the commercial exploitation of some nanomaterials until more information is available and

permit stricter regulatory access. At the same time, there is a possibility that for a number of low-quantity nanomaterials only the minimum information requirements within REACH need to be fulfilled or that they will lie outside the quantity limits of REACH and thus are not subject to the provisions of the REACH regulation at all.

Participants in the nanoregulation debate are concerned that if a nanomaterial is registered together with its bulk form, specific nanoscale effects requiring regulatory attention might not be adequately addressed. Since the regulation requires that safety has to be ensured for the registered substance in whatever size or form and for manufacturing and all identified uses, a registration dossier must include all relevant information on the nanomaterial. The information requirements could even be more detailed than those within a registration process for a "new substance" since in a "one substance – one dossier" approach, the respective quantity thresholds might be significantly higher. But a registration process that covers all forms of a substance brings a number of legal and practical issues into REACH process. It will impact the registration and evaluation processes as well as classification and labelling, restriction and authorisation. These issues are currently under discussion within ECHA, among the competent authorities and stakeholders. They could be addressed in greater depth, if not resolved in the course of the Commission's regulatory review in 2011 and the work of the institutions concerned, in the final report of this project.

Besides these specific problems concerning nanomaterials, there are also general aspects of REACH which must be considered for the discussion. The provisions of REACH shall not be applied for substances used in medicinal products and/or food or feedingstuffs. In addition there are also exceptions for the provisions of information in the supply chain for preparations in the finished state for medicinal products, cosmetic products, medical devices and food or feedingstuffs. For the registration of substances in articles also specific exceptions exists (article 7 and article 15 REACH). Thus specific parallel sectoral product regulations for food, medical devices, cosmetics, plant protection and biocidal products have to be screened in detail with respect to the regulation of nanomaterials.

In its resolution of April 2009, the European Parliament accounts for all discussed points regarding the problem of categorization and identification of nanomaterials, the problem of the quantitative thresholds and the different exceptions for provisions in REACH. The Parliament calls specifically on the Commission to evaluate the need to review REACH concerning inter alia (European Parliament 2009a):

- simplified registration for nanomaterials manufactured or imported below one tonne,
- consideration of all nanomaterials as new substances,
- a chemical safety report with exposure assessment for all registered nanomaterials,
- notification requirements for all nanomaterials placed on the market on their own, in preparations or in articles.

3.1.3. Products regulations

3.1.3.1. Food regulation

Food regulation is now largely determined at EU level, and national food laws in EU Member States generally implement decisions taken by EU authorities. The *Regulation EC/178/2002* establishes the general principle of food law. The legal responsibility for ensuring food safety lies with food business operators, but EU law authorizes regulators to use oversight mechanisms such as pre-market review, positive and negative lists, post-market surveillance and labelling in certain product categories. Working closely with national authorities, the European Food Safety Agency performs two functions, which are the provision of independent scientific advice to risk management and the communication of food-related risks.

In its review of regulatory aspects of nanomaterials, the Commission concludes that in general, EU food and feed legislation contains the necessary provisions to address safety concerns related to nanomaterials. However, EU institutions are considering necessary adjustments to existing regulations in order to close potential gaps in the regulatory coverage of nanomaterials (see also European Parliament 2009a). The tools in food regulation differ in terms of the use of positive lists of authorized substances (Food contact materials, additives, supplements), but also with regard to explicit or implicit references to nanotechnology and nanomaterials. To address potential differences between authorised substances in nanoform and in bulk form, some statues have recently been adjusted to take into account factors such as particle size or the use of nanotechnology (regulations on enzymes and additives). More such adjustments are going on (novel food).

The *Novel Foods Regulation (EC/258/97)* applies to foods and food ingredients not consumed in the EU before 15 May 1997 and establishes a legal requirement for all novel foods to be approved before they are introduced to the market (pre-market control, food producers need to submit a safety assessment). Several categories are listed under which a food can be considered as "novel". In its existing formulation, which is currently under review, the regulation does not explicitly mention nanotechnology or particle size as a relevant criterion. In January 2008, the European Commission adopted a proposal that would readjust the scope of the novel food legislation including new technologies derived from nanosciences (CEC 2008c). In March 2009, the European Parliament voted on the novel foods proposal at first reading. The parliament endorsed the principles of the proposal and urged the Commission to introduce mandatory labelling of nanomaterials in the list of ingredients, and to include a definition of nanomaterials (European Parliament 2009b).

The European Parliament's proposal includes a definition for the term "engineered nanomaterial" (see also chapter 1.3.2, Annex I). Many of the amendments proposed by the parliament have been incorporated into the Council position that was adopted at first reading in March 2010 (CEC 2010). The Commission is considering the EP's request for the systematic labelling of all food containing nanomaterials with a favourable disposition. An amended novel foods regulation may require approval of nano-specific test methods before foods produced with nanotechnologies can be assessed or authorized for sale. This regulation could thus slow the commercialisation of nano-enabled foods in the EU (Breggin

et al. 2009). The European Council's own version, which was agreed in June 2009, however does not explicitly make authorisation of food produced using nanotechnologies conditional upon the development of such test methodologies (European Council 2009). Discussions continue as part of the second reading (European Parliament 2010a).

The new regulation on a *common authorization procedure for food additives, enzymes and food flavourings (EC/1331/2008)* stipulates that enzymes, additives and flavourings "must not be placed on the market or used in foodstuff […] unless they are included on a Community list of authorized substances".

The *new food additive regulation (EC/1333/2008)*, which was also published in December 2008, explicitly mentions nanotechnology. Article 12 on "Changes in the production process or starting material of a food additive already included in a Community list" states:
"When a food additive is already included in a Community list and there is a significant change in its production methods or in the starting materials used, or there is a change in particle size, for example through nanotechnology, the food additive prepared by those new methods or materials shall be considered as a different additive and a new entry in the Community list or a change in the specifications shall be required before it can be placed on the market."

According to the *regulation for food enzymes (EC/1332/2008)* food enzymes should only be approved if they are safe and if they fulfil a technological need. A safety assessment has to be carried out before the authorization of a specific enzyme. Enzymes that are already authorised but are produced by a "significantly different" method that involves, for instance, a "change in a particle size" are subject to an additional evaluation. The *regulation on food flavourings (EC/1334/2008)* does not make any specific references to particle size or nanotechnology as a criterion for safety assessments.

All food contact materials and articles, including food-packaging, but also cooking utensils, food processing and transport equipment, are regulated by *framework regulation EC/1935/2004*. In principle, manufacturers are responsible for ensuring that food contact materials are safe and that they do not transfer constituent substances to foodstuffs under normal or foreseeable conditions of use in a way that endangers human health, or bring about an unacceptable change in the composition of the food, or cause a deterioration in the organoleptic characteristics of the food (i.e. taste, colour, odour and texture). The Food Contact Material Regulation also establishes special restrictions on "active" and "intelligent" food contact materials. These materials can be subject to an authorization and a safety evaluation under other regulations, such as the Novel Food, Flavouring, or Additive Regulations, if they fall within the scope of those regulations. For example, if a component released by an active material changes the composition of food so that the component is a food additive, that component cannot be used unless it is included on the list of approved additives.

Labelling requirements for food products is an example for a post-market regulatory tool. The *presentation, advertising, and labelling of foodstuffs* is regulated by *Directive 2000/13/EC,* which requires labelling of a variety of information, including ingredients,

durability, net quantity and storage condition. Article 4, Section 3 of the Directive also stipulates that the food product should include information on "the physical condition of the foodstuff or the specific treatment which it has undergone (e.g. powdered, freeze-dried, deep-frozen, concentrated, smoked) in all cases where omission of such information could create confusion in the mind of the purchaser". In addition, more specific labelling requirements apply to products with health and nutrition claims, mineral waters, dietetic and weight reduction foods, foods for special medical purposes, vitamins and minerals, and food supplements.

While there is no general labelling requirement for nanomaterials in food, specific requirements may apply to certain categories of food products, e.g. where nanomaterials in food are considered to be novel foods. Current regulatory rules and practice in the EU thus point to a selective approach to labelling, but the European Parliament issued a call for a more comprehensive labelling system in its 25 March 2009 vote on the Commission proposal for a revised Novel Foods Regulation. It remains to be seen whether the final compromise between the European Council and European Parliament adopts the latter's preference for a general nanomaterials labelling regime for food (Breggin et al. 2009).

3.1.3.2. Cosmetics regulation

The adoption of the new *Regulation EC/1223/2009 on cosmetic products* published in December 2009 changes the regulation of nanomaterials in cosmetics in Europe. In contrast to the former cosmetic directive, the regulatory authority over cosmetics was centralized at the EU level, because the regulation is directly applicable and legally binding in the Member States. The Cosmetics Regulation is the first EU legislation that dedicates an entire Article (16) to nanomaterials. Paragraph 1 of Article 16 explicitly states that for every product that contains nanomaterials, "a high level of protection of human health" shall be ensured. For this purpose, the regulation contains specific guidelines on safety assessments and the cosmetic product safety report, which are obligatory for all manufacturers. For the exposure evaluation of a cosmetic product, the manufacturer must pay particular consideration to "any possible impacts on exposure due to particle size". With regard to the toxicological profile of a product, particular consideration must be given to particle sizes and nanomaterials, as well as to the interaction of substances (Annex I, Paragraphs 6 and 8).

In addition to these requirements, the regulation stipulates that prior to placing a cosmetic product on the market, the responsible person must notify the Commission of "the presence of substances in the form of nanomaterials" and their identification including the chemical name (IUPAC) and other descriptors as specified in paragraph 2 of the Preamble to Annexes II to VI. It also creates a greater legal certainty with regard to the coverage of nanomaterials by explicitly mentioning them. It defines such materials (see also Annex 1). Article 19 establishes a general labelling requirement for nanomaterials in cosmetic products: "All ingredients present in the form of nanomaterials shall be clearly indicated in the list of ingredients. The names of such ingredients shall be followed by the word 'nano' in brackets."

These new provisions are expected to strengthen market surveillance. In addition, the regulation stipulates that the European Commission shall make publicly available "a catalogue of all nanomaterials used in cosmetic products, including those used as colorants, UV filters and preservatives in a separate section, placed on the market, indicating the categories of cosmetic products and the reasonably foreseeable exposure conditions" (Article 16 Paragraph 10(a)).

In summary, the cosmetics regulation expands pre-market regulation of products containing nanomaterials including notification, but not the authorisation of their use. In addition post-market tools were established (e.g. good manufacturing practices, labelling, recalls). As in other regulatory contexts, the EU has adopted an approach based on case-by-case risk assessment of nanomaterials.

3.1.3.3. Medical device regulation

A "medical device" is defined in the *Medical Devices Directive-MDD (93/42/EEC)* as any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

This definition covers an extremely wide range of products, including, for example first aid bandages, prostheses, X-ray equipment, Electrocardiographs, heart valves or dental materials.

All medical devices must meet the applicable "essential requirements" on safety, performance and labelling as outlined in Annex I of the Directive. As regards medical devices, "Commission services will examine the possibility to make the placing on the market of devices presenting risks associated with nanomaterials subject to a systematic pre-market intervention" (Precautionary principle, CEC 2008a).

For the regulatory practice, a medical device has to be distinguished from a medicinal product, which is defined in article 1 of the directive 2001/83/EC:

- any substance or combination of substances presented as having properties for treating or preventing disease in human beings;

or

- any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological

functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis

In order to determine whether a product is a device or a medicine, the legal definitions of both need to be considered, along with the claims for the product, the mode of action on the human body and intended purpose of the product. Nanomedicinal products, however, may exhibit a complex mechanism of action combining mechanical, chemical, pharmacological and immunological properties and combining diagnostic and therapeutic functions. These novel applications of nanotechnology will span the regulatory boundaries between medicinal products and medical devices. Important problems result for the non-uniform legal practice concerning borderline products in terms of their conform classification to existing law. For this purpose a medical devices expert group on borderline and classification was established.

The European regulatory system for medicinal products offers specific routes for authorising medicinal products. But there are also no specific rules for risks related with nanomaterials (CEC 2008a). The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency has produced a reflection paper on nanotechnology-based medicinal products for human use. According to this paper, the evaluation and prevention of potential hazards related to the use of any given "nanomedicinal" product is already foreseen under the existing EU pharmaceutical legislation. Additional specialised expertise may be required for the evaluation of the quality, safety, efficacy and risk management of such nanomedicinal products (CEC 2008a).

3.1.3.4. Pesticides and biocidal products regulation

Pesticides fall under the *Plant Protection Product Directive (91/414/EEC)*, which includes a positive list of approved substances. Substances can be included on this list, if they will be subjected to toxicological and ecotoxicological tests.

Nanomaterials are not explicitly mentioned in the new *Regulation EC/1107/2009* concerning the *placing of plant protection products on the market*, which currently repeals the directive 91/414/EEC and which shall apply from 14 June 2011. In addition, there are no specific labelling provisions besides the general regulations for chemicals. Nanoscale forms of plant protection products don't need an update of the authorization, if bulk forms are already approved.

Also the active substances of biocidal products are subjected to authorisation in a positive list according to the *Biocidal Product Directive (98/8/EC).* A biocidal product is any substance which is used to control or kill harmful organisms, such as bacteria, fungi, moulds and yeasts. Sterilisers and disinfectants are good examples of a biocidal product. The Biocides Directive requires the authorisation of a wide range of biocide products (including disinfectants, preservatives and a number of other specialist products) as well as non-agricultural pesticides (wood preservatives, public hygiene insecticides, rodenticides, surface biocides and antifouling paints). Only biocidal products which contain an active substance which is listed on Annex I of the Directive will be authorized for use.

In the Commission's proposal for a regulation concerning the placing on the market and use of biocidal products, intended to repeal and replace the current Directive 98/8/EC, active substances at the nanoscale are implicitly included in the term "active substances" (CEC 2009b). Specific regulations for nanomaterials are not provided in this proposal whereas the EU Parliament included biocides in the requirements for nanospecific regulations (European Parliament 2009a). In contrast to the Commission's proposal, the recently published report of the European Parliament and of the Council on this proposal includes several amendments regarding nanomaterials. A definition was proposed for the term "nanomaterial" (see also chapter 1.3.2). It was further stated that "where nanomaterials are used … the risk to the environment and to health has been assessed separately" and "based on current knowledge or lack thereof, a biocidal product containing nanomaterials disqualifies as low-risk" (European Parliament 2010b).

Based on the above, current technical notes for guidance (on data requirements, risk assessment and decision making) would need to be amended in order to properly address risks of nanomaterials in biocidal and plant protection products.

3.1.4. Worker protection and environmental protection regulation

3.1.4.1. Worker protection regulation:

The most important regulation in the area of occupational health and safety at work is the *Framework Directive 89/391/EEC* on the introduction of measures to encourage improvements in the safety and health of workers. This Directive places a number of obligations on employers to take measures necessary for the safety and health protection of workers. Prevention and protection principles are listed in the Directive. The planning and introduction of new technologies must be subject to consultation with the workers or their representatives. The directive furthermore contains various provisions regarding worker information and consultation and participation of workers in discussions on all questions relating to safety and health at work. In addition, the directive provides for the possibility to adopt individual directives laying down more specific provisions with respect to particular aspects of safety and health.

In general, the Directive applies to most occupational risks including those arising from the presence of nanomaterials at the workplace. But the requirements of the Framework Directive and the daughter Directives do not explicitly mention nanomaterials and nanotechnologies. In implementing the EU occupational safety and health directives, the Member States may introduce more strict requirements at national level.

In the resolution the European Parliament calls specifically on the Commission to evaluate the need to review worker protection legislation concerning inter alia:

- the use of nanomaterials only in closed systems or in other ways that exclude exposure of workers as long as it is not possible to reliably detect and control exposure,
- a clear assignment of liability to producers and employers arising from the use of nanomaterials,

- whether all exposure routes (inhalation, dermal and other) are addressed;

Furthermore, the European Parliament underlines the importance for the Commission and/or Member States to ensure full compliance with, and enforcement of, the principles of Community legislation on the health and safety of workers when dealing with nanomaterials, including adequate training for health and safety specialists, to prevent potentially harmful exposure to nanomaterials (European Parliament 2009a).

3.1.4.2. Installations regulation:

The *Directive (2008/1/EC) concerning integrated pollution prevention and control* ("IPPC Directive") covers approximately 52,000 industrial installations across the EU and requires installations falling under its scope to operate in accordance with permits including emission limit values based on the application of best available techniques (BAT). In principle, the IPPC Directive could be used to control environmental impacts of nanomaterials at IPPC installations through the inclusion of such considerations into the Commission's BAT Reference Document process (CEC 2008a).

The *Seveso II Directive (96/82/EC)* applies to establishments where named dangerous substances are present above specific quantities (or thresholds). It imposes a general obligation on operators to take all measures necessary to prevent major accidents and to limit their consequences for man and the environment. If certain nanomaterials are found to demonstrate a major accident hazard, they may be categorised, together with appropriate thresholds, in the context of the Directive (CEC 2008a).

3.1.4.3. Water and Air regulation:

The *Water Framework Directive (2000/60/EC)* sets common principles for action to improve the aquatic environment and to progressively reduce the pollution from priority substances and phasing out emissions, discharges and losses of priority hazardous substances to water. A list of 33 priority substances has been established in 2001. According to the Commission (CEC 2008a) nanomaterials could be included among the Priority Substances depending on their hazardous properties. Environment Quality Standards would in these cases be proposed by the Commission. For groundwater, Member States will have to establish quality standards for pollutants representing a risk, in which case nanomaterials may also be included.
The European Parliament calls specifically on the Commission to evaluate the need to review emission limit values and environmental quality standards in air and water legislation to supplement the mass-based measurements by metrics based on particle number and/or surface to adequately address nanomaterials (European Parliament 2009a)

3.1.4.4. Waste regulation:

Directive 2006/12/EC on waste sets the general framework and imposes an obligation on Member States to ensure that waste treatment does not adversely affect health and the environment. The hazardous waste Directive (91/689/EEC) defines which wastes are hazardous and lays down stricter provisions. Hazardous waste must be characterised by

certain properties set out in an Annex to the Directive and feature on the European Waste List as hazardous. Wastes containing nanomaterials could be classified as hazardous, if the nanomaterials displays relevant properties which render the waste hazardous.

Specific legislation has been adopted to deal with particular waste streams e.g. electrical and electronic equipment, end of life vehicles, packaging and packaging materials, as well as batteries. There are also regulations concerning specific waste treatment processes, such as incineration and landfill. In the Communication from the Commission on "Regulatory Aspects of Nanomaterials" it was stated that current EU waste legislation includes requirements for the management of specific waste materials that may contain nanomaterials whilst not explicitly addressing the risks of nanomaterials. In principle, appropriate action can be proposed or implemented under the current legislative framework. Similarly, action can be taken by Member States in implementing current provisions in the framework of national policies
In contrast the European Parliament calls specifically on the Commission to evaluate the need to review waste legislation concerning inter alia:

- a separate entry for nanomaterials in the list of waste established by a Council Decision in 2001 having regard to Council Directive (91/689/EEC) on hazardous waste,
- a revision of the waste acceptance criteria in landfills,
- a revision of relevant emission limit values for waste incineration to supplement the mass-based measurements by metrics based on particle number and/or surface (European Parliament 2009a).

3.2. Further possible regulatory measures

3.2.1. Register

Many participants in the recent debate on nanomaterials regulation demand a register, either for nanomaterials themselves, for products containing nanomaterials, or both, on the EU level. The European Parliament in its resolution of April 2009 called on the Commission "to compile before June 2011 an inventory of the different types and uses of nanomaterials on the European market, while respecting justified commercial secrets such as recipes, and to make this inventory publicly available …" The Belgian EU presidency in September 2010 proposed "to develop harmonized compulsory databases of nanomaterials and products containing nanomaterials" that are intended to be the base for traceability, market surveillance, gaining knowledge for better risk prevention and for the improvement of the legislative framework; and at the same time in their design take into account the need for providing information to the citizens, workers and consumers regarding nanomaterials and products containing nanomaterials as well as the industry's need for data protection.

Some member states have already introduced legislation that supports this request, or are performing feasibility studies. France, in its so-called Grenelle II Act adopted on 29 June 2010 introduced a notification scheme for nanoparticulate substances and its applications where information is gathered that shall be made available to both authorities and the

general public[8] (Grenelle II Law 2010). The German Federal Environmental Agency has commissioned a legal feasibility study on the introduction of a nanoproduct register in Germany whose results were published in May 2010 (Hermann and Möller 2010).

The rationale behind a register is to collect information on new nanomaterials and/or on products containing nanomaterials in order to fill a need for more (detailed) information on materials and products that are put on the market but not sufficiently documented in the course of existing regulations. Registers are usually intended to enable clear identification any nanomaterials, intermediates or finished products placed on the market, and of their respective of producers, importers and distributors. Register concepts recently discussed can be distinguished by three criteria:

- Registers for use by public authorities and publicly available registers
- Registers for materials and intermediates, and registers for (consumer) products
- Voluntary and mandatory registers

They differ in purpose of the register and in addressees of the collected data.

Many of the existing approaches for *registers* aim at informing the *public authorities* to better enable them to cope with risk management issues such as worker protection, occupational health or consumer protection. In this context, the collected materials data should be used to provide indications for potential hazards and possible exposure of human and the environment. For risk management purpose not only the amount of the used material is of relevance, and where it is used, but also information on their physical, chemical and biological properties as well as their possible adverse effects on human and the environment, like reactivity, toxicity, persistence, etc. (see chapter 3). These data on a specific nanomaterial are, in principle, comparable to the dataset that has to provided in the course of a REACH registration. But in order to assess the possible exposure to nanomaterials, such registers do also ask for information of the application of nanomaterials e.g. in which products nanomaterials are used and in which form.

Another approach for a register focuses on providing information on products containing nanomaterials for the general public. Rationale behind this type of register is that consumers should have the opportunity to inform themselves about whether the products they use contain nanomaterials, in which form, and in which amount, and to enable them to make an informed choice in their purchases. Since consumers are usually not experts in nanoscience, the information must be sufficient simple and well understandable. Databases for that purposes generally do not need to contain detailed physical or chemical properties of the materials used.

Many calls for a nano-register do not clearly differentiate between publicly available registers and registers for use by public authorities and between registers for

[8] "Persons who manufacture, import or distribute nanoparticulate substances, in the form of nanoparticles or contained in unbounded mixtures, or materials designed to discharge such substances under normal or reasonably expected conditions of use, shall periodical declare to the administrative authority, for the purposes of traceability and public information, the identity, quantities and applications of these substances, as well as the identity of the professional users to whom they have been sold either for payment or free of charge. (…) The information relating to the identity and applications of the substances thereby declared shall be made available to the public."

nanomaterials and registers for "nanoproducts". Some proponents even advocate "all-in-one" solutions. But ignoring these distinctions might provoke resistance among stakeholders. A number of enterprises, e.g., fear that the disclosure of detailed information on nanomaterials they produce or use in order to manufacture products makes sensitive and commercially valuable information available to competitors. This is one reason why industry is reluctant regarding a public register of nanomaterials. A register for use by public authorities only is likely to gain greater backing since industry would easier accept to deliver sensitive and detailed data if the data are handled confidentially.

Registers, regardless of their actual design, can be made mandatory or voluntary. First regulatory initiatives, started in mid 2000s, in some countries included testing schemes for voluntary reporting schemes that could have served as a basis for registers. Three voluntary reporting schemes, and experiences with their implementation and compliance, are discussed in more detail in the next paragraphs:

UK VOLUNTARY REPORTING SCHEME FOR ENGINEERED NANOSCALE MATERIALS by DEFRA
The „Voluntary Reporting Scheme" was initially set up by the UK Department for Environment, Food and Rural Affairs (DEFRA) as a 2-year trial initiative. Its aim was to collect data on synthetic nanomaterials from producers, commercial users, research and waste management. The scheme is characterised, on the one hand, by a narrow definition of the material that should be covered:
"In summary, the focus of the scheme is materials that:

- are deliberately engineered (i.e. not natural or unintentional by-products of other processes);
- have two or more dimensions broadly in the nanoscale; and
- are 'free' within any environmental media at any stage in a product's life-cycle" (DEFRA 2006)."

Especially the last criterion of the definition offers room for interpretation. On the other hand, an extensive amount of data is requested. For each material a form of 13 pages has to be completed. Requested information is for example:

- Composition and structural formula of the substance, degree of purity (%), nature of impurities, percentage of (significant) main impurities;
- Information about potential human health and environmental exposure pathways and likelihood of exposure (11 questions on toxicological data, 9 questions on ecotoxicological data);
- Information about agglomeration or aggregation, and deagglomeration and disaggregation properties;
- Physical form of the material at 20°C and 101.3 kPa, melting point, boiling point, vapour pressure, surface tension, water solubility, flammability, self ignition temperature.

In order to guaranty homogeneous results a guideline for the completion of these forms was developed (DEFRA 2008). The collection of the data started in September 2006 and was closed in September 2008. During this period, eleven forms have been submitted from

industry and two from academia[9]. In June 2009 Defra announced on his website[9]: "…we are currently reviewing the scheme in order to take a decision on a suitable way forward."

NANOSCALE MATERIALS STEWARDSHIP PROGRAMME BY EPA

In January 2008, the Office of Pollution Prevention and Toxics Department of the Environmental Protection Agency (EPA) in the US launched the "Nanoscale Materials Stewardship Program". Within this programme, US enterprises producing, importing or using nanomaterials are requested to deliver voluntary information on these materials. This information should cover physical and chemical properties, use, potential of possible hazards, routes of exposure, and risk management measures.

Subject of the programme were all "engineered nanoscale materials" which are, according to the programme: "any particle, substance, or material that has been engineered to have one or more dimensions in the nanoscale", where "nanoscale" is defined as "the size range between the atomic/molecular state and the bulk/macro state. This is generally, but not exclusively, below 100 nm and above 1 nm." (EPA 2007)

Although this definition of the nanoscale takes up the conventional size range from one to hundred nm, the addition of "generally but not exclusively" opens up considerable room for interpretation.

Until December 2008, 29 U.S. enterprises delivered information on 123 nanomaterials, consisting of 58 different chemicals. However, only a few enterprises delivered a complete data set. Most of the materials reported are used in research and development. Similar to existing REACH regulation, in the U.S. law that regulates the introduction of new or already existing chemicals (the Toxic Substances Control Act (TSCA)), materials are registered by their elementary composition and molecular structure. Therefore, nanomaterials are not included separately. However, 18 "new" materials could have been identified within this program. EPA extrapolated, by cross-checking the data-base on nanomaterials of Nanowerk and the consumer products data base of the PEN Project on Emerging Nanotechnologies, that around 1300 nanomaterials should have been placed on the market. On the background of this estimate, the 123 nanomaterials which have actually been reported within the program seem to be only a tiny part of all existing nanomaterials. But comparing this number to the Swiss inventory (see below), which identified 20 types of nanoparticles, this appears to be a rather high number. Regarding the disclosure of the information on the materials it has to be mentioned that the data on the materials are only published if the enterprises agreed.

„SWISS NANO-INVENTORY" – AN ASSESSMENT OF THE USAGE OF NANOPARTICLES IN THE SWISS INDUSTRY BY IST

Between 2005 and 2007, a survey has been performed in order to assess the extent of use and importance of nanoparticles in the Swiss industry (Schmid & Riediker 2008). In addition, the „Institute universitaire romand de Santé au Travail" (IST) investigated the need and possible measures for occupational health and environmental issues. They use a different definition for nanoparticles as it was used for the UK Voluntary Reporting Scheme: "a) All nanoparticles according to the ISO nomenclature TS 27687:2007 .

[9] http://www.defra.gov.uk/environment/quality/nanotech/policy.htm

b) All particles with mean diameter between 100 to 1000 nm were assumed to contain nanoparticles, unless there was concrete information about the size distribution and the stability of aggregates.
c) Agglomerates of nanoparticles with unclear information about the potential liberation of primary particles.
d) All nano-surface treatments applications as long as there was not a defined chemical bottom up pathway purely based on polymerisation and proven not to result in particle or droplet creation during the application." (Schmid & Riediker 2008)
Especially b) and d) are significant extensions of common definitions of nanomaterials.

In a pilot study, 198 enterprises were interviewed by phone. For a subsequent survey, a questionnaire was sent out to 1626 Swiss enterprises of different industrial sectors. The return rate of 58% was remarkably high. On the basis of these responses, an extrapolation for the entire industry estimated that about 0.6% of Swiss enterprises (about 500 companies) were producing or using nanoparticles. About 20 types of nanoparticles which are at present used within Swiss industry were identified. SiO_2 and TiO_2 nanoparticles were the two predominant types. Five particle types (iron oxides, TiO_2, AlO_3, Ag, carbon black) were shown to be produced in higher amounts (kilo-tons per year). The study reveals that also very small companies (>10 employers) could use large amounts of nanoparticles.

All three approaches presented above were based on different definitions of the material which should be subject of the register. In addition, the different methodological approaches result also in different outcomes concerning both data quality and amount. The discrepancy between the number of nanomaterials which have been identified by the Nanoscale Materials Stewardship Program and the Swiss inventory are striking and shows that sound results could only achieved with a clear and harmonised definition. But the definition of the material which should be subject of a register has to balance specificity with manageability. A further success factor is the level of detail of the requested information. The following reasons for the limited success of the UK reporting schemes have been discussed (Morgan 2008) but are necessarily not restricted to this approach: Too many objectives, too little focus; restricted resources of SMEs; producers do not know whether the scheme applies to them; lacking clarity regarding the use of data; unclear incentives for enterprises. All three approaches show that there is a significant amount of advisory service necessary in order to inform and help enterprises to complete the forms comprehensively and correctly.

As a consequence of these pilot projects, a number of stakeholders and regulators argue that voluntary schemes should be abandoned in favour of mandatory registers. Clearly, mandatory schemes would ensure a greater participation by affected parties. But at the same time, the introduction of a mandatory register would put higher burden on industries concerned, and pose similar challenges which have already been discussed in section 3.1 regarding existing and future regulations of nanomaterials. It would need to provide a clear and functional definition of the subject of registration (nanomaterial, nanoproduct). Since such a register would have to bridge different sectors and therefore to be in accordance with different product specific regulations such as the regulation on cosmetics, on food and food additives, pesticides etc., the need for a harmonized and enforceable framing of the

regulatory subject would increase. In addition, it has to conform to several further regulatory regimes, such as REACH and occupational health.

3.2.2. Codes of Conduct

In order to address the concerns that handling of nanomaterials bears additional risks which are not covered sufficiently by existing safety measures, there have been several attempts to implement soft law measures like "code of conducts". Codes are commonly used to coordinate action on voluntary basis and have been proven as effective complementary approach to hard law in specific cases. At present, there are a number of codes of conduct on nanotechnology that might affect EU entities. They differ mainly with regard to addressees and scope. But they have in common to elaborate guidelines to deal with new risks, which extent and magnitude is not known at present. Although to commit to the guidelines or principles is voluntary, the rationale behind Codes of Conduct is that an enterprise or an organisation which adopts the code can demonstrate safe handling of nanomaterials. In addition, a broadly accepted code might also support the implementation of these principles within the organisation.

EU-CODE OF CONDUCT FOR RESPONSIBLE NANOSCIENCE AND NANOTECHNOLOGIES (N&N) RESEARCH
The code of the European Commission is addressed to Member States, industry, universities, funding organisations, and researchers. The code is focussed on research. The commitment to the code is voluntary. The code is characterised by mostly general and non nano-specific principles. But the commitment to these principles would have fare reaching consequences, if taken seriously. The most contested principle might be principle 3.7: "Researchers and research organisations should remain accountable for the social, environmental and human health impacts that their N&N research may impose on present and future generations" (CEC 2008b).

Because the principles are of general character, there is lot of space for interpretation. The code does not contain advices, guidelines, checklists, indicators or any other suggestions regarding the operationalisation and the implementation of the code. The code is adopted by the European Commission. The Commission claims that the code serves as guideline for research policy in nanotechnology. It is requesting that the Member States adopt and implement the code. At the moment no measures for checking the compliance with the code or for enforcement of non-compliance were proposed. At present it is unclear how the implementation by the Member States will be coordinated, in order to avoid an unacceptable variety of interpretations of the principles. In January 2010 the Commission has launched a research project, NanoCode (http://www.nanocode.eu) aiming at exploring possible path of implementation and its coordination among the member states.

CODE OF CONDUCT FOR RESPONSIBLE NANOTECHNOLOGY ("RESPONSIBLE NANOCODE")
In 2006, the Royal Society, Insight Investment, the Nanotechnology Industries Association (NIA), and later Nanotechnology Knowledge Transfer Network (Nano KTN) have created a working group to develop a code of conduct related to nanotechnology for industries.

The code is based on seven principles and a series of examples of good practice. The commitment to the code is voluntary. The code is addressed to industries and is focused on responsible production of nanomaterials and products. After refinement, the code (the seven principles including a list of indicators for good practice for each principle) has been open to public consultation (Autumn 2007). In an update paper in 2008, examples of best practice are finalised. In 2008, a sub group has developed a procedure for a benchmarking process. Because the code does not include a kind of certification or organises a verification process, it is not known if and how many enterprises have adopted this code. Furthermore there is no procedure to verify if a company, which has committed itself to the code, follows its principles. A benchmarking process was planned for 2009 (Nanowerk 2008), but information on its outcomes have not become available so far.

IG-DHS CODE OF CONDUCT NANOTECHNOLOGY

The Interessengemeinschaft Detailhandel Schweiz (IG-DHS, Syndicate of Swiss retailers) is a union of the six biggest retailers in Switzerland. Together they are clearly dominating the market. The code is an agreement among the members of the syndicate. It is characterised by a call for information from enterprises operating upstream in the value chain: producers and suppliers. This request for information is rather extensive. The producers and suppliers have to declare whether a product contains nanomaterials. They should explain the benefit of the nanomaterial in use as compared to traditional materials. Furthermore, they should specify the effects of the nanomaterial, its technical specification and possible hazards, which may be related to its use. In addition, producers and suppliers are requested to present their risk management and workers' safety strategies related to nanotechnology (IG DHS 2008). Due to the market power of the syndicate, this code is expected to have a strong impact on upstream industries.

RESPONSIBLE CARE

From a regulatory perspective, the Responsible Care (http://www.responsiblecare.org) initiative could be compared with a Code of Conduct. Originally developed by the International Council of Chemical Associations (ICCA), Responsible Care is an overall approach by the chemical industry to demonstrate corporate responsibility (ICCA 2008; Renn et al. 2009). It has been developed and modified since 1985. The Responsible Care Global Charter was adopted in October 2004 and launched in February 2006. It promotes six general principles with a scope for interpretation similar to the EU Code. The Responsible Care initiative encourages the development of specific codes, including one on nanomaterials, but in the Responsible Care Charter nanomaterials are not mentioned explicitly. According to the initiators, the Charter covers nanomaterials adequately. The ICCA provides guidelines, indicators for evaluation, and checklists to help companies to meet their commitments. It also defines procedures for verifying whether member companies have implemented the elements of RC. Enterprises have to deliver verification of the implementation of the principles biannually. At present, the charter has been adopted by 67 of the 110 largest chemical companies covering 53 countries.

BASF CODE OF CONDUCT NANOTECHNOLOGY

The BASF Code of Conduct was developed by the company during 2004. It is an internal code addressing practices in one of the largest chemical companies in the world. The scope

of the code is the responsible and safe production of nanomaterial as well as open and transparent communication (BASF 2008). It is linked to its corporate identity and the Responsible Care initiative (see above). As a result of the code, a "Guide to safe manufacture and for active involving nanoparticles at workplaces in BASF AG" was developed (BASF 2006). Furthermore, BASF decided to indicate nanoparticles in the safety data sheet, although other enterprises do not reciprocate. In the safety data sheet, downstream users and customers can find detailed information on properties, possible hazards of the purchased material and guidelines of handling. BASF is still committed to its code.

Codes of conduct differ in addressees and focus. However, this variety may lead to a mutual impediment. Industries who already have adopted the Responsible Care charter, for example, might have little incentives to adopt one of the other Codes of Conduct on nanotechnology. It is widely criticised that Codes of Conducts are too general and "empty", hence leaving too much room for interpretation. Therefore, their directive character is limited. An alternative would be to address concrete issues case by case and work out agreements in order to handle them. The case of the Code of Conduct of the IG-DHS is somewhat different. Here it is obvious that framework settings (market power) are essentially related to the effectiveness of the governance approach. For industry, there could be several reasons for committing to a code: The chemical industry fears distrust of consumers – which could be traced back to times were accidents and growth of ecological knowledge started questioning the benefit of the chemical industry. Further reasons are ratings from the financial market and from corporate social responsibility watchdog bodies. However, it is not given that codes meet the expectations of NGOs and substantially change their critical attitudes towards activities of big industries. Official or independent certifications or assessment systems could be more effective.

3.2.3. Labelling and certifications

Labelling of products containing nanomaterials or having been produced using nanotechnology has proven to be a highly controversial issue in the debate on nanotechnology regulation. Five main distinctions can be identified:

- Objects to be labelled: nanomaterials and nanointermediates sold for further processing by (industrial) downstream users or consumer products,
- Scope: nanoparticles, manufactured particulate nanomaterials, nanomaterials, use of nanotechnology in the manufacturing process, etc.;
- Purpose of labelling: product identification, information, advertising, warning, etc.;
- Content and presentation of labels: in the list of ingredients, separately on the front side of the packaging, etc.;
- Binding force: voluntary or mandatory labelling.

Labelling of consumer products has gained the most attention. We will therefore focus on issues related to this approach.

In its resolution of 24th April 2009, the European Parliament called for a general labelling of all consumer products (European Parliament 2009a): "all ingredients present in the form of nanomaterials in substances, mixtures or articles should be clearly indicated in the labelling

of the product." In the cosmetics regulation (EC/1223/2009), these product labelling requirement for nanomaterials have already been implemented. According to article 19 of the regulation, "all ingredients present in the form of nanomaterials shall be clearly indicated in the list of ingredients. The names of such ingredients shall be followed by the word 'nano' in brackets."

Despite the fact that the EU regulates labelling of several types of consumer products, no other regulation currently requires product labels to indicate the presence of nanomaterials or the use of nanotechnologies in its manufacturing process.

Labelling of consumer products which contain nanomaterials or which are produced using nanotechnology remains highly contested among stakeholders. On the one hand, recent surveys indicate that consumers would vote for a labelling. There are several consumer and environmental protection organisations who have been calling for labelling products containing nanomaterials such as Institute of Food Science & Technology (2006), Afsset (2006), BUND (2008) or the International Center for Technology Assessment. Against the background of the lack of nano-specific regulation in many areas, they argue that the consumer has a "right to know" and must have the opportunity to make an informed choice, e.g. between foods containing MPN and foods without. In addition, labelling could become important as a means of building trust through increased transparency.

Others argue that labelling should not be used as a substitute for a comprehensive risk assessment. Labels could be misleading, especially when failing to notify consumers about product- and material-specific risks and benefits. Some stakeholders warn that a general labelling could be costly way to inform consumers about the presence of materials most of which will be most likely of little consequence to human health and the environment. Some industries worry about potentially negative effects resulting from ill-designed product labels. They are afraid that a 'nano'-label could be misinterpreted by consumers and turn into a 'warning-label'. Another group maintains that labelling delegates the responsibility for decisions regarding the use of "risky" substances to consumers and doubts whether this it is an appropriate societal practice.

Part of the controvery might emenate from an unspecific framing of the labelling concept. What should be labelled? How? For what reason? And with what purpose? Considering labelling for consumer products one has to take into account that the use of nanomaterials in product covers very different nanomaterial forms. It could be bulk material which is nano-structured such as in nano-foams or aerogels. In the components of electronic devices, nanomaterials might be used in the form of coatings or as particles which are used in packaging materials of integrated circuits. Manufactured particulate nanomaterials, such as powders of amorphous silica[10], are utilized as additional ingredients in food.

[10] Amorphous silica, used as processing aid in food processing and ripple aid in food, is a good example for the complexity of the labelling discussion. It mainly consists of SiO_2 agglomerates which have a mean diameter above 100 nm. Food industry therefore claims that these particles are not nanoparticles and therefore should not be subject to labelling. In addition, synthetic amorphous silica has been approved for use in foodstuffs in the 1960s as food additive E551. It has been used since with almost unchanged structure and particle size and therefore could be considered as being safe. Others claim that since it may consist of primary particles of a diameter under 100 nm, and that there is a chance for deagglomeration, these products should be labelled.

To add to the complexity, some structures naturally occurring in food products can be considered as being nanoparticles[11]. The question is whether – and how – they should be included or excluded from regulation. Some well established food processing techniques might change some of these nanostructures or may lead to the formation of nanoparticles. It is open to dispute whether these nanoparticles are to be considered as "purposely designed" or "engineered" or "intentionally produced".

In a nutshell, consumer product labelling, especially when mandatory, faces the same terminological and definitional problem like other regulations (see also chapter 1 and 3.1). When the definition of the subjects to be labelled is too broad, the effect of the labelling might be rather low because the role of a label as discriminator will be weakened. When chosen too narrow, and especially when linked to materials properties, a variety of different labelling schemes will need to be established that – most likely – will label the same material in different applications differently and therefore lead to a number of procedural and legal problems. Any attempt to develop a broader (mandatory) labelling scheme for nanoproducts therefore should include a multi stakeholder forum that permits all affected parties and civil society to introduce their respective proposals, justifications and concerns. Science could support this process, but ultimately design and scope of labelling schemes are political decisions.

Three additional points might partly overlap with the current labelling debates. The first one is linked to the challenge of verifying the labelling claims or to enforce (non-)labelling violations. At present, appropriate measurements techniques to determine and characterise nanomaterials in products are largely missing. Some participants in the debate argue that therefore any labelling scheme would be of low value since quality control mechanisms are missing. But examples from the past have shown that analysis techniques could be developed earlier than expected and even if enforcement presently is very difficult, the thread of being convicted in the near future might be a risk too high to be taken for the majority of businesses.

A second controversy is related to the notions of "risk based" versus "ethical" labelling. Some consumer organisations argue that their labelling proposals are based not only on safety concerns, but also on ethical considerations. Opponents doubt that these ethical concerns could be sufficiently specified to design a labelling scheme, or those ethical concerns themselves are legitimate reasons for introducing a mandatory labelling regime.

Thirdly, some developments that are connected to the discussion of labels as regulatory instruments have gained a momentum of its own. Some companies have recently introduced voluntary labelling in both positive (contains …) and negative (free of …) forms. The validity of these labels is guaranteed by testing organisations through a certification system. Three examples for these certifications are "Cenarios", developed by the Swiss consultancy "Innovationsgesellschaft" together with the German "TÜV-SÜD", the German "Hohenstein Quality Label for Nanotechnology in the Textiles Sector" and „Nano-Inside". The goals of and criteria for certification are different. While the CENARIOS certification aims at risk management and is comparable to ISO 9000 or to an EMAS certification, the

[11] e.g. micelles in milk

main goal of the Hohenstein Label is to conquer the inflationary use of Nanotechnology for advertisement purpose in the textiles sector. Nano Inside shares similar intentions like the Hohenstein label but is not restricted to a certain field of application.

Although the impact of these certification schemes appears to be rather limited so far since only few companies have applied for certification, a broader emergence of private labelling schemes may lead to an increasingly complex and inconsistent set of labelling rules. This might imply a number of new challenges. A growing variety of nano labels, based on different criteria and aiming at different purposes (information, advertising, warning, etc.) might be even more confusing for consumers than the already existing medley of "nano" claims. It could raise doubts about the ability of industry and governments to develop nanotechnology responsibly. In addition, it could complicate the marketing of nanoproducts known to be reasonably safe and socially desirable, and affect international trade. Therefore, attempts should be made to introduce an (internationally) coordinated approach to labelling of nanomaterials and nanoproducts.

4. OPTIONS FOR ACTION

After years of reluctance toward acknowledging that there might be limitations to the existing regulatory regime of nanomaterials among many political decision makers, regulatory agencies and industry representatives throughout Europe, a number of policy and regulatory initiatives have recently been started. It would hardly be an exaggeration to say that the European Parliament has played an important role in that process, especially by addressing a number of open regulatory problems early on and by inviting discussions on the earlier mainstream position.

To develop new regulatory approaches for intentionally produced nanomaterials is a demanding task. A number of fundamental questions have accompanied this process, and many of them appear to be still unanswered. This is partly due to a number of still unsolved scientific problems and uncertainties as well as technical challenges, partly also due to different normative perspectives that the plurality of decision makers and stakeholders involved in the process have on regulation of chemicals and technologies, and the "right" balance between a responsible development and safe use of nanomaterials. The latter includes the protection of humans and environment on the one hand and the ability to innovate and socioeconomic interests on the other.

To specify these challenges more precisely, a number of key questions in the regulatory discourse could be identified. Aspects of these questions are already discussed in the preceding chapters of this report; some more will be addressed during the further course of the project.

The first question is whether there is sufficient evidence to consider nanomaterials as being different from bulk, especially in regulatory contexts. It is closely linked to the problem of finding an adequate legal definition for nanomaterials in EU legislatory documents. A number of definitions have been proposed by regulators, scientific committees and standardisation organisations over the last few years. These numerous and sometimes conflicting definitions, generally written from a scientific and not from a legal/regulatory perspective, have led to competing framings and considerable confusion in regulatory debates. The European Parliament might have contributed to this by using different definitions in different pieces of legislation. One could even argue that uncertainties about a sensible definition of nanomaterials – or the lack thereof – might have further complicated the efforts to develop an effective regulatory policy for nanomaterials.

In the light of this debate, the *Parliament could want to consider supporting the progress towards a harmonised legal/regulatory definition of nanomaterials.* Four arguments might be helpful to assist this process:

- Legal definitions of nanomaterials have to describe the object of regulation sufficiently precise to be clear to all parties affected by it. They have to consider practices of production and application of nanomaterials as well as to be enforceable by the responsible authorities.
- A legal definition of nanomaterials incorporates not only scientific and technological knowledge (and its respective uncertainties), but also includes the results of policy

choices and political decisions. It therefore should be science-based but does not necessarily have to be identical to scientific definition(s) of the same term.

- The breath of the legal definition has to be matched with both the regulated artefact and the regulatory goals. A legal definition of nanomaterials has to take into account that these may occur in nature including in a number of natural products that are consumed by humans, could be incidentally produced as results of various human activities, or can be intentionally manufactured. This situation results in different hazard assessments, diverse exposure scenarios and various starting points for regulatory intervention, depending on the aims of the regulation. Meaningful regulation is limited to human activities; therefore a legal definition of nanomaterials should focus on manufactured nanomaterials.
- A legal definition of nanomaterials based on "new" properties occurring at the nanoscale might be difficult to achieve. Therefore, a size range in which the most size-dependent properties appear could serve as an appropriate, albeit imperfect, heuristic. Although any choice of a size range would be imperfect with respect to certain regulatory goals, since there are no direct, material-independent relations between size and "nanoscale properties", a size range from 1 nm to a value not below 100 nm might cover many configurations of materials that give reasons for regulatory concern. For various reasons, an upper size limit cannot directly be derived from scientific results but would be the result of a balancing of goals and interests and therefore should be subject to political decisions.

The second key challenge in the current debates on regulation of nanomaterials originates from a conflict of two different regulatory approaches. One position can be - in a way stylized – summarised as strongly precautionary-oriented, putting nanomaterials under general suspicion because of their new properties and the limited knowledge about their (potential) environmental, health and safety implications. In this approach, nanomaterials are usually defined rather broad and a number of strong measures are proposed to supervise and control the entire life cycle of nanomaterials or products containing nanomaterials or being manufactured using nanotechnologies. Given the considerable broadness of the definitions of nanomaterials and nanotechnologies, a large number of both natural and artificial materials and products as well as various technological processes will be affected by this regulation. Important questions to be discussed in connection with this approach are: Do the regulatory agencies and other affected parties have sufficient resources to implement and enforce this regulation? What are the implications of this approach on existing and future social practices, technological innovation and economic development? Are there mechanisms to "release" nanomaterials from that regulatory regime, assumed they were proven to be "safe"? And how "safe" is safe enough to justify this decision?

Another regulatory approach is closely linked to evidence from toxicological, ecotoxicological and biological research. Its proponents argue that particularly (or solely) those nanomaterials should be regulated that give rise to concerns regarding their EHS implications, either because toxicological research has shown that a hazard exists or because the physico-chemical properties of the nanomaterial allow to predict a certain

hazard potential (e.g. when the nanomaterials exist in free form, are known to be insoluble, biopersistent, etc.).

Both positions – in different ways – have to deal with profound limitations of the risk assessment of nanomaterials. The methodology for the assessment of chemicals risks – including, but not limited to nanomaterials – applied in most countries consists of four parts - hazard identification, hazard assessment (including dose-response relationships), exposure assessment, and risk characterization (see also chapter 2.1.). Each of these four elements holds a number of limitations (elaborately discussed in chapter 2.3.3.) that are not easily overcome:

The majority of nanotoxicological work done contributed to the field of hazard identification, attempting to reveal the toxicity of MPNs in respect to type and nature. Toxicity testing faces some intrinsic limitations; some of them can be overcome in future, others won't (cf. chapter 2.4). There is evidence that some manufactured particulate nanomaterials (MPN) may be hazardous to human health, depending on their characteristics. But it is currently impossible to systematically link reported properties of MPN to the observed effects for effective hazard identification. In addition, it is still under debate what the most relevant endpoints are and how they are linked to systemic effects. Aside from this, one has to keep in mind that for many nanomaterials, no toxicological studies have been performed so far. This is especially the case for manufactured nanoobjects with only one external dimension on the nanoscale ("nanoplates"), for engineered nanostructured materials and almost all naturally occurring nanoparticles. The vast majority of researchers in nanotoxicology has focused on particulate nanomaterials, either intentionally or incidentally produced by human activity.

So far, only few studies claim to have observed a dose–response relationship for MPN, and even in these cases it is still unclear whether a no-effect threshold can be established. To establish causality between physico-chemical properties of MPN (which are potential access points for measurement, regulation and enforcement) and an observed hazard for hazard characterisation remains a challenging task. This is not least because of the lack of reliable characterisation of the MPN used in earlier toxicological studies and the fact that related measurement technologies partly still need to be developed.

A problem repeatedly discussed in this context is that so-called "no effect studies", i.e. nanotoxicological studies that have failed to show effects of MNP on various endpoints, to a large extent remain unpublished. The reasons for that are manifold and span from methodological challenges to limited opportunities and incentives for publication. Then again, no effects studies are a valuable repository for hazard characterization and its limited accessibility could be seen as a waste of scientific resources. *Parliament could therefore consider supporting the publication of these data by backing the provision of funds for a database or a similar project. It might even consider making the publication of no effect data mandatory when research projects on nanotoxicology have been supported with EU funds.*

Exposure assessment of MPN faces similar problems of data availability. Some 'proof of principle'-studies have tried to assess consumer and environmental exposure to nanomaterials, but assessments considering realistic exposure conditions are still missing. Some institutions have begun to collect exposure data under realistic circumstances, especially at the workplace. But the knowledge necessary for reliable exposure assessments is bounded by difficulties in monitoring exposure to MPN in the workplace and other environments, ignorance about the biological and environmental pathways of MPN, missing knowledge about the release of MPN from products over their life cycle, and other factors.

Hence, risk characterization that builds on hazard and exposure assessment is at this time (and most probably in short- and medium-term) not feasible or certainly not scientifically reasonable and only preliminary.

The situation described above might suggest that the risk assessment methodology as a whole is inadequate to timely inform political decisions regarding the regulation of nanomaterials, at least in the short- to medium-term. In the light of the various knowledge gaps, it would need enormous efforts to perform valid and broadly accepted risk assessments for specified nanomaterials. Whether these materials are considered "reasonably safe" or "of high concern", both claims will remain unproven for many years. Moreover, its role and validity as justifications for regulatory strategies of these claims will be contested. One might even argue that risk assessment methodology in general is not appropriate for complex subjects like nanomaterials.

Therefore *Parliament could consider supporting the development of a suitable risk characterisation heuristic* (mainly based on physico-chemical properties of nanomaterials and plausible exposure scenarios) and its implementation, at least for a transition period, in legislation already taking place. First concepts for such heuristics have been proposed, e.g. in Germany and Switzerland, but their usability for regulatory purposes and possible needs for further refinements still need to be discussed.

Another question still under debate is whether existing legislation can be – or should be – adapted to MPN or whether a new regulatory framework for nanomaterials should be developed. Most scholars and practitioners in regulatory law as well as most political decision makers prefer a so-called incremental approach. They favor to adapt the existing legal framework to enable nanotechnology regulation and amending it in order to deal with the unintended implications of this technology. This approach has a number of challenges, limitations and potential gaps since existing legislation is not designed to accommodate some specific aspects of nanomaterials or nanotechnologies. A number of these aspects have been briefly discussed in chapter 3 of this report, they are among others:

- developing a legal definition for nanomaterials;
- integration of nanomaterials into the REACH systematics and procedures, including the development of suitable guidance documents;
- being able to identify and address the relevant adverse effects of the production, use and disposal of nanomaterials and nanoproducts;

- enabling appropriate integration of nano-specific aspects into existing pieces of legislation for sectors, applications, products, or substances;
- covering borderline products (like medical devices or nanomedicinal products) that cross different classic regulatory contexts and for whom regulators have additional uncertainties for the regulatory coverage of emerging nanomaterials risks;
- finding adequate regulatory instruments;
- enforcing compliance with existing and emerging regulation.

These – and other – aspects need to be addressed as soon as possible for the incremental approach to be successful and to go along with a responsible development and use of nanomaterials and nanotechnology.

Some scholars as well as some stakeholders argue that the limitations of the incremental approach are so serious that an entirely new regulatory framework for nanomaterials is needed. But many voices do not further conceptualize this idea. *Parliament could want to consider commissioning a conceptual study project that develops a new regulatory framework for nanotechnology*, tests its feasibility and discusses its advantages and disadvantages compared to the current incremental approach. This discussion could become more urgent since various technology vision documents forecast the development of future-generation nanomaterials, including active nanomaterials with overlapping aspects of information technology, biotechnology and cognitive technologies. Although these trends are difficult to foresee, regulators will have to monitor these developments and therefore need both the (scientific and budgetary) resources and the regulatory instruments for being able to answer with flexible responses.

REFERENCES

- Afsset (2006): Nanomaterials - Effect on the Environment and Human Health July 2006: French Agency for Environmental and Occupational Health Safety, <http://www.afsset.fr/upload/bibliotheque/138750949955923936400847724164/afsset-report-nanomaterials.pdf>.
- Amodeo T, Dutouquet C, Le Bihan O, Frejafon E, Masquelier C, Attouo M. Manufactured nanoparticle detection using Laser-Induced Breakdown Spectroscopy (LIBS). Presentation at the NanoSafe conference 2008, <http://www.nanosafe.org/home/liblocal/docs/Oral%20presentations/O2a-2_Dutouquet.pdf>.
- Aruoja V, Dubourguier HC, Kasemets K, Kahru A. Toxicity of nanoparticles of CuO, ZnO and TiO2 to microalgae Pseudokirchneriella subcapitata. Sci Total Environ. 2009; 407(4):1461-8.
- Bai Y, Zhang Y, Zhang J, Mu Q, Zhang W, Butch ER, Snyder SE, Yan B. Repeated administrations of carbon nanotubes in male mice cause reversible testis damage without affecting fertility. Nat Nanotechnol. 2010; 5(9):683-9.
- Bar-Ilan O, Albrecht RM, Fako VE, Furgeson DY. Toxicity assessments of multisized gold and silver nanoparticles in zebrafish embryos. Small. 2009; 5(16):1897-910.
- Balbus JM, Maynard AD, Colvin VL, Castranova V, Daston GP, Denison RA, Dreher KL, Goering PL, Goldberg AM, Kulinowski KM, Monteiro-Riviere NA, Oberdörster G, Omenn GS, Pinkerton KE, Ramos KS, Rest KM, Sass JB, Silbergeld EK, Wong BA. Meeting report: hazard assessment for nanoparticles--report from an interdisciplinary workshop. Environ Health Perspect. 2007; 115(11):1654-9.
- BASF (2006): Guide to safe manufacture and for activities involving nanoparticles at workplaces in BASF AG, <http://basf.com/group/corporate/en/function/conversions:/publish/content/sustainability/dialogue/in-dialogue-with-politics/nanotechnology/images/BASF_Guide_to_safe_manufacture_and_for_activities_involving_nanoparticles.pdf>.
- BASF (2008): Code of Conduct Nanotechnology, <http://basf.com/group/corporate/en/function/conversions:/publish/content/sustainability/dialogue/in-dialogue-with-politics/nanotechnology/images/BASF_Code_of_Conduct_Nanotechnology.pdf>.
- Baun A, Hartmann NB, Grieger K, Kusk KO. Ecotoxicity of engineered nanoparticles to aquatic invertebrates: a brief review and recommendations for future toxicity testing. Ecotoxicology. 2008; 17(5):387-95.
- Bhaskar S, Tian F, Stoeger T, Kreyling W, de la Fuente JM, Grazú V, Borm P, Estrada G, Ntziachristos V, Razansky D. Multifunctional Nanocarriers for diagnostics, drug delivery and targeted treatment across blood-brain barrier: perspectives on tracking and neuroimaging. Part Fibre Toxicol. 2010; 7:3.
- BMBF (German Federal Ministry of Education and Research) (2007): Nano-Initiative – Action Plan 2010. Berlin 2007, <http://www.bmbf.de/pub/nano_initiative_action_plan_2010.pdf>.
- Braydich-Stolle LK, Lucas B, Schrand A, Murdock RC, Lee T, Schlager JJ, Hussain SM, Hofmann MC. Silver nanoparticles disrupt GDNF/Fyn kinase signaling in spermatogonial stem cells. Toxicol Sci. 2010; 116(2):577-89.
- Breggin L, Falkner R, Jaspers N, Pendergrass J, Porter R. Securing the promise of Nanotechnologies – Towards Transatlantic Regulatory Cooperation. Programme Paper;

Chatham House (Royal Institute of International Affairs), 2009, <http://www2.lse.ac.uk/internationalRelations/centresandunits/regulatingnanotechnologies/nanopdfs/REPORT.pdf>.

- Borm PJ, Robbins D, Haubold S, Kuhlbusch T, Fissan H, Donaldson K, Schins R, Stone V, Kreyling W, Lademann J, Krutmann J, Warheit D, Oberdörster E. The potential risks of nanomaterials: a review carried out for ECETOC. Part Fibre Toxicol. 2006; 3:11.
- Boxall AB, Tiede K, Chaudhry Q. Engineered nanomaterials in soils and water: how do they behave and could they pose a risk to human health? Nanomedicine (Lond). 2007; 2(6):919-27.
- BUND (Bund für Umwelt und Naturschutz Deutschland) (2008): Endstation Mensch - Aus dem Labor auf den Teller - Die Nutzung der Nanotechnologie im Lebensmittelsektor, <http://www.bund.net/fileadmin/bundnet/publikationen/nanotechnologie/20080311_nanotechnologie_lebensmittel_studie.pdf>.
- Buseck PR, Adachi K. Nanoparticles in the Atmosphere. Elements. 2008; 4(6):389-94.
- Canesi L, Ciacci C, Vallotto D, Gallo G, Marcomini A, Pojana G. In vitro effects of suspensions of selected nanoparticles (C60 fullerene, TiO2, SiO2) on *Mytilus hemocytes*. Aquat Toxicol. 2010; 96(2):151-8.
- Card JW, Magnuson BA. Proposed minimum characterization parameters for studies on food and food-related nanomaterials. J Food Sci. 2009; 74(8):vi-vii.
- CEC (2005): Commission of the European Communities (2005). Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee: Nanosciences and Nanotechnologies: An action plan for Europe 2005-2009. COM (2005) 243 final, Brussels, 7.6.2005.
- CEC (2008a): Commission of the European Communities. Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee: Regulatory Aspects of Nanomaterials, COM (2008) 366 final (SEC(2008) 2036), Brussels, 17.6.2008.
- CEC (2008b): Commission of the European Communities. Commission Recommenation on a Code of Conduct for Responsible Nanoscience and Nanotechnologies Research, C(2008) 424 final, Brussels, 07.2.2008.
- CEC (2008c): Commission of the European Communities (2007): Proposal for a Regulation of the European Parliament and the Council on Novel Foods and amending Regulation (EC) No XXX/XXXX [common procedure] [SEC(2008) 12][SEC(2008) 13]: Explanatory Memorandum, COM(2007) 872 final, 2008/0002 (COD), Brussels, 14.1.2008.
- CEC (2008d): Commission of the European Communities (2008). Follow-up to the 6th Meeting of the REACH Competent Authorities for the Implementation of Regulation (EC)1907/2006 (REACH), CA/59/2008 rev. 1., Brussels, 16.12.2008.
- CEC (2009a): Commission of the European Communities. Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee: Nanosciences and Nanotechnologies: An action plan for Europe 2005-2009. Second Implementation Report 2007-2009. COM (2009) 609 final (SEC(2009)1468), Brussels, 29.10.2009.
- CEC (2009b): Commission of the European Communities. Proposal for a Regulation of the European Parliament and the Council concerning the placing on the market and use of biocidal products. COM(2009) 267 final, 2009/0076 (COD), Brussels, 12.6.2009.
- CEC (2010): Commission of the European Communities. Communication from the Commission to the European Parliament pursuant to Article 294(6) of the Treaty on the Functioning of the European Union concerning the position of the Council on the

adoption of a Regulation of the European Parliament and of the Council on novels foods, amending Commission Regulation (EC) No 1331/2008 and repealing Regulation (EC) No 258/97 and Commission Regulation (EC) No 1852/2001. COM (2010) 0124 final - COD 2008/0002, Brussels, 24.3.2010.

- Choksi AN, Poonawalla T, Wilkerson MG. Nanoparticles: a closer look at their dermal effects. J Drugs Dermatol. 2010; 9(5):475-81.
- Chu M, Wu Q, Yang H, Yuan R, Hou S, Yang Y, Zou Y, Xu S, Xu K, Ji A, Sheng L. Transfer of quantum dots from pregnant mice to pups across the placental barrier. Small. 2010; 6(5):670-8.
- Cimitile M. Nanoparticles in Sunscreen Damage Microbes. Environmental Health News. March 24, 2009, <http://www.scientificamerican.com/article.cfm?id=nanoparticles-in-sunscreen>.
- Collins PG, Avouris P. Nanotubes for electronics. Sci Am. 2000; 283(6):62-9.
- DEFRA (Department for Environment, Food and Rural Affairs) (2006): UK Voluntary Reporting Scheme for engineered nanoscale materials, <http://www.defra.gov.uk/environment/quality/nanotech/documents/vrs-nanoscale.pdf>.
- DEFRA (2008): Nanomaterials: Hazards and risks to health and the environment. A supplementary guide for the UK Voluntary Reporting Scheme, <http://www.defra.gov.uk/ENVIRONMENT/nanotech/policy/pdf/nano-hazards.pdf>.
- Directive 89/391/EEC of the Council of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work. OJ L 183/1, 29.6.1989.
- Directive 91/414/EEC of the Council of 15 July 1991 concerning the placing of plant protection products on the market. OJ L 230/1, 19.8.1991.
- Directive 91/689/EEC of the Council of 12 December 1991 on hazardous waste. OJ L 377/20, 31.12.1991.
- Directive 93/42/EEC of the Council of 14 June 1993 concerning medical devices. OJ L 169/1, 12.07.1993.
- Directive 96/82/EC of the Council of 9 December 1996 on the control of major-accident hazards involving dangerous substances. OJ L 10/13, 14.1.1997.
- Directive 98/8/EC of the European Parliament and the Council of 16 February 1998 concerning the placing of biocidal products on the market. OJ L 123/1, 24.4.98.
- Directive 2000/60/EC of the European Parliament and the Council of 23 October 2000 establishing a framework for Community action in the field of water policy. OJ L 327/1, 22.12.2000.
- Directive 2000/13/EC of the European Parliament and the Council of 20 March 2000 on the approximation of the laws of the Member States relating to the labelling, presentation and advertising of foodstuffs. OJ L 109/29, 6.5.2000.
- Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001 on the Community code relating to Medicinal Products for human use. OJ L 311/67, 28.11.2004.
- Directive 2006/12/EC of the European Parliament and the Council of 5 April 2006 on waste. OJ L 114/9, 27 4 2006.
- Directive 2008/1/EC of the European Parliament and the Council of 15 January 2008 concerning integrated pollution prevention and control. OJ L 24/8, 29.01.2008.
- Donaldson K, Stone V. Current hypotheses on the mechanisms of toxicity of ultrafine particles. Ann Ist Super Sanita. 2003; 39(3):405-10.

- Elder A, Oberdörster G. Translocation and effects of ultrafine particles outside of the lung. Clin Occup Environ Med. 2006; 5(4):785-96.
- Elder A, Gelein R, Silva V, Feikert T, Opanashuk L, Carter J, Potter R, Maynard A, Ito Y, Finkelstein J, Oberdörster G. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. Environ Health Perspect. 2006; 114(8):1172-8.
- Elder AC, Gelein R, Finkelstein JN, Cox C, Oberdörster G. Pulmonary inflammatory response to inhaled ultrafine particles is modified by age, ozone exposure, and bacterial toxin. Inhal Toxicol. 2000;12 Suppl 4:227-46.
- Elder A, Vidyasagar S, DeLouise L. Physicochemical factors that affect metal and metal oxide nanoparticle passage across epithelial barriers. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2009; 1(4):434-50.
- ENRHES (2010): Engineered Nanoparticles: Review of Health and Environmental Safety. An International Collaborative Review involving Researchers from Edinburgh Napier University, the Institute of Occupational Medicine, the Technical University of Denmark, the Institute for Health and Consumer Protection of the European Commission's Joint Research Centre, and the Institute of Nanotechnology. Project Report, January 2010, <http://nmi.jrc.ec.europa.eu/documents/pdf/ENRHES%20pdf>.
- Environment Committee of the European Parliament (2006): Amendment No. 217 to Article 56 REACH from Carl Schlyter, Caroline Lucas and Hiltrud Breyer on 10.10.2006.
- EPA (US Environmental Protection Agency) (2007): Nanotechnology White Paper, <http://www.epa.gov/osa/pdfs/nanotech/epa-nanotechnology-whitepaper-0207.pdf>.
- European Council (2009): Proposal for a Regulation of the European Parliament and of the Council on Novel Foods and Amending Regulation (EC) No. XXX/XXXX [common procedure] (LA) (First reading), 10754/09, Brussels, 17.6.2009.
- European Parliament (2009a): Resolution of 24 April 2009 on regulatory aspects of nanomaterials (2008/2208(INI)).
- European Parliament (2009b): European Parliament legislative resolution of 25 March 2009 on the proposal for a regulation of the European Parliament and of the Council on novel foods and amending Regulation (EC) No XXX/XXXX [common procedure] (COM(2007)0872 – C6-0027/2008 – 2008/0002(COD)), (T6-0171/2009), Strasbourg 2009.
- European Parliament (2010a): Recommendation for second Reading on the Council position at first reading for adopting a regulation of the European Parliament and of the Council on novel foods, amending Regulation (EC) No 1331/2008 and repealing Regulation (EC) No 258/97 and Commission Regulation (EC) No 1852/2001 (11261/3/2009 – C7-0078/2010 – 2008/0002(COD)), A7-0152/2010, Brussels, 10.5.2010.
- European Parliament (2010b): Report on the proposal for a regulation of the European Parliament and of the Council concerning the placing on the market and use of biocidal products (COM(2009)0267 – C7-0036/2009 – 2009/0076(COD)) A7-0239/2010, Brussels, 1.9.2010.
- Fadeel B, Garcia-Bennett AE. Better safe than sorry: Understanding the toxicological properties of inorganic nanoparticles manufactured for biomedical applications. Adv Drug Deliv Rev. 2010; 62(3):362-74.
- Farkas J, Christian P, Urrea JA, Roos N, Hassellöv M, Tollefsen KE, Thomas KV. Effects of silver and gold nanoparticles on rainbow trout (*Oncorhynchus mykiss*) hepatocytes. Aquat Toxicol. 2010; 96(1):44-52.
- Ferry JL, Craig P, Hexel C, Sisco P, Frey R, Pennington PL, Fulton MH, Scott IG, Decho AW, Kashiwada S, Murphy CJ, Shaw TJ. Transfer of gold nanoparticles from the water column to the estuarine food web. Nat Nanotechnol. 2009; 4(7):441-4.

- Frampton MW, Utell MJ, Zareba W, Oberdörster G, Cox C, Huang LS, Morrow PE, Lee FE, Chalupa D, Frasier LM, Speers DM, Stewart J. Effects of exposure to ultrafine carbon particles in healthy subjects and subjects with asthma. Res Rep Health Eff Inst. 2004; (126):1-47; discussion 49-63.
- GAO (U.S. Government Accountability Office) (2010): Nanotechnology: Nanomaterials Are Widely Used in Commerce, but EPA Faces Challenges in Regulating Risk; May 2010. GAO-10-549, <http://www.gao.gov/new.items/d10549.pdf>.
- Geiser M, Rothen-Rutishauser B, Kapp N, Schürch S, Kreyling W, Schulz H, Semmler M, Im Hof V, Heyder J, Gehr P. Ultrafine particles cross cellular membranes by nonphagocytic mechanisms in lungs and in cultured cells. Environ Health Perspect. 2005; 113(11):1555-60.
- Geiser M, Kreyling WG. Deposition and biokinetics of inhaled nanoparticles. Part Fibre Toxicol. 2010; 7:2.
- Gormley AJ, Ghandehari H. Evaluation of Toxicity of Nanostructures in Biological Systems. In: Nanotoxicity-From In Vivo and In Vitro Models to Health Risks, S. Sahu (Ed), Wiley (2009), pp 115-159.
- Gwinn MR, Vallyathan V. Nanoparticles: health effects--pros and cons. Environ Health Perspect. 2006; 114(12):1818-25.
- Grenelle II Law 2010, loi n°2010-788 du 12 juillet 2010 portant engagement national puor l'environement. JORF n°0160 du 13 juillet 2010 page 12905.
- Hall S, Bradley T, Moore JT, Kuykindall T, Minella L. Acute and chronic toxicity of nano-scale TiO_2 particles to freshwater fish, cladocerans, and green algae, and effects of organic and inorganic substrate on TiO_2 toxicity. Nanotoxicology. 2009; 3(2): 91-7.
- Handy et al. (2008a): Handy RD, Owen R, Valsami-Jones E. The ecotoxicology of nanoparticles and nanomaterials: current status, knowledge gaps, challenges, and future needs. Ecotoxicology. 2008; 17(5):315-25.
- Handy et al. (2008b): Handy RD, von der Kammer F, Lead JR, Hassellöv M, Owen R, Crane M. The ecotoxicology and chemistry of manufactured nanoparticles. Ecotoxicology. 2008; 17(4):287-314.
- Henry TB, Menn FM, Fleming JT, Wilgus J, Compton RN, Sayler GS. Attributing effects of aqueous C60 nano-aggregates to tetrahydrofuran decomposition products in larval zebrafish by assessment of gene expression. Environ Health Perspect. 2007; 115(7):1059-65.
- Hermann A, Möller M: Rechtliche Machbarkeitsstudie zu einem Nanoproduktregister – Endbericht. Ökoinstitut, Berlin, Freiburg 2010, <http://www.oeko.de/oekodoc/1031/2010-083-de.pdf>.
- ICCA (2008): Responsible Care status report, <www.responsiblecare.org/filebank/Status%20Report%2001_05.pdf>.
- ICRP (International Commission on Radiological Protection) (1994): Human Respiratory Tract Model for Radiological Protection. ICRP Publication 66. Ann ICRP. 1994; 24(1-3). Elsevier Science Ltd., Oxford.
- IG DHS (2008): Code of Conduct - Nanotechnologien, 5 February 2008, <www.innovationsgesellschaft.ch/media/archive2/publikationen/CoC_Nanotechnologies_english.pdf>.
- Institute of Food Science & Technology (2006): Information Statement – Nanotechnologies, <http://www.ifst.org/document.aspx?id=128>.
- ISO/TC 229 (2008): International Orgnaisation for Standardisation (ISO), Technical Committee (TC) 229: Technical Specification CEN ISO TS 27687(2008):

Nanotechnologies – Terminology and definitions for nanoobjects – Nanoparticle, nanofibre and nanoplate.

- ISO/TC 229 (2010): International Orgnaisation for Standardisation (ISO), Technical Committee (TC) 229: Technical Report ISO/TR 11360 (2010): Nanotechnologies – Methodology for the classification and categorization of nanomaterials.
- JRC of European Commission (2010): Lövestam, G.; Rauscher, H.;Roebben, G.; Sokull Klüttgen, B.; Gibson, N.; Putaud, J.-P.;; Stamm, H.: Considerations on a Definition of Nanomaterial for Regulatory Purposes. European Union 2010.
- Kanapilly GM, Diel JH. Ultrafine 239PuO2 aerosol generation, characterization and short-term inhalation study in the rat. Health Phys. 1980; 39(3):505-19.
- Kiss B, Bíró T, Czifra G, Tóth BI, Kertész Z, Szikszai Z, Kiss AZ, Juhász I, Zouboulis CC, Hunyadi J. Investigation of micronized titanium dioxide penetration in human skin xenografts and its effect on cellular functions of human skin-derived cells. Exp Dermatol. 2008; 17(8):659-67.
- Kreyling WG, Semmler M, Erbe F, Mayer P, Takenaka S, Schulz H, Oberdörster G, Ziesenis A. Translocation of ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low. J Toxicol Environ Health A. 2002; 65(20):1513-30.
- Kreyling WG, Semmler-Behnke M, Seitz J, Scymczak W, Wenk A, Mayer P, Takenaka S, Oberdörster G. Size dependence of the translocation of inhaled iridium and carbon nanoparticle aggregates from the lung of rats to the blood and secondary target organs. Inhal Toxicol. 2009; 21 Suppl 1:55-60.
- Krug HF, Kern K, Wörle-Knirsch JM, Diabaté S. Toxicity of Nanomaterials – New carbon conformations and metal oxids. In: Nanomaterials: toxicity, health and environmental issues. Kumar CSSR (ed.), 2006, Wiley-VCH, pp. 155-87.
- Kulthong K, Srisung S, Boonpavanitchakul K, Kangwansupamonkon W, Maniratanachote R. Determination of silver nanoparticle release from antibacterial fabrics into artificial sweat. Part Fibre Toxicol. 2010; 7:8.
- Lademann J, Weigmann H, Rickmeyer C, Barthelmes H, Schaefer H, Mueller G, Sterry W. Penetration of titanium dioxide microparticles in a sunscreen formulation into the horny layer and the follicular orifice. Skin Pharmacol Appl Skin Physiol. 1999; 12(5):247-56.
- Lademann J, Richter H, Schaefer UF, Blume-Peytavi U, Teichmann A, Otberg N, Sterry W. Hair follicles - a long-term reservoir for drug delivery. Skin Pharmacol Physiol. 2006; 19(4):232-6.
- Lin S, Reppert J, Hu Q, Hudson JS, Reid ML, Ratnikova TA, Rao AM, Luo H, Ke PC. Uptake, translocation, and transmission of carbon nanomaterials in rice plants. Small. 2009; 5(10):1128-32.
- Luther W. Industrial application of nanomaterials – chances and risks. Technology analysis. Future Technologies Division of VDI Technologiezentrum GmbH, Düsseldorf, 2004, <http://www.nano.uts.edu.au/nanohouse/MPNs%20risks.pdf>.
- Marquis BJ, Love SA, Braun KL, Haynes CL. Analytical methods to assess nanoparticle toxicity. Analyst. 2009; 134(3):425-39.
- Maynard AD, Aitken RJ, Butz T, Colvin V, Donaldson K, Oberdörster G, Philbert MA, Ryan J, Seaton A, Stone V, Tinkle SS, Tran L, Walker NJ, Warheit DB. Safe handling of nanotechnology. Nature. 2006; 444(7117):267-9.
- Morgan S. The British Way - the Voluntary Reporting Scheme of the DEFRA. NanoRegulation 2008, 16. - 17. 9. 2008, St. Gallen, Swiss.

- Mostofi R, Wang B, Haghighat F, Bahloul A, Jaime L. Performance of mechanical filters and respirators for capturing nanoparticles--limitations and future direction. Ind Health. 2010; 48(3):296-304.
- Müller M, Fritz M, Buchter A. Nanotoxikologie. Zbl Arbeitsmed 2008; 58:238–52.
- Mueller NC, Nowack B. Exposure modeling of engineered nanoparticles in the environment. Environ Sci Technol. 2008; 42(12):4447-53.
- Nanowerk (2008): Nanotechnology accountability: Responsible Nano Code update Newsletter; www.nanowerk.com/news/newsid=5890.php OECD (2003): Organisation for Economic Co-operation and Development, Environment Directorate. Description of Selected Key Generic Terms Used in Chemical/Hazard Assessment. OECD Series on Testing and Assessment Number 44. ENV/JM/MONO(2003)15. Paris, 30-Oct-2003.
- Nel A, Xia T, Mädler L, Li N. Toxic potential of materials at the nanolevel. Science. 2006; 311(5761):622-7.
- Nemmar A, Vanbilloen H, Hoylaerts MF, Hoet PH, Verbruggen A, Nemery B. Passage of intratracheally instilled ultrafine particles from the lung into the systemic circulation in hamster. Am J Respir Crit Care Med. 2001; 164(9):1665-8.
- Nemmar A, Hoet PH, Vanquickenborne B, Dinsdale D, Thomeer M, Hoylaerts MF, et al. Passage of inhaled particles into the blood circulation in humans. Circulation. 2002; 105(4):411-4.
- Oberdörster G, Sharp Z, Atudorei V, Elder A, Gelein R, Lunts A, Kreyling W, Cox C. Extrapulmonary translocation of ultrafine carbon particles following whole-body inhalation exposure of rats. J Toxicol Environ Health A. 2002; 65(20):1531-43.
- Oberdörster G, Oberdörster E, Oberdörster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect. 2005; 113(7):823-39.
- Oberdörster G, Stone V, Donaldson K. Toxicology of nanoparticles: A historical perspective. Nanotoxicology. 2007; 1(1):2-25.
- Oberdörster G, Elder A, Rinderknecht A. Nanoparticles and the brain: cause for concern? J Nanosci Nanotechnol. 2009; 9(8):4996-5007.
- Oberdörster (2010a): Oberdörster G. Safety assessment for nanotechnology and nanomedicine: concepts of nanotoxicology. J Intern Med. 2010; 267(1):89-105.
- Oberdörster (2010b): G. Oberdörster at the NanoAgri 2010 Conference, <http://www.nanoagri2010.com/ fao_mini_papers_extra_files.pdf>.
- OECD (2003): Environment Directorate. Description of Selected Key Generic Terms Used in Chemical/Hazard Assessment. OECD Series on Testing and Assessment Number 44. ENV/JM/MONO(2003)15. Paris, 30-Oct-2003.
- OECD (2008): Working Party on Manufactured Nanomaterials Guidance for the use of the OECD Database on Research into the Safety of Manufactured Nanomaterials (2008), <http://www.oecd.org/>.
- OCED (2010): Working Party on Manufactured MPNs (WPMN), see for recent example see ENV/JM/MOMO(2010)42.
- Ostrowski A, Martin T, Conti J, Hurt I, Harthorn B. Nanotoxicology: characterizing the scientific literature, 2000–2007. J Nanopart Res. 2009; 11(2):251-7.
- PEN (2010): The Project of Emerging Nanotechnologies, update 8.9.2010. <http://www.nanotechproject.org/inventories/consumer/analysis_draft/>.
- Pacurari M, Castranova V, Vallyathan V. Single- and multi-wall carbon nanotubes versus asbestos: are the carbon nanotubes a new health risk to humans? J Toxicol Environ Health A. 2010; 73(5):378-95.

- Poland CA, Duffin R, Kinloch I, Maynard A, Wallace WA, Seaton A, Stone V, Brown S, Macnee W, Donaldson K. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. Nat Nanotechnol. 2008; 3(7):423-8.
- Regulation EG/987/2008 of the Commission of 8. October 2008 zur Änderung der Verordnung (EG) Nr. 1907/2006 des Europäischen Parlaments und des Rates zur Registrierung, Bewertung, Zulassung und Beschränkung chemischer Stoffe (REACH) hinsichtlich der Anhänge IV und V. ABl. L 268/14, 9.10.2008.
- Regulation EC/178/2002 of the European Parliament and the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food SafetyAuthorityand laying down procedures in matters of food safety. OJ L 31/1, 1.2.2002.
- Regulation EC/258/97 of 27 January 1997 concerning novel foods and novel food ingredients. OJ L 43, 14.2.1997, p. 1–6.
- Regulation EC/1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No. 1907/2006. OJL 353/1, 31.12.2008.
- Regulation EC/1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309/1, 24.11.2009.
- Regulation EC/1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products. OJ L 342/59, 22.12.2009.
- Regulation EC/1331/2008 of the European Parliament and the Council of 16 December 2008 establishing a common authorization procedure for food additives, enzymes and food flavourings . OJ L 354/1, 31.12.2008.
- Regulation EC/1332/2008 of the European Parliament and the Council of 16 December 2008 on food enzymes and amending Council Directive 83/417/EEC, Council Regulation (EC) No 1493/1999, Directive 2000/13/EC, Council Directive 2001/112/EC and Regulation (EC) No 258/97 on food enzymes. OJ L 354/7, 31.12.2008.
- Regulation EC/1333/2008 of the European Parliament and the Council of 16 December 2008 on food additives. OJ L 354/16, 31.12.2008.
- Regulation EC/1334/2008 of the European Parliament and the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. OJ L 354/34, 31.12.2008.
- Regulation EC/1907/2006 of the European Parliament and the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). OJ L 396/1, 30.12.2006.
- Regulation EC/1935/2004 of the European Parliament and the Council of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC.OJ L338/4, 13.11.2004.
- Regulation EC/1107/2009 of the European Parliament and the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309/1, 24.11.2009.
- Renn O, Grobe A, Jäger A. Appropriate Risk Governance Strategies for Nanotechnology Applications in Food and Cosmetics. Policy Brief of the International Risk Governance Council, Geneva, April 2009, <www.irgc.org/IMG/pdf/IRGC_PBnanofood_WEB.pdf>.

- Risk Commission (2003): Ad hoc Commission on "Revision of Risk Analysis Procedures and Structures as well as of Standard Setting in the field of Environmental Health in the Federal Republic of Germany". Final Report. Berlin, June 2003.
- RIVM (2009): Exposure to nanomaterials in consumer products. RIVM Letter Report 340370001/2009. Authors: S.W.P. Wijnhoven, S. Dekkers, W.I. Hagens, W.H. de Jong. RIVM Bilthoven, <http://www.rivm.nl/bibliotheek/rapporten/340370001.pdf>.
- Roller M, Pott F. Lung tumor risk estimates from rat studies with not specifically toxic granular dusts. Ann N Y Acad Sci. 2006; 1076:266-80.
- Rouse JG, Yang J, Ryman-Rasmussen JP, Barron AR, Monteiro-Riviere NA. Effects of mechanical flexion on the penetration of fullerene amino acid-derivatized peptide nanoparticles through skin. Nano Lett. 2007; 7(1):155-60.
- Ryman-Rasmussen JP, Riviere JE, Monteiro-Riviere NA. Penetration of intact skin by quantum dots with diverse physicochemical properties. Toxicol Sci. 2006; 91(1):159-65.
- SCENIHR (2006): European Commission, Directorate-General for Health and Consumers, Scientific Committee on Emerging and Newly Identified Heallth Risks. Modified opinion on: The appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies. Brussells, 2006.
- SCENIHR (2007a): European Commission, Directorate-General for Health and Consumers, Scientific Committee on Emerging and Newly Identified Heallth Risks. The Appropriateness of the Risk Assessment Methodology in Accordance with the Technical Guidance Documents for New and Existing Substances for Assessing the Risks of Nanomaterials. Brussels, 2007.
- SCENIHR (2007b): European Commission, Directorate-General for Health and Consumers, Scientific Committee on Emerging and Newly Identified Heallth Risks: Opinion on the Scientific Aspects of the Existing and Propsed Definitions Relating to Pruducts of Nanoscience and Nanotechnologies. Brussels, 2007.
- SCENIHR (2010): European Commission, Directorate-General for Health and Consumers, Scientific Committee on Emerging and Newly Identified Heallth Risks: Scientific Basis for the Definition of the Term "Nanomaterial". Brussels, 2010.
- Schmid G, Decker M, Ernst H, Fuchs H, Grünwald W, Grunwald A, Hofmann H, Mayor M, Rathgeber W, Simon U, Wyrwa D. Small Dimensions and Material Properties. A Definition of Nanotechnology. Europäische Akademie Bad Neuenahr-Ahrweiler, Graue Reihe Nr. 35, November 2003, <http://www.ea-aw.de/fileadmin/downloads/Graue_Reihe/GR_35_Nanotechnology_112003.pdf>.
- Schmid K, Riediker M. Use of Nanoparticles in Swiss Industry: A Targeted Survey. Environmental Science & Technology. 2008; 42(7):2253-60.
- Schmid O, Möller W, Semmler-Behnke M, Ferron GA, Karg E, Lipka J, Schulz H, Kreyling WG, Stoeger T. Dosimetry and toxicology of inhaled ultrafine particles. Biomarkers. 2009; 14 Suppl 1:67-73.
- Scott-Fordsmand JJ, Krogh PH, Schaefer M, Johansen A. The toxicity testing of double-walled nanotubes-contaminated food to Eisenia veneta earthworms. Ecotoxicol Environ Saf. 2008; 71(3):616-9.
- Semmler M, Seitz J, Erbe F, Mayer P, Heyder J, Oberdörster G, Kreyling WG. Long-term clearance kinetics of inhaled ultrafine insoluble iridium particles from the rat lung, including transient translocation into secondary organs. Inhal Toxicol. 2004; 16(6-7): 453-9.

- Tiede K, Boxall AB, Tear SP, Lewis J, David H, Hassellov M. Detection and characterization of engineered nanoparticles in food and the environment. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2008 Jul; 25(7):795-821.
- Volkheimer G. Passage of particles through the wall of the gastrointestinal tract. Environ Health Perspect. 1974; 9:215-25.
- Walczyk D, Bombelli FB, Monopoli MP, Lynch I, Dawson KA. What the cell "sees" in bionanoscience. J Am Chem Soc. 2010; 132(16):5761-8.
- W&W (2005): Willems & van den Wildenberg (W&W). Roadmap Report on Nanoparticles. A roadmap report prepared in the framework of the NanoRoadMap (NRM) project, cofunded by the 6th Framework Programme (FP6) of the European Commission. Barcelona, November 2005.
- Xia T, Li N, Nel AE. Potential health impact of nanoparticles. Annu Rev Public Health. 2009; 30:137-50.
- Xia XR, Monteiro-Riviere NA, Riviere JE. An index for characterization of nanomaterials in biological systems. Nat Nanotechnol. 2010 Sep; 5(9):671-5.
- Zhu et al. (2009a): Zhu X, Wang J, Zhang X, Chang Y, Chen Y. The impact of ZnO nanoparticle aggregates on the embryonic development of zebrafish (Danio rerio). Nanotechnology. 2009; 20(19):195103.
- Zhu et al. (2009b): Zhu X, Zhu L, Chen Y, Tian S. Acute toxicities of six manufactured nanomaterial suspensions to Daphnia magna. J Nanopart Res. 2009; 11(1):67-75.
- Zhu et al. (2010a): Zhu X, Chang Y, Chen Y. Toxicity and bioaccumulation of TiO2 nanoparticle aggregates in Daphnia magna. Chemosphere. 2010; 78(3):209-15.
- Zhu et al. (2010b): Zhu X, Wang J, Zhang X, Chang Y, Chen Y. Trophic transfer of TiO(2) nanoparticles from Daphnia to zebrafish in a simplified freshwater food chain. Chemosphere. 2010; 79(9):928-33.
- Zhu et al. (2010c): Zhu J, Ozdemir SK, Xiao Y-F, Li L, He L, Chen D-R, et al. On-chip single nanoparticle detection and sizing by mode splitting in an ultrahigh-Q microresonator. Nat Photon. 2010; 4(1):46-9.
- Zuin S, Pojana G, Marcomini A. Effect-Oriented Physicochemical Characterization of Nanomaterials. In: Monteiro-Riviere NA, Tran CL, editors. Nanotoxicology: Characterization, Dosing and Health Effects. New York, USA: Informa Healthcare; 2007. p. 19-58.

GLOSSARY AND ABBREVIATIONS

Acute exposure: High dose contact with a toxic substance that occurs once or only for a short time (up to 14 days for humans).[12]

ADME: Absorption, Distribution, Metabolism, and Excretion

Alveoli: The alveoli are the final branches of the respiratory tree and act as the primary gas exchange units of the lung.

Biopersistent: means that MPNs with this property are stable (no dissolving, degradation or corrosion) in a biological environment like e.g. the lung.

CAS number: CAS numbers (officially CAS registry numbers, also CAS RNs or CAS #s) are unique numerical designators for chemical elements, compounds, polymers, biological sequences, mixtures and alloys. Chemical Abstracts Service (CAS), a division of the American Chemical Society, assigns these designators to every chemical that has been described in the scientific literature. CAS also maintains and sells a database of these chemicals, known as the CAS registry, containing more than 55 million organic and inorganic substances and 62 million sequences.

CASG Nano: Competent Authorities Subgroup on Nanomaterials

Chronic exposure: low dose contact with a toxic substance that occurs over a long time periode (more than 1 year for humans).[5].

CLP: Regulation EC/1272/2008 on Classification, Labelling and Packaging

CNT: Carbonanotubes

CoC: Code of Conduct

CSR: Corporate social responsibility

Cytotoxicity: is the degree to which a substance or noxe can damage cells.

DWCNT: Double walled carbon nanotubes

EC number: The European Commission Number (also EC number, EC-No and EC#) is the seven-digit code that is assigned to chemical substances that are commercially available within the European Union through EINECS; ELINCS or the NLP list. It is made up of seven digits according to the pattern xxx-xxx-x. EINECS numbers start with a "2"; ELINCS numbers with a "4" and NLP numbers with a "5" as the first digit.

ECHA: European Chemicals Agency

EFSA: European Food Safety Authority

EHS: Environmental Health and Safety

EINECS: European Inventory of Existing Commercial Chemical Substances (O.J. C 146A, 15.6.1990). EINECS lists all substances, excluding polymers, that were commercially available in the EU from 1 January 1971 to 18 September 1981. EINECS is a definitive inventory of substances exempt from notification that served, in the first instance, community-wide as a legal tool for distinguishing "existing" from "new" chemicals.

ELINCS: European List of Notified Chemical Substances. ELINCS consists of all chemical substances notified within the European Community after 18 September 1981 until 31st May 2008. With the expiry of Council Directive 92/32/EEC of 30 April 1992 (amending for the seventh time Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances), the notification scheme was revoked and replaced by the REACh Regulation.

EMEA: European Medicines Agency

[12] http://www.greenfacts.org/glossary/abc/index.htm

Endpoints: are defined occurrences after an observation period of an experiment or study that are biological indicators for interactions resulting in different biological effects (in vitro assays) or a disease related outcome (in vivo studies).

Habitat: The area or natural environment where an organism or ecological system normally lives.

Free radicals: are atoms or molecules containing unpaired electrons, therefore "free" radicals. Electrons have a very strong tendency to be in a paired than an unpaired state. Free radicals indiscriminately pick up electrons from other atoms, which in turn converts those into secondary free radicals, thus setting up a chain reaction which can cause substantial biological damage.

Functionalisation: is an action of surface modification of a material by bringing physical, chemical or biological characteristics different from the ones originally found on the surface of a material.

Genotoxicity: is the degree to which a substance or noxe can damage the cellular genetic material (DNA) affecting its integrity.

GIT: Gastro intestinal tract

ICCA: International Council of Chemical Associations

IRGC: International Risk Governance Council

MNP: Manufactured Nanoparticles

MPN: Manufactured particulate nanomaterials

MWCNT: Multi walled carbon nanotubes

NLP: "No Longer Polymers". In the EU Chemicals Regulation, the definition of the term "polymer" was changed in the 7th amendment (92/32/EEC) of the Directive 67/548/EEC. This change meant that some substances which were considered to be polymers under the reporting rules when the European Inventory of Existing Commercial Chemical Substances (EINECS) was being established were no longer considered to be polymers under the 7th amendment. As all substances which were not present in the EINECS inventory were notifiable, and since polymers were not reportable for EINECS, all "no-longer polymers" should in theory be notified. In the adoption process of the 7th amendment in 1992, however, the Council of Ministers made it clear that these no-longer polymers should not, retrospectively, become subject to notification. The Commission was requested to draw up a list of no-longer polymers. Substances to be included in this list have been on the EU market between September 18, 1981, and October 31, 1993 and satisfy the requirement that they were considered to be polymers under the reporting rules for EINECS but are no longer considered to be polymers under the 7th amendment.

Noxe: (pl. noxae) Latin for pollutant; a toxic substance/chemical that exerts a harmful effect on the human body or any other organism.[13]

Oxidative stress: is the imbalance between free radicals (also ROS) and antioxidants production in a biological system. When the free radical concentration is increasing the normal redox state of tissues is out of balance which can cause cellular effects

PEN: Project on Emerging Nanotechnologies

RC: Responsible Care

Reactive oxygen species (ROS): are chemically-reactive molecules like free radicals, containing oxygen. Reactive oxygen species are highly reactive due to the presence of unpaired electrons. ROS is a natural by-product of the normal metabolism of oxygen and have important roles in cell signalling. Environmental stress (e.g. UV or heat exposure) can increase ROS levels dramatically. This cumulates into a situation known as oxidative stress.

REACH: Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

[13] or http://www.dict.cc/englisch-deutsch/noxa.html

RIP: REACH Implementation Projects
SCCS: Scientific Committee on Consumer Safety
SCENIHR: Scientific Committee on Emerging and Newly Identified Health Risks
STP: Science and technology policy
SWCNT: single walled carbon nanotubes
TSCA: Toxic Substances Control Act

ANNEX I: MOST IMPORTANT EUROPEAN AND GLOBAL DEFINITIONS, INTENTIONS, ADVANTAGES, DISADVANTAGES

Definitions by ISO/TC 229 (2008) and CEN

Subject	Rational, hierarchic definition system related to nanotechnology (core terms, particles, particle clusters, nano-objects and types of nano-objects) "Nanomaterial Tree" (classification of nanomaterial concerning the shape)
Intention	Technical specification for a future standard to facilitate communications between organizations and individuals in industry and those who interact with them
Definitions	**Nanoscale:** Size range from approximately 1 nm to 100 nm This definition is accompanied by two notes: Note 1: Properties that are not extrapolations from lager size will typically, but not exclusively, be exhibited in this size range. For such properties this size limits are considered approximate. Note 2: The lower limit is introduced to avoid single and small groups of atoms from being designated as nano-objects or elements of nanostructures, which might be implied by the absence of a lower limit. **Nanomaterial:** Material with any external dimension in the nanoscale or having internal or surface structure in the nanoscale **Nano-object:** Material with one, two or three external dimensions in the nanoscale Additional terms likeParticle (Primary Particle), Agglomerates and Aggregates (Secondary Particles), different components of the nanomaterial tree based on different shapes of nano-objects used as a generic term for all discrete nanoscale objects (nanoparticle, nanoplate, nanofibre, nanotube, nanorod, nanowire)
Problems	Definitions differ from actual scientific, public and media used terms For example: carbon nanotubes are classified as nanofibres and not as nanoparticles, usual designated in toxicological studies Note that the two categories of nanomaterial nano-object and nano-structured material are partly overlapping: nano-objects can be nanostructured Note that the definition of a particle also includes "soluble" liquids, e.g. micelles in emulsions
Support	Helpful for a sophisticated scientific communication and regulatory activity

Definitions by SCENIHR

Subject	Framework for a hierarchy of terminology (SCENIHR 2007b) and a elaborate proposed working definition of the term "nanomaterial" (SCENIHR 2010)
Intention	Development of a framework, based on existing terms, on common sense, and on the need to reflect the needs of risk assessment The terms should not conflict with commonly used words like substances, matter or material Working definition for the term "nanomaterial" for regulatory purposes (SCENIHR 2010)
Definitions	**Nanoscale:** A feature characterised by dimensions of the order of 100 nm or less **Nanomaterial:** Any form of a material composed of discrete functional parts, many of which will have one or more dimensions in the nanoscale **Nanoparticle:** A discrete entity which has three dimensions of the order of 100 nm or less **Engineered Nanomaterial:** Any form of a material that is deliberately created such that it is composed of discrete functional parts, either internally or at the surface, many of which will have one or more dimensions of the order of 100 nm or less. Additional terms like nanostructure, nanoparticle, nanosheet, nanorod, nanotube, nanoparticulate matter
Problems	The definition for nanoparticles deviates from that used in previous SCENIHR opinions (2006, 2007a) thus one or more rather than all three dimensions being of the order of 100 nm or less (means nano-object in the system of ISOTC229) The terms for nanosheet, nanorod, nanofibre are not consistent with ISO terminology There is no scientific evidence in favour a single upper limit nor to quality the appropriateness of the 100 nm value within the definition of "nanoscale" It is not possible to identify a specific size or a specific generic property that is introduced with size for the definition of "nanomaterial". These uncertainties result in a already not enforceable term for regulatory settings (SCENIHR 2010). Note that Including internal structures would also include nanoporous materials such as membranes, this seems to be counterintuitive
Support	The revised definition for nanoparticles is more consistent with terminology used in particle toxicology The definitions are more relevant for risk assessment purposes, based on considerations of size, shape and properties The proposed working definition for "nanomaterial" considers the number size distribution and introduces a mean size and a standard deviation. This results in a tiered approach for risk

	assessment depending on the amount of information (SCENIHR 2010)

Definitions by OECD

Subject	Working definition for the term "manufactured nanomaterial" and other terms
Intention	Applying an adopted draft definition for "manufactured nanomaterial" given by ISO/TC 229 while awaiting a formally agreed ISO definition Elaborate additional criterions and possible discriminators for the identification of a nanomaterial concerning physico-chemical properties
Definitions	**Nanoscale:** Size range typically between 1 nm to 100 nm **Nanomaterial:** Material which is either a nano-object or is nanostructured **Manufactured nanomaterials:** Nanomaterials intentionally produced to have specific properties or specific composition, a size range typically between 1 nm and 100 nm and material which is either a nano-object (i.e. that is confined in one, two, or three dimensions at the nanoscale) or is nanostructured (i.e. having an internal or surface structure at the nanoscale)
Problems	The definition is based solely on size because physico-chemical properties even useful for risk assessment can not be translated into a general definition Note that Fullerene molecules are included in the scope of manufactured nanomaterials aggregates and agglomerates are considered to be nanostructured materials along the lines of ISO End-products containing nanomaterials are not themselves nanomaterials
Support	Including ISO definitions for a broader application of the term "manufactured nanomaterials"

Definition by Cosmetic Products Regulation

Subject	Means of the term "nanomaterial" for regulatory purpose
Intention	The regulation establishes rules for cosmetic products available on the market, in order to ensure the functioning of the internal market and a high level of protection of human health Compliance with legal requirements must be verified at the level of market surveillance
Definitions	**Nanomaterial:** (Article 2.1 (k) Nanomaterials means an insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm Article 2.3: … the Commission shall adjust and adapt point (k) of paragraph 1 to technical and scientific progress and to definitions subsequently agreed at international level …
Problems	Besides the size scale specific properties like "insoluble" or "biopersistent" are elements of the definition. According to SCENIHR (2010) there is ambiguity in terms of what is implied when nanomaterial is dissolved. For example the terms solubility and dispersion are used interchangeabely. This creates potential interpretation problems with regard to the property solubility. Persistence is used primarily in a risk assessment context to define chemicals that are retained in the body or in the environment. In this respect persistence can be considered as the opposite of soluble or (bio)degradable. But this property is rather a part of the characterisation and may change for each individual nanomaterial. As a result it is not possible to identiy a specific property for a general definition of nanomaterial. Note that Soluble nanoscale objects are not considered as nanomaterial (e.g. chemical macromolecules, liposomes, micelles, vesicles) The possibility is included for a revision of the definition based on scientific and/or international developments
Support	Additional properties like "insoluble" or "biopersistent" comprises types of nanomaterial with the highest health attention. Insoluble, non-degradable nanomaterials would have a high priority for risk assessment as biopersistence/accumulation may be associated with chronic hazardous effects. This is relevant in the scope of a particular regulation like cosmetic products, and therefore it should be possible to adapt a general definition to the needs of a specific implementation (JRC 2010).

Definition by the Recast of the Novel Foods Regulation

Subject	Means of the term "engineered nanomaterial" for regulatory purpose
Intention	Novel foods are subjects of a pre-market control or pre-market notification. In this context the risk management in relation to nanomaterials can be verified by authorities before placing on the market
Definitions	**Engineered nanomaterial:** (Article 3.2 f) "engineered nanomaterial" means any intentionally produced material that has one or more dimensions of the order of 100 nm or less or is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have size above the order of 100 nm but retain properties that are characteristic to the nanoscale Article 3.3: … the Commission shall adjust and adapt point (c) of paragraph 2 to technical and scientific progress and with definitions subsequently agreed at international level …
Problems	The definition may create ambiguities as within this one definition several aspects dealing with size have been included (e.g. "of the order of 100 nm or less", "above the order of 100 nm"). This may be ambiguous and not clear. The possibility is included for a revision of the definition based on scientific and/or international developments
Support	The definition combines size and non-specified properties that are characteristic to the nanoscale Adapted from the SCENIHR definition

Definition by the Recast of the Biocidal Product Directive

Subject	Means of the term "nanomaterial" for regulatory purpose
Intention	Active substances of biocidal products are subjected to authorization in a positive list; nanomaterials can be used as active substances
Definitions	**Nanomaterial:** Nanomaterial means any intentionally produced material that has one or more dimensions of the order of 100 nm or less or is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have size above the order of 100 nm but retain properties that are characteristic to the nanoscale
Problems	The same definition for the term "nanomaterial" as used for the term "engineered nanomaterial" in Novel Foods Regulation. The definition may create ambiguities as within this one definition several aspects dealing with size have been included (e.g. "of the order of 100 nm or less", "above the order of 100 nm"). This may be ambiguous and not clear.
Support	The definition combines size and non-specified properties that are characteristic to the nanoscale Adapted from the SCENIHR definition