EUROPEAN PARLIAMENT

Science and Technology Options Assessment

S T O A

Nano*Safety* - Risk Governance of Manufactured Nanoparticles

FINAL REPORT

(IP/A/STOA/FWC/2008-096/LOT5/C1/SC3)

PE 482.685

EUROPEAN PARLIAMENT

DIRECTORATE GENERAL FOR INTERNAL POLICIES
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SCIENCE AND TECHNOLOGY OPTIONS ASSESSMENT

Nano*Safety* - Risk Governance of Manufactured Nanoparticles

Final Report

Abstract

This report deals with the potential environmental, health and safety (EHS) risks of engineered nanomaterials (ENM). Because of the great uncertainties regarding their actual health and environmental effects and numerous methodological challenges to established risk assessment procedures (toxicology, exposure and hazard assessments, life cycle assessment, analytics, and others), risk management of ENM is confronted with serious challenges. On the other hand, precautionary regulatory action with regard to ENM 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 focused on two important perspectives of regulation: Risk management strategies for ENM as discussed or proposed for the EU or its Member States, and risk communication problems and needs for EHS risks of ENM.

Findings of the project were discussed with MEPs in several workshops. In addition, the project used also a participatory method in order to investigate the risk communication expectations of the general public.

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DISCLAIMER

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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.

Developing 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.

Characterising 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 on 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 characterise 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 characterised, whereby the latter can influence the reactivity of the MPN.

The problem of the scientific characterisation 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 Joint Research Centre of the European Commission (JRC) has just recently published its own Recommendation on the definition of the term "nanomaterial". With that document, an overarching definition has been proposed that could serve as a starting point for developing sector-specific definitions for specific requirements.

Since at the time of the beginning of the NanoSafety project a broadly agreed definition of nanomaterials did not exist, a working definition to be used within the project was developed. Considering that insoluble nanoparticles and nanoscale carbon allotropes (buckyballs and carbon nanotubes), when mobile in their immediate environments, are of concern 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 the 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, the project focussed 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 continued. Four arguments might be helpful to assist this process:

- Legal definitions by nanomaterials have to describe the object of regulation sufficiently precisely 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 should therefore be science-based but does not necessarily have to be identical to scientific definition(s) of the same term.
- The breadth 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 they may occur in nature including in a number of natural products that are consumed by humans, that they can be incidentally produced as a result of various human activities, or that they 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 and their consequences; therefore a legal definition of nanomaterials should focus on manufactured nanomaterials.
- Since regulatory goals are set as a result of a political process, which seeks to balance various expectations and interests, they may vary with different contexts. It is unlikely that this will change in the near future. For that reason, within specific regulatory processes, additional clarifications and specifications of a "harmonised definition" will be required that might lead to variations of the "general" definition in the resulting legal documents. The overarching definition here can only provide a general framework.

- 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 and may differ within different regulatory contexts.

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 schematic way – 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 broadly 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 us 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 characterisation. 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 MPN in respect to its type and characteristics. The current knowledge suggests that inhalation is the main portal of entry of MPN into the body. Epidemiological studies about MPN 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 lung. It was demonstrated that, to a certain amount, MPN can be removed by clearance mechanisms (especially in bronchia) and/or the immune system (especially in alveoli) of the lungs. These mechanisms are less effective with 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 may even 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) may lead to pathological conditions and can cause toxic effects.

In general, the assumption that the move to the nanoscale implies 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 seemed to be more toxic if trace impurities of iron or solvents were present.

Toxicity testing of MPN currently faces some methodological limitations; some of them can be overcome in the 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 least because of the lack of reliable characterisation data 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 practices and conventions of the science system. No-effect studies are a valuable repository for hazard characterisation and their limited accessibility could be seen as a waste of scientific resources and valuable toxicological information. 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 characterisation 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.

Concern assessment

Understanding concerns, expectations and perceptions that individuals, groups or different cultures may link to nanomaterials is an important factor in getting to know better how individuals and groups perceive and assess risks, what actions (or non-actions) are perceived as being risky for what reasons and how the different actors in risk management and communication are expected to take action. Investigations of the evolving socio-cultural and political context in which research at the nanoscale is conducted, the societal needs that nanotechnology may satisfy and the popular images that experts, politicians and representatives of the various publics associate with nanoscience and nanotechnology are additional elements in improving the societal knowledge about adequate risk management procedures.

Generally speaking, the landscape of research into perceptions of nanotechnology and nanomaterials – and the related concerns – among European citizens is somewhat patchy. Recent quantitative research has shown that 46 % of Europeans have ever heard of nanotechnology, while 54 % have not. One third of the respondents believed that nanotechnology may do harm to the environment, is not safe to human health and is not safe to future generations, respectively. One third expressed an opposite view and one third didn't know. Research also showed that perceived safety is by far the most influential variable on overall support of or opposition to nanotechnology, followed by benefit, worries related to unnaturalness and lastly inequity.

Additional insights for studying perceptions and concerns related to nanoparticles can be gained from the results of qualitative methods. Studies with members of the general public showed that the majority of people still have little or no idea of what nanotechnology is or about its possible implications. Despite this, members of the public have already expressed similar concerns to those associated with other technologies perceived as being risky, particularly around governance structures and corporate transparency. Many citizens were astonished about the broad scope, spectrum and extent of 'nanoproducts' already available. They arbitrarily mixed terminology and used nanoparticles, nanotechnology and sometimes also 'nanoproducts' quasi synonymously. They stated that due to the lack of knowledge, a reasonable balancing of chances versus risks is difficult and occasionally not possible. They were concerned about the degree of transparency of communication, credibility of and trust in institutions as well as the ability of government and the private sector to manage risks. Almost all refused the application of nanoparticles in the food sector. The citizens were less reluctant to the use of 'nanoproducts' in cosmetics and other sectors. Moreover, they supported nanotechnologies that are linked to a wider social good or to a perceived individual benefit.

Different stakeholders from civil society organisations, industry and academia, although usually not explicitly expressing concerns themselves, react on the main concerns expressed by members of the groups they represent. These are grouped into specific combinations of concerns, taking into account priorities and abstractions of their specific motivations. An analysis of the requests and recommendations for further handling of risk and improvement of governance procedures they formulate allows for some insights into the underlying concerns.

Environmental and consumer civil society organisations call for an increase of safety research and a (partial) moratorium for the marketing of certain products. Some even call for a full, but temporary moratorium of the application of nanoparticles. They support a broader scoped definition with regard to size, also including aggregates and agglomerates, foster dialogues involving all stakeholders and public participation, and favour mandatory regulatory measures including a general labelling obligation and a harmonised traceability system. Most industry representatives consider the current regulatory framework as generally being sufficient and support the development of, when necessary adapted, risk assessment approaches and safe handling guidelines that are based on case-by-case decisions and assessments by scientific agencies that deal with e.g. application contexts. They argue that comprehensive legal obligations would lead to increasing bureaucracy and a decrease of their international competitiveness. Especially concerning the call of the general public (and CSO stakeholders) for more information that should be available in registries or in the form of a labelling of 'nanoproducts', industry stakeholders emphasise that voluntary information via public communication and their participation in public events with an informative character are sufficient. Members of academia support and participate in dialogues involving all stakeholders, call for an increase of EHS research funding and for the most part support a nanomaterial definition that is based on a narrow size scope with conditional exceptions (e.g. inclusion of aggregates and agglomerates).

Challenges for risk assessment and risk governance

The situation described above might suggest that the risk assessment methodology as a whole is inadequate to inform in a timely manner 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, role and validity of these claims as justifications for regulatory strategies 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 to consider that regulations represent not only a restriction for companies, but can also serve as a guideline for strategic decisions and provide legal certainty.

Lawmakers on national and European level are dealing already with the implementation of nanospecific aspects in currently enacted or forthcoming regulation 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. The adaptation 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 extent – MPNs lie within the scope of this regulation. Other policies concerning nanomaterial aspects are mentioned in this project, mainly the food regulation, the regulation on cosmetic products and 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. Advantages and problems of voluntary registers and codes 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 adapting 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. Although the European Commission has announced that it is not seeking to develop a separate regulatory legislation for nanomaterials and all necessary regulation will instead be planned under the existing REACH legislation, some experts proposed to merge and further elaborate basic rules for handling nanomaterials in an overall "NanoAct". These ideas need further conceptualisation, tests of their feasibility and discussions of their advantages and disadvantages compared to the current incremental approach.

A number of these issues are briefly discussed in this report, including among others:

- developing a legal definition for nanomaterials; consideration of nanomaterials as "stand alone" substances or as a nanoform of existing substances
- 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 which regulators have additional uncertainties for the regulatory coverage of emerging nanomaterials risks;
- finding adequate regulatory instruments;
- review and adjustment of specific testing methods, standards and strategies;
- labelling of nanomaterials in consumer products of concern (cosmetic products labelling takes effect in 2013, food ingredient labelling takes effect in 2014, no labelling provision for plant protection products, biocidal products and textiles);

- 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 most proponents do not further conceptualise 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 scientific and budgetary support.

Importance of risk communication

In the process of anticipatory governance of potential EHS risks (like in the case of manufactured particulate nanomaterials), dialogical risk communication plays the dominant role. It should put people that are concerned about certain hazards and risks in a position to redeem their claim to be 'capable of informed risk appraisal' by making them appropriate offers of information, dialogue and participation. Although parliaments usually are not active actors in dialogical risk communication, they can actively contribute to the implementation of risk communication measures by encouraging voluntary activities as well as by making various risk communication measures mandatory in relevant legislative acts. This is especially true for the involvement of concerned parties and representatives of organised societal groups (like industrial associations, trade unions, environmental organisations, consumer protection associations or other civil society organisations) and the participation of the general public in processes of governance of EHS risks of nanomaterials.

The primary goal of a dialogue with all stakeholders and the general public consists in creating trust. Transparent and credible information on nanoproducts will contribute to consumers' trust and freedom of choice. Their need for information with regard to individual concerns and perceived risks should be taken seriously. Clear, understandable information about ingredients, functions and effects of nanomaterials in consumer products, and about product safety, are required by many citizens as well as by consumer organisations, not least in order to enable informed choice, a "right to know", on the side of the customer. This information is expected to be provided by industry and made freely accessible. New concepts for such information provision need to be developed.

1. MANUFACTURED PARTICULATE NANOMATERIALS (MPN) – IMPORTANCE AND FUNDAMENTALS OF RISK GOVERNANCE

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 which are enabled by results of nanoscience and nanotechnology developments. 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 industrialised 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 these 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 their 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 their 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 "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] 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).

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 do not 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. A sample of *particles with a high surface area* 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 noble-metal based catalysts as well as in metal oxide catalysts (e.g. 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) can, when added to polymers, 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 absorption of ultraviolet or infrared light, 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, the *biological properties* of nanoparticles may also 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 summarises the atmospheric abundance of nanoparticles as a function of environment.

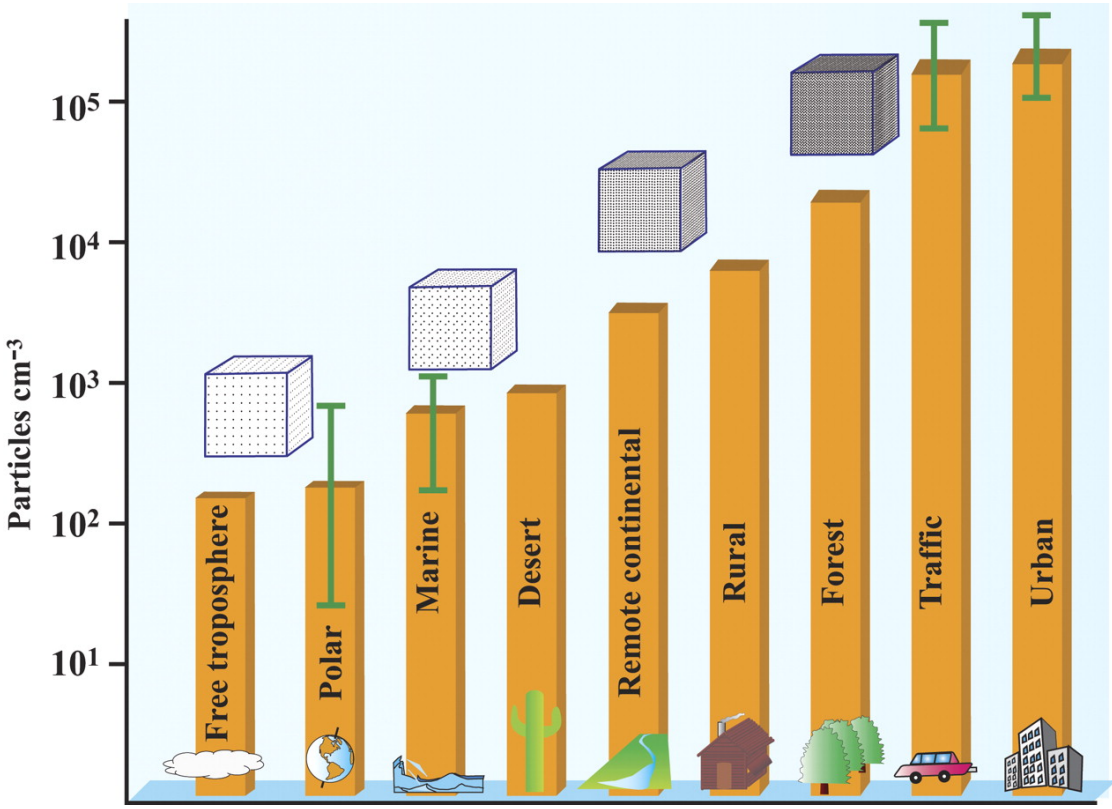

Figure 1: Number concentrations (particles per cubic centimetre) of nanoparticles in the atmosphere in various environments (taken from Buseck & Adachi 2008)

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 than by naturally occurring nanoparticles can appear.

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 capitalise 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, 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}.

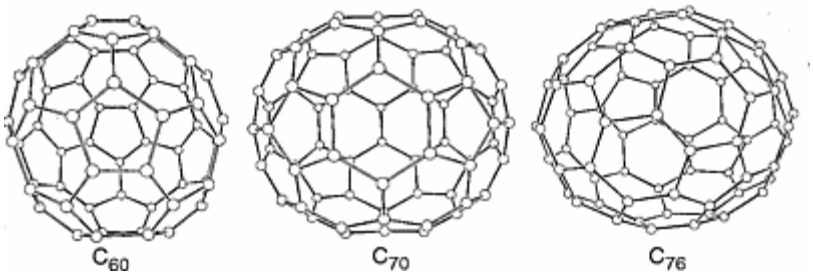

Figure 2: Variations of spherical fullerenes (buckyballs)

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 categorised 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 functionalisation 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. Because nanotechnologies – 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. To the well-known methodological challenges of market analysis one can add fuzzy definitions of both nanoparticles and nanoproducts, the diversity of potential commercialisation pathways and the complexity of the nanomaterials value chain.

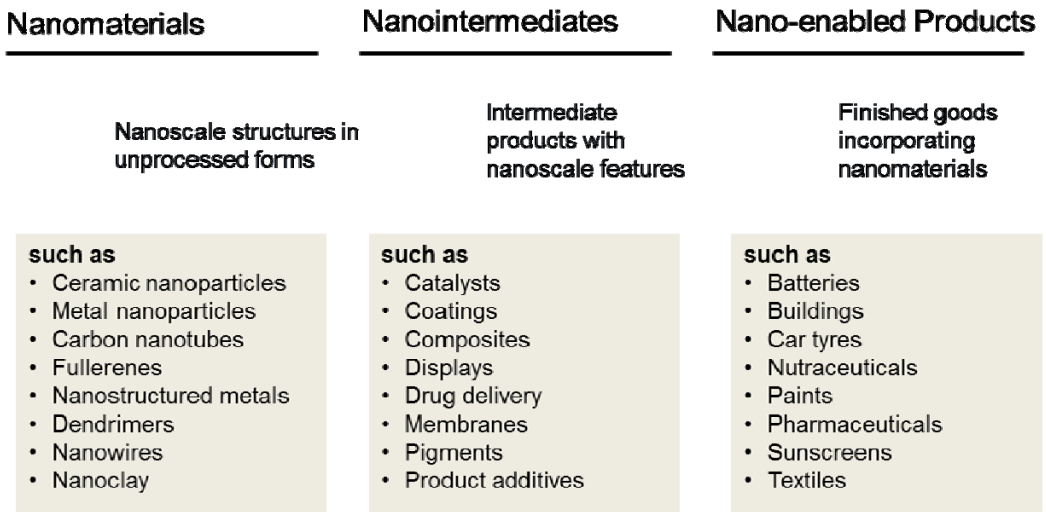

Figure 3: Nanomaterials as enabling technology (adapted from GAO 2010)

Notwithstanding these limitations, 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.

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 1.

	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 1: 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 researchers studying the societal and EHS implications 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. As of October 2011, it lists over 1300 products, produced by almost 600 companies, located in 30 countries. (PEN 2011). 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. 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 of 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 the "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 in 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 characterisations of its subject, scientific definitions have to be precise and unambiguous and based on objective scientific evidence.

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).

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.

1.3.1. Elements of definitions of nanomaterials

Practically all definitions proposed by international organisations used a characteristic set of criteria and keywords like size scale, additional properties and references with regard to a possible inclusion of aggregates, agglomerates and internal structures. All 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 proposed to use clear lower and upper limits for a definition and suggested that a lower limit of 1 nm and an upper limit of 100 nm or greater would be a reasonable choice. Whether there are additional data for hazard characterisation of materials with sizes higher than 100 nm would be subject to further discussion. Moreover, the discussion should take into account size distributions and the non-uniformity of samples as well.

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 particle clusters called agglomerates and aggregates. ISO/TC 229 (2008) names these particle forms 'secondary particles', which may have dimensions above100 nm. 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. The Scientific Committee on Emerging and Newly Identified Health Risks (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.

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.

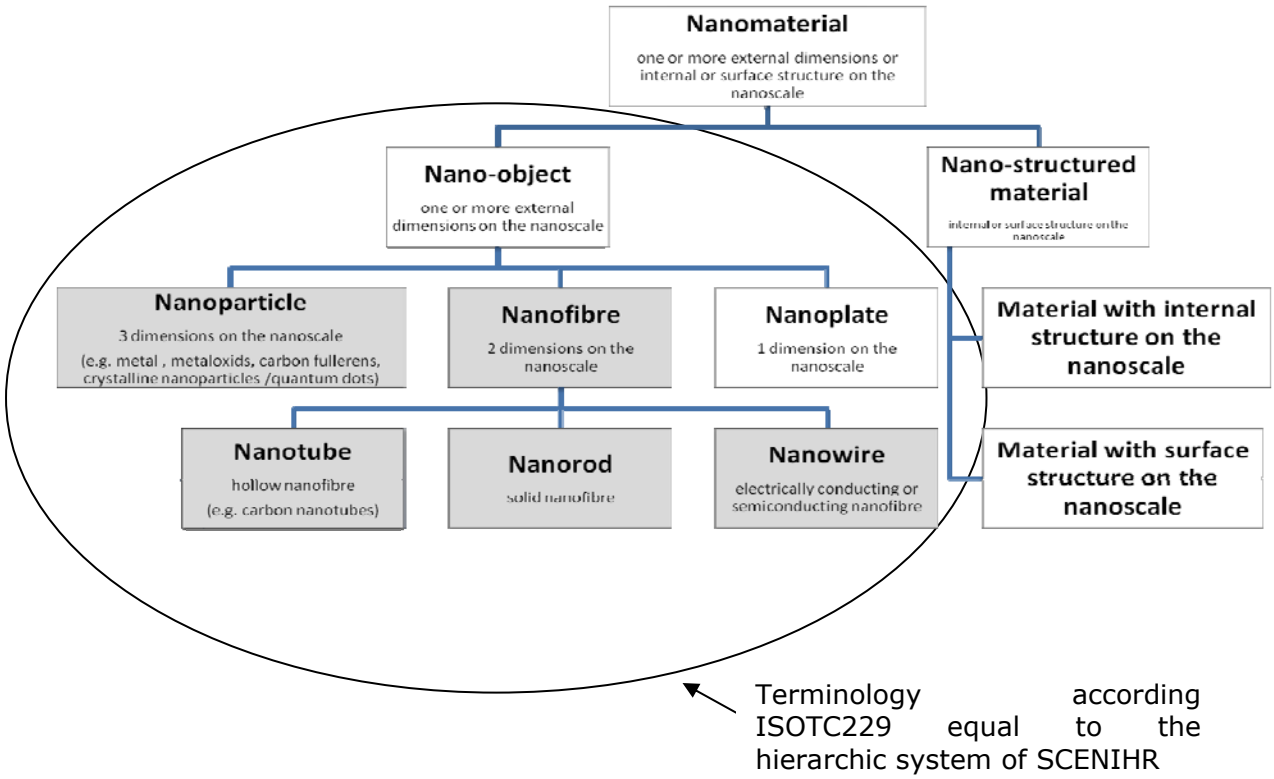

Figure 4: Types of nanomaterials in a hierarchic system. Those who are subject of toxicological research according to an international collaborative review called ENRHES–report[2] are grey filled. (Material with internal structure on the nanoscale means: e.g. nano-composites, nanoporous membranes, aggregates, agglomerates. Material with surface structure on the nanoscale means: e.g. coatings, functionalised membranes).

[2] Engineered Nanoparticles: Review of Health and Environmental Safety, 2010. ENHRES was a FP7 project that has performed a comprehensive and critical scientific review of the health and environmental safety of various different nanoparticles. The project team considered sources, pathways of exposure as well as the health and environmental outcomes of concern and developed prioritised recommendations for future EHS research and regulation.

1.3.2. Working definition for the purpose of this report

Current research indicates that, of all possible configurations of nanomaterials, two subgroups 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 environmental, health and safety (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. In its current general understanding as well as in the framing proposed in the ISO document it appears to be far too broad for a definition in a governance context. 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 our discussion on EHS risks only on ***'manufactured'particulate nanomaterials*** – *abbreviated with* ***MPN***('intentionally produced' or 'engineered' could be used synonymously). Incidental products of human activities (like industrial, combustion, welding, automobile or diesel) or naturally occurring nanomaterials lie beyond the scope of this report.

1.4. On the risk management framework

Risk management is a complex process. Over the last decades, several models for risk management have been proposed. The most recent one has been introduced by the International Risk Governance Council (IRGC) in 2005 (IRGC 2005) and developed further into a new conceptual framework for the risk governance of nanotechnology in a white paper published in 2006 (IRGC 2006).

Risk Governance, according to the IRGC, *"includes the totality of actors, rules, conventions, processes, and mechanisms concerned with how relevant risk information is collected, analysed and communicated and management decisions are taken. Encompassing the combined risk-relevant decisions and actions of both governmental and private actors, risk governance is of particular importance in, but not restricted to, situations where there is no single authority to take a binding risk management decision but where instead the nature of the risk requires the collaboration and co-ordination between a range of different stakeholders. Risk governance, however, not only includes a multifaceted, multi-actor risk process but also calls for the consideration of contextual factors such as institutional arrangements (e.g. the regulatory and legal framework that determines the relationship, roles and responsibilities of the actors and co-ordination mechanisms such as markets, incentives or self-imposed norms) and political culture including different perceptions of risk"* (Renn 2008).

It lies outside the scope of this report to comprehensively discuss the advantages and shortcomings of the IRGC model in comparison to its predecessors. We have chosen to use it as a conceptual framework for the NanoSafety project for a number of more or less practical reasons:

- The IRGC framework is more sophisticated than other risk management models. It acknowledges that managing the risks of emerging technologies in modern societies involves a multitude of different actors and is a dynamic process with various iterations and feedbacks.
- It acknowledges that risk governance decisions have to be taken in instances of complexity, uncertainty and ambiguity. Therefore, strategies should be based on a corrective and adaptive approach and take into account the level and extent of available knowledge and a societal balancing of the predicted risks and benefits.
- The framework includes two innovative concepts for the governance of (potential) EHS risks arising from the use of manufactured particulate nanomaterials (MPN): It integrates a scientific risk-benefit assessment (including environment, health, and safety (EHS) and ethical, legal and other social issues (ELSI)), with an assessment of risk perception and the societal context of risk (referred to in the white paper as concern assessment).
- Inherent to all elements of this framework is the need for all interested parties to be effectively engaged, for risk to be suitably and efficiently communicated by and to the different actors and for decision-makers to be open to public concerns.

The IRGC Framework consists of four phases (Figure 1): Pre-Assessment (Phase 1), Risk Appraisal (Phase 2), Tolerability and Acceptability Judgement (Phase 3) and Risk Management (Phase 4).

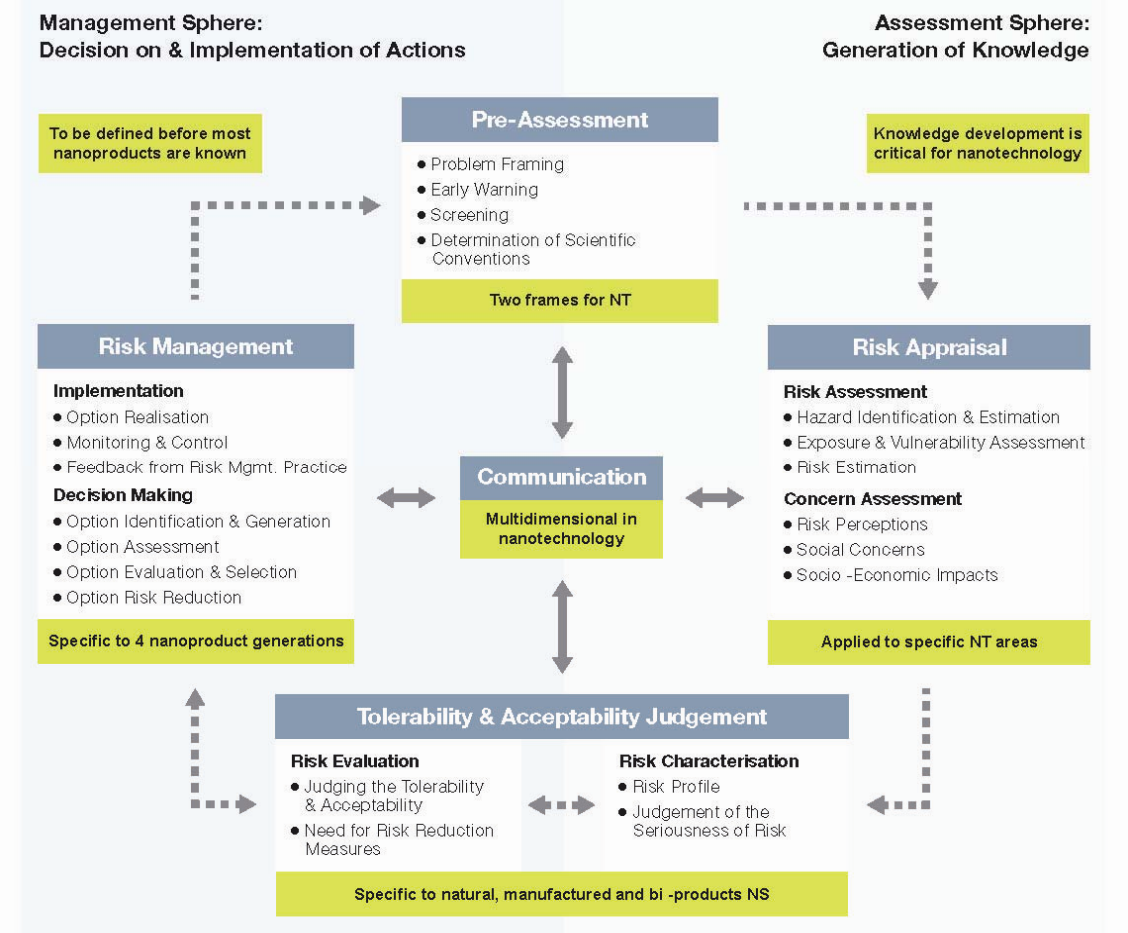

Figure 5: Steps in IRGC Risk Assessment and Management Framework for Nanotechnology (NT); NS denotes Nanostructures (taken from IRGC 2006).

The focus of the NanoSafety Project is on the risk appraisal of MPN. Risk appraisal is the second phase of the IRGC risk governance framework and comprises two elements: risk assessment and concern assessment. For MPN risks, the classic risk assessment component - dealing with hazard, exposure and risk - is particularly important. Its challenges and problems which are exacerbated by the situation that the speed of product development and application exceeds the ability of risk assessors to appraise any new risk(s) are summarised briefly below.

1.4.1. Risk assessment

The properties of manufactured particulate nanomaterials (MPNs) differ significantly from those of lager particles of the same material. This makes them suitable for new or improved applications which are expected to be a major opportunity for the economic and sustainable development of many countries. However, the new and extraordinary properties deriving from the nano-size that make MPN attractive for a number of applications are just the same as those which concern scientists, policy makers, a number of stakeholders and parts of the general public. Experiences of the past, e.g. with chemicals, asbestos or ultrafine particles, showed that new materials may be a source of new threat for human health and the environment (Oberdörster et al. 2005).

The scientific community is requested to answer the question whether MPNs pose environmental, health and safety (EHS) risks or not, and to provide policy makers with the appropriate knowledge to perform risk assessment as a prerequisite for science-based risk management and risk governance.

Risk assessment is a well-established and formalised process intended to *"calculate or estimate the risk to a given target organism, system or (sub)population , including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system."* (OECD 2003) ***The Risk Assessment process consists of four steps: hazard identification, hazard characterisation (usually summarised as hazard assessment), exposure assessment, and risk characterisation*** (Figure 6).

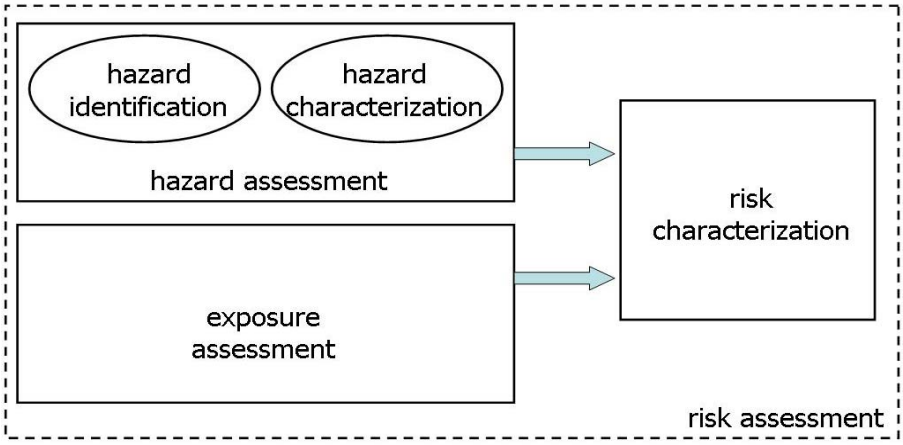

Figure 6: Risk assessment regarding possible adverse substances or materials. The terminology used refers to the framework of the OECD (2003).

According to the Risk Commission (2003), a scientific risk assessment process primarily deals with consequences of the effects of noxious agents to human health. The main roles of the four steps in the process are described by crucial questions:

1. The question of characterisation of the hazard potential ("Hazard Identification"). What dangers to human health or the environment may basically arise from the noxious agent in question?
2. The question of dose-response relationships ("Hazard Characterisation"): 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 ("Exposure Assessment"): to what extent is the relevant population group exposed to the noxious agent?
4. The question of the overall estimate of the risk ("Risk Characterisation"): 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 achieved through a critical aggregation of the answers to questions 1 to 3.

Risk assessment resembles a process in which the probability of a harmful effect to individuals or populations is quantified. This is often expressed by using the formula "Hazard x Exposure = Risk". Thereby, in toxicology risk is colloquially defined by two characteristics: (1) the hazard of the material that needs to be identified and characterised and (2) the contact with the hazardous material which is the exposure (Krug et al. 2006). Chapter 2 of this final report gives an updated overview on the state of the art of nanotoxicology, the challenges for a scientific risk assessment and still existing limitations.

1.4.2. Concern assessment

Risk management has to react not only to new scientific results regarding a hazard or an exposure to it. It also reacts to changing societal or cultural factors like altering expectations on risk reduction procedures, new judgements about tolerability and acceptability of risks, developing value systems or shifting risk perceptions of different actors. One of these questions that have to be addressed within this framework is what the concerns of the general public and the stakeholders are when it comes to a widespread market introduction and usage of manufactured particulate nanomaterials. In short: within a risk governance process that considers the political and institutional conditions in modern societies, risk assessment has to be complemented by a **concern assessment**.

In a book article that addresses conceptual issues of the IRGC framework raised by external experts in a round of formal comments, the lead authors define ***concern assessment*** as

> "*a social science activity aimed at providing sound insights and a comprehensive diagnosis of concerns, expectations and perceptions that individuals, groups or different cultures may link to the hazard*" (Renn and Walker 2008).

Understanding these different concerns, expectations and perceptions is an important factor in getting to know better how individuals and groups perceive and assess risks and what actions (or non-actions) are perceived as being risky for what reasons. In addition, it helps to comprehend how the different actors are expected to develop and implement adequate measures in risk management and risk communication. Investigations of the evolving socio-cultural and political context in which research at the nanoscale is conducted, the societal needs that nanotechnology may satisfy and the popular images that experts, politicians and representatives of the various publics associate with nanoscience and nanotechnology (IRGC 2006) are additional elements in improving the societal knowledge about adequate risk management procedures.

Fundamental for the comprehensive diagnosis of concerns is the **meaning of risk**. According to IRGC (2005) and Renn and Walker (2008), risk is characterised in general as a "*mental construction*", which means that risk is "*not a real phenomena but originates in the human mind. Actors, however, creatively arrange and reassemble signals that they get from the 'real world' providing structure and guidance to an ongoing process of reality enactment. So risks represent what people observe in reality and what they experience.*"

Generally speaking, the **perception of technological risks** depends on two sets of factors. The first consists of psychological factors such as perceived threat, familiarity, personal control options and positive risk-benefit ratio. The second set includes political and cultural factors such as perceived equity and justice, visions about future developments and effects on personal interests and values. While the first set of components can be predicted to some degree on the basis of the properties of the technology itself and the situation of its introduction, the second set is almost impossible to predict (IRGC 2006).

While risk assessment can build upon a long tradition of scientific discussion, methodological development and established organisational and institutional practices, concern assessment is still in its early stages. Notwithstanding that, a systematic assessment of the concerns and preferences of the various actor groups and the public at large, a systematic feedback of its results to the related regulatory and legislative processes are necessary prerequisites to improve our understanding of the likely societal responses to the developments in nanomaterials and nanotechnology.

This is also important for the implementation of risk governance structures that are accepted as socially responsible and avoid public controversies and potential conflicts. Chapter 3 gives a first insight into the different methods of concern assessment and the available results on perceptions and concerns with regard to nanomaterials and nanotechnologies.

1.4.3. The central role of risk communication

Risk communication is a multifaceted term. At first sight, one can distinct between two understandings that can be described as instrumental or dialogical communication.

In the instrumental perspective, risk communication is basically seen as a tool in the hands of risk managers, policy makers and public officials to prevent "ineffective, fear-driven, and potentially damaging public responses to serious crises such as unusual disease outbreaks and bioterrorism. Moreover, appropriate risk communication procedures foster the trust and confidence that are vital in a crisis situation" (DoHHS 2002). Covello and Sandman describe this instrumental role of risk communication more vividly: "*Where data indicate that a hazard is not serious, yet the public is near panic, it can be used to calm people down; for this kind of situation, its goal is to provide reassurance. But it can also help generate a sense of urgency where data indicate that the hazard is serious, yet the public response is one of apathy. It has been effective, for example, in motivating people to buckle up their seat belts, to quit smoking, to test for radon in their houses, and to evacuate their homes during an emergency.*" (Covello and Sandman 2001)

This approach might have its virtues in specific situations. In the process of anticipatory governance of potential EHS risks (like in the case of manufactured particulate nanomaterials that is discussed in this report), **risk communication** has another role. Here, risk communication should make people that are concerned about certain hazards and risks "*appropriate offers of information, dialogue and participation that* ***put them in a position to redeem their claim to be 'capable of informed risk appraisal'.*** *This concept of being in a position to make an informed risk appraisal denotes the ability to make, on the basis of knowledge of the objectively demonstrable consequences of risk-generating events or activities, the residual uncertainties and other risk-relevant factors, a personal appraisal of the risks in question that corresponds to the individual's own values for shaping his own life and to his personal criteria for assessing the acceptability of these risks for society as a whole*" (Risk Commission 2003).

In the context of risk communication, different modes of interaction between the relevant actors are needed throughout the whole risk governance process. Basically, all those who are directly or indirectly affected by the consequences of the individual decision, i.e. whose interests or values are positively or negatively influenced, should be involved in the process that has to ensure that[3]:

- those who are central to risk framing, risk and concern assessment or risk management understand what is happening, how they are to be involved and, where appropriate, what their responsibilities are; and
- others outside the immediate risk appraisal or risk management process are informed and engaged.

In all, one can distinguish four basic modules within risk communication, which may be used successively or as alternatives, depending on the situation, the type of risk, and the phase in the regulation process:

(1) Internal coordination procedures within authorities as well as **consultation and coordination** between different authorities and competent bodies, especially in cases where various administrative fields of competence are involved, are at the core of risk communication processes.

(2) In cases where the initial situation or the data situation is complex and it is not possible to arrive at a clear assessment of the risks within the existing administrative structures and capabilities, **discourse with proven experts** who reflect the pluralistic spectrum of scientific opinion and, where appropriate, with directly concerned parties may help to achieve further clarification, particularly of the areas of uncertainty, and a well-balanced assessment.

(3) **The involvement of concerned parties and representatives** of organised societal groups (like industrial associations, trade unions, environmental organisations, consumer protection associations or other civil society organisations) basically serves the purpose of mutual information about the available risk-related data and the evaluation and interpretation of the risk under discussion. In addition, one can draw on the specialist knowledge and experience of manufacturers, distributors and concerned parties, explicate conflicts of objectives in the normative evaluation of a risk and in the process of weighing up the advantages and disadvantages of different management options, take accounts of the interests and values of the individual interest groups and develop trustful relationships by means of transparent arguments and mutual understanding.

[3] The elaboration hereafter extensively follows the concepts and arguments of the German "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" (Risk Commission 2003) and the International Risk Governance Council (IRGC 2006) that were only slightly modified by the authors of this report.

(4) Especially in cases where the risks themselves or the consequences of risk regulation could lead to considerable infringement of basic rights and/or could spark off a public controversy, a **participation of the general public** is to be considered. Furthermore, some parties advocate the early involvement of "the public" in risk governance for various other reasons. They state that incorporating everyday "lay" knowledge supplements expert knowledge or initiates additional justifications and broadens the range of concerns and objects of protection covered in the governance process. It is argued that public involvement signalises awareness for the importance of the concerns of affected citizens or that it increases the readiness of concerned parties to refrain from litigation if they have played a part in the decision and their interests have been included. Some even suggest that early involvement of the general public should be considered an entirely new way of policy making in modern societies.

With respect to the general public, the **principal function of risk communication is to enable concerned citizens to make their own balanced risk-judgement**, this means that any person or social group affected by risks should be sufficiently well informed to make a personal judgement of the risks, which meets their own criteria.

The form of communication consists of four instruments:

- Documentation: This serves transparency. A good and broadly accessible medium for this purpose would be the internet, documenting e.g. the process and results of scientific research on MNP EHS risks.
- Information: This serves to share knowledge among the communication partners. Here it is important that the concerns of those informed are adequately taken up. With regard to MNP risk governance, public information should comprise the principles and procedures used to test nanotechnology products, to assess potential health or ecological impacts and to monitor the effects. Communication tools for information about the benefits and non-intended side effects of MPN include e.g. consumer hot lines and web platforms, a web-based product register or product labelling.
- Two-way communication or dialogue: This serves to exchange arguments, experiences, impressions and judgments. There must be willingness on both sides to listen to and learn from each other.
- Participation in risk analyses and management decisions: This serves to include people adequately in decisions which concern their lives.

The **aim of dialogue, engagement and participation,** the latter two elements in this list, should be to address fundamental issues and characteristics of the risk problem like the degree of complexity, the nature of uncertainty and ambiguity. High ambiguities require the most inclusive strategy for participation since not only directly affected groups but also those indirectly affected have something to contribute to a debate. To translate these rather abstract requirements into actual political action remains a demanding task. This is mainly due to the fact that "the public" is an abstract concept which is framed differently by different actors. One of the key problems in developing formats for public participation is that the general public – by definition – is neither organised, nor can it be represented adequately by self-appointed representatives.

A number of innovative tools such as consensus conferences, citizens' juries, focus groups, scenario workshops etc. which are more dialogue-oriented than the classic forms (like exhibiting documents for inspection and providing opportunities to submit comments) and make for more effective participation by non-organised citizens have been developed and tested and numerous experiences regarding the design of participatory procedures have been gained.

But on the other hand, the basic question – how the results of participatory elements could be intertwined with the classic and legitimated procedures of political decision making – is still under discussion. The search for an answer to this question goes far beyond the practical aspects of how participatory methods are arranged and extends to the fundamental discussion of how individuals interact with one another, how people are organised in communities, institutions and societies, and what the value of participation is (EuropTA 2000). The democratic framework – direct or representative – within which participation is discussed; different values, assumptions, goals, interests and expectations of the organisers and participants in participative exercises; varying political cultures – all these and more factors influence the different meanings attached to participation by various social actor groups.

2. RISK ASSESSMENT

2.1. Risk assessment of MPNs and its limitations

In order to gain knowledge to feed the risk assessment procedures a variety of activities on national and multinational level took over the last approximately 15 years – mainly focusing on scientific (toxicological, biological, analytical) and regulatory aspects. Research about biological and toxicological effects of nanoparticles has been massively intensified and "Nanotoxicology" as a new field emerged from the classical toxicology. Nanotoxicologists study biological effects of MPNs on living organisms and in ecosystems – scientific work that is included to the amelioration of studies leading to prevention of adverse effects (Oberdörster 2010a) – using 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, but it is still under discussion whether standard procedures of risk assessment are suitable or not (e.g. Müller et al. 2008, Fadeel and Garcia-Bennett 2010, Roller 2011).

This discussion involves also regulators and their scientific committees: For example, the EU Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) stated already in their 2007 opinion that the current methodologies are generally likely to be able to identify the hazards associated with the use of MPNs. However, they see the need for modifications for the guidance on the assessment of risks since the assessment faces several limitations (SCENIHR 2007 and 2009). Main limitations for current procedures to assess the risks of MPNs are:

- Equipment and methods for characterisation and detection of MPNs is often not appropriate and need further optimisation. Thus, in some cases the detection or characterisation of certain properties is still impossible (Maynard et al. 2006, Tiede et al. 2008, Marquis et al. 2009, Leach et al. 2011).
- Despite ongoing research and international efforts, high quality exposure and dosimetry data is still missing. Many exposure related studies are published on occupational scenarios while much fewer studies are published on environmental and consumer exposure as well as about both acute and chronic exposures (ENRHES 2010, Aschberger et al. 2011). A definition or concept for dose/concentration of MPNs is also still missing.
- Since scientific work used in hazard identification and characterisation is not necessarily intended for the purpose of risk assessment, results are often not comparable because the used conditions are differing from study to study (e.g. different cell types/animals, testing conditions, handling, etc). Moreover, a proper characterisation as well as the use of standardised methods including appropriate controls is missing – especially in "older" studies. And studies that showed no significant (hazardous) effects are usually not published, even though they are curial to relive MPNs from the suspicion of hazard (Krug and Wick 2011).
- There is an ongoing debate on the significance of high dose in vitro or in vivo studies conducted so far and whether or not the used methods are suitable for hazard characterisation (e.g. Oberdörster 2010b).

- Moreover exacerbating factors - such as surface functionalisation, dispersing behaviour in biological media or the use of solvents in case of non-dispersing nanoparticles (e.g. fullerenes) in aqueous media - that are problematic for various reasons (e.g. it may produce testing artefacts; Henry et al. 2007), are not addressed sufficiently in many studies (ENRHES 2010, Aschberger et al. 2011).
- For eco-toxicological studies it is in general difficult to simulate real environmental scenarios since the dose is quite unknown and the extrapolation of data very limited. Furthermore, it is still impossible to detect MPNs in biological matrixes (ENRHES 2010, Aschberger et al. 2011).

An elaborated overview on those limitations can be found in the Phase II report of the NanoSafety project (Fleischer et al. 2010). However, these facts have been recognised by the scientific community and involved regulators and thus, the quantity of publications which can be used for risk assessment is continuously increasing. To speed up this process an international coordination of research activities is needed, as it has been addressed by the OECD, namely by the Working Party on Manufactured MPNs (WPMN), and also the International Alliance for Nano-EHS Harmonisation (IANH).

Even though, one overarching difficulty will most probable always stay: In contrast to the vast majority of substance classes of hazardous chemicals that need to undergo risk assessment, MPNs share no common characteristics besides that the primary particles are in nano-scale. Although, there are a number of approaches to categorise MPNs in a kind of "hazard classes" or develop EHS risk prediction systems (e.g. Foss Hansen et al. 2007, Xia et al. 2009, Xia et al. 2010, Burello and Worth 2011, Puzyn et al. 2011), it is consensus in the nanotoxicology community that due to the knowledge gaps and intrinsic limitations of characterisation of MNPs today only a "case by case" assessment is responsible and sound. Thus, risk assessment of MPNs requires the full dataset for each and every kind of MPN. This makes the progress of gathering the relevant data for this case-by-case approach extremely slow – although the literature body is increasing constantly. Therefore also today, a complete risk assessment is only possible for a small selection of high abundant MPNs (e.g. Krug and Wick 2011, Aschberger et al. 2011).

Besides this, the question of definition of MPNs poses another challenge for risk assessment, although numerous guidelines by both national and international institutions (ISO, OECD, BSI, DIN) exist - as Krug and Wick (2011) highlighted: "*These definitions usually fix the range between 1 nm und 100 nm as being relevant. [But] in spite of this clear definition at last, the term "nano" is not uniformly used in the nanotoxicology literature. [...] Moreover, strict size limits make little sense for the issues of biology and even chemical and physical effects may not appear only within the low nanometer range. [...] There is tacit agreement among biologists and toxicologists that particles that can take different, partly not yet defined paths in organisms are referred to as nanoparticles.*" Thus, the definition of MPNs is a recurring theme in the governance of MPNs.

2.2. State of the art in nanotoxicology

This section aims to give an overview on the main findings of nanotoxicological research and highlight exemplary scientifically sound knowledge on selected, high abundant MPNs. An elaborate literature review as e.g. the ENRHES project (2010) provided would go beyond the scope of this report.

2.2.1. The importance of the physico-chemical properties of MPNs

Knowledge about the characteristics of MPNs is important for risk assessment because reliable hazard assessment of MPNs - with its highly standardised in vitro and in vivo studies that are needed to guarantee the reproducibility and consequently the consistency of the data - requires accurate information about the tested material. In comparison to bulk material, a different set of physico-chemical properties is relevant for determine the EHS risk. Among the different nano-specific parameter that are proposed in the nanotoxicological literature (e.g. Card and Magnuson 2009, ENRHES 2010, Oberdörster 2010a, Stone et al. 2010, Mudunkotuwa and Grassian 2011) in general the size, the shape and the surface properties which influence the reactivity of the MPNs appear to be most meaningful. These parameters influence the reactivity of the particles in a biological environment (see figure 7) as well as the so-called ADME-profile which stands for "Absorption, Distribution, Metabolism, and Excretion" and describes the disposition of the nanomaterials within the organism (see next section). However, for MPNs the surface properties are of special importance; for example: *Using particles with three different diameters of 1 mm, 100 nm, and 10 nm of a particular material of unchanged mass, the specific surface of these particles increases each decimal step by a factor of 10, and the number of particles even increases by a factor of 1000* (Krug and Wick 2011).

Moreover, it is important to know the aggregation and agglomeration behaviour of MPNs in biological environment because it makes a difference whether a single particle of e.g. 50 nm reaches the cells of an organism or an agglomerate that is >1 µm "large". Moreover, contaminates, surface modifications and functionalisation of the MPN influence their physico-chemical properties and thus, their toxicity (e.g. Shi et al. 2011).

In addition, for the toxicity of a MPN the intrinsic physical and chemical properties of the "bulk material" it is made of are also important. For example, the toxicity mechanism of silver nanoparticles is based on the release of antimicrobial silver ions (Choi et al. 2009, Johnston et al. 2010); the same applies for the toxicity of other metal and metal oxide nanoparticles, e.g. ZnO (Kool et al. 2011). Due to their nanosize the particles can enter the cell or are even taken up actively by receptor binding (see figure 8). Once inside the cell, already a relatively small amount of nanoparticles release a toxic "cargo" of ions that leads to multiple damage or even the death of the cell. The nanotoxicologist call this transport principle also the "Trojan Horse Effect" of MPNs (Beyersmann and Hartwig 2008; Krug and Wick 2011 and literature therein).

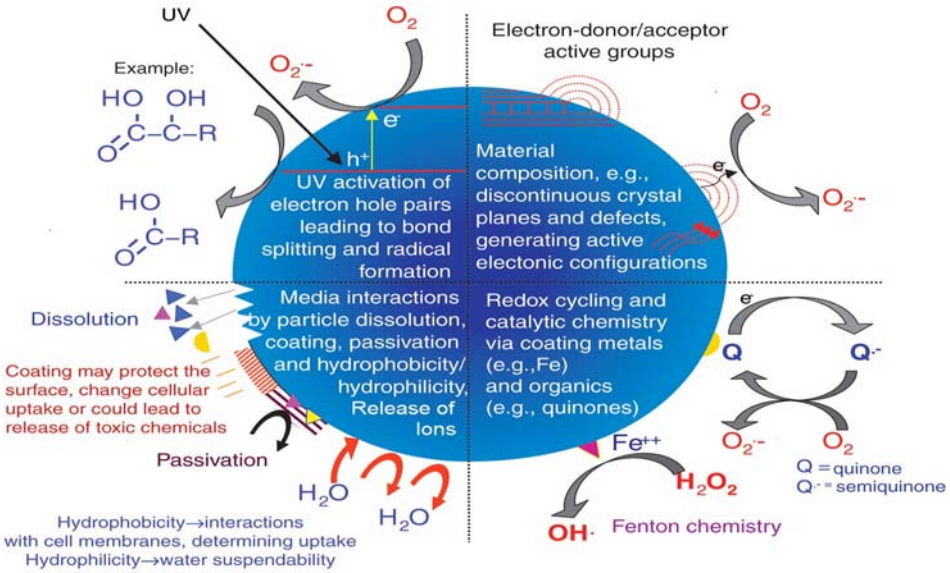

Figure 7: Possible mechanisms by which MPNs interact with biological tissue. Examples illustrate the importance of material composition, electronic structure, bonded surface species (e.g., metal-containing), surface coatings (active or passive), and solubility, including the contribution of surface species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

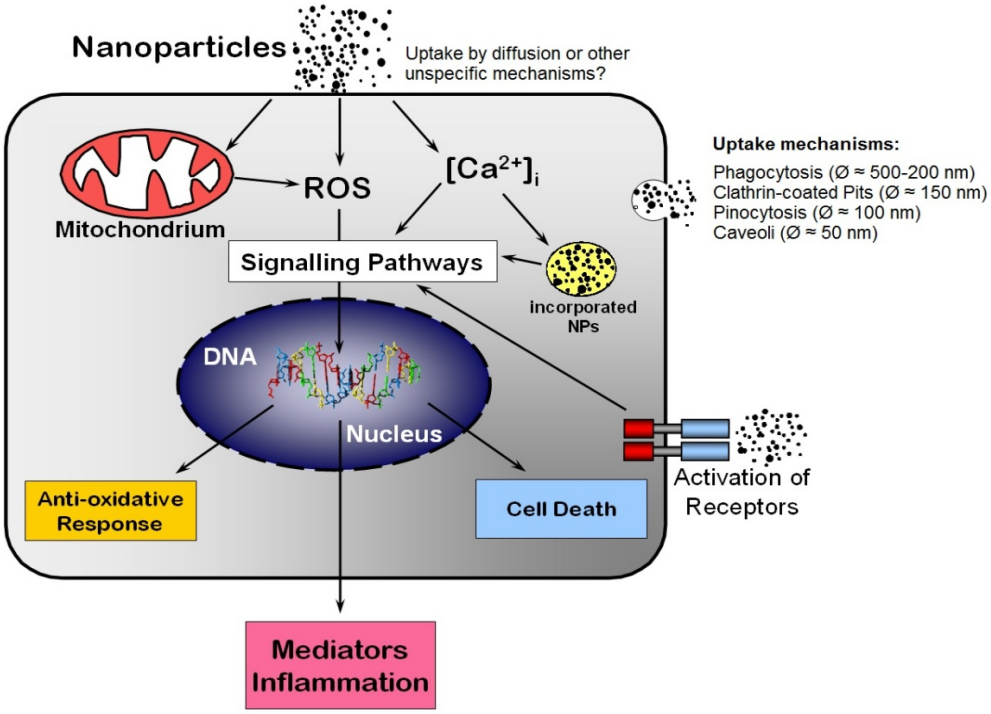

Figure 8: Model of the effects of MPNs on cells (modified from Donaldson and Stone 2003, Krug et al. 2006).[4]

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

In regard to the toxicology of MPNs, the interface between the nanomaterial and biological systems that finally influence the interaction of the MPN with biological material is highly important. In a biological matrix MPNs are not found "naked" in most of the cases but rather covered by proteins and/or lipids which are adsorbing on the surface (Walczyk et al. 2010). This so-called corona leads to changes of the physico-chemical properties and determines the distribution of the MPNs.

2.2.2. Exposure scenarios and toxicokinetics

In order to design meaningful experiments for hazard identification and characterisation it is necessary to know:

(1) in what concentrations humans and other organism are exposed to a certain MPN ("exposure assessment"), and

(2) on which routes the MPNs may be taken up, translocated and further distributed into the body/organism ("assessment of ADME-profiles").

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). 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) 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). Still, most of the available studies concentrate on occupational exposure although some recent studies also try to assess consumers and environmental exposure (e.g. Boxall et al. 2007, Mueller and Nowack 2008, Wijnhoven et al. 2009). Nevertheless, it is almost impossible to assess consumer and environmental exposure today for several reasons including the lack of labelling or registration obligations as well as missing lifecycle assessment of nanoproducts. For example, it is consensus that nanoparticles fixed into a matrix, e.g. in car paint or high-strength nanomaterial of special tennis rackets, they do not pose any danger. But without life cycle assessment it is unclear what happens to them when the product wears off or is recycled.

Along with the question of exposure, the ports of entry of MPNs into the human body as well as their distribution and excretion within plays an important role in risk assessment (see figure 9). MPNs can enter the human body by inhalation, ingestion or via the skin pores but also subsequent to inhalation via the olfactory nerve and by parenteral administration like injection for medical purposes. The latter uptake route appears to be a special case for risk assessment since the MPNs are brought into the body in an intended way and medical context where own risk assessment criteria applies. Since natural barriers such as the skin or the intestinal epithelium can be bypassed through injection, other types of barrier tissue such as the blood–brain barrier or the placenta tissue of pregnant women become relevant (e.g. Trickler et al. 2010, Almeida et al. 2011, Keelan 2011, Yamashita et al. 2011).

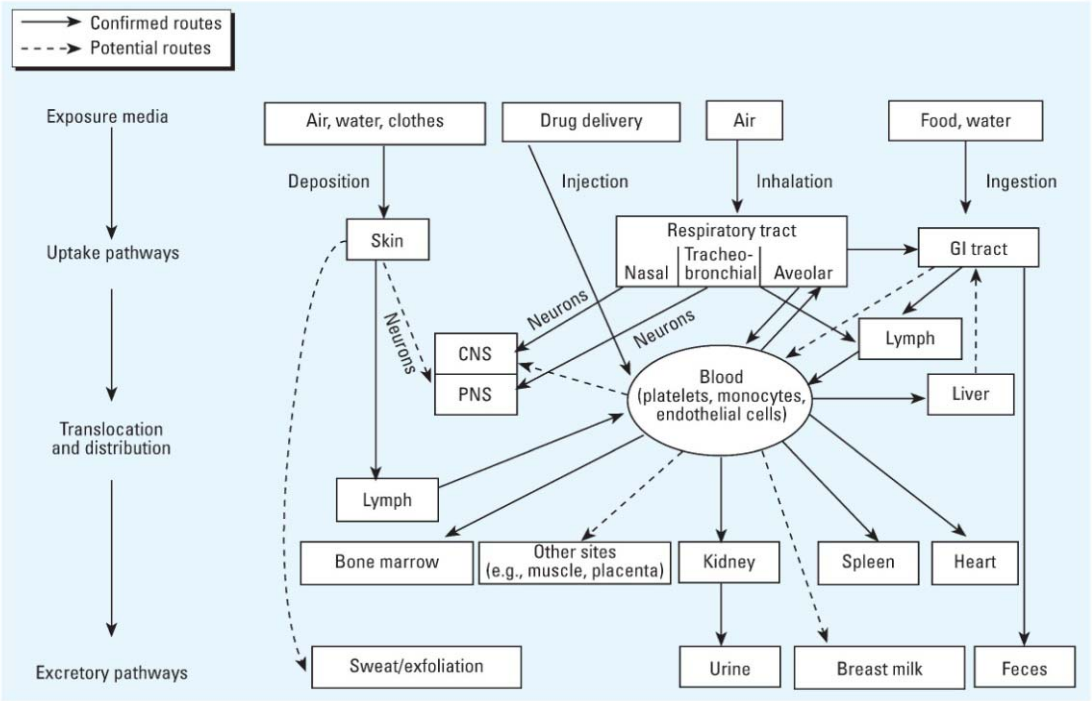

Figure 9: Biokinetics of MPNs. Although many uptake and translocation routes have been demonstrated (arrows), others still are hypothetical and need to be investigated (dashed arrows). Translocation rates are largely unknown, as are accumulation and retention in critical target sites and their underlying 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.)

Among the possible uptake routes, the lung appears to be the most important portal of entry. 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 (ICRP 1994, Elder et al. 2009). However, it was demonstrated that to a certain amount MPNs can be removed by clearance mechanisms and/or immune system of the lungs. Thereby, it seems that these mechanisms are less effective by a decreasing particle size. Nevertheless, the amount of particles that are translocated into the blood stream is relatively low (>0.05 %) and dependent to the physico-chemical properties of the MPN (Kreyling et al. 2009). The overall 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 abovementioned corona formation can change the translocation rate and possibly increase the hazardous effects.

Furthermore, it has also been shown that a small amount (1-2 percent) of the translocated MPNs is taken up by sensory nerve endings in the upper and lower respiratory tract (Elder et al. 2006) which bypasses the blood-brain barrier (Oberdörster et al. 2009, Geiser and Kreyling 2010).

The skin is the largest organ of the human body being the best barrier to the environment. The penetration of the intact skin can be excluded as it has been demonstrated by in vivo studies (e.g. Crosera et al. 2008, 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. Moreover, one has to note the indications that translocation through the dermis of damaged skin (e.g. wounds, sunburn, chronic skin diseases) may be a port for entry in the blood system (Rouse et al. 2007, Borm et al. 2006, Kiss et al. 2008) and thus, at present under investigation (e.g. Bolzinger et al. 2011, Monteiro-Riviere et al. 2011). Since sunscreens and other cosmetics contain titanium dioxide or zinc oxide nanoparticles the question is of high importance if MPNs can penetrate the skin and reach the blood system. This question has initiated a passionate debate in Australia on the use of nanoparticles in sunscreens – especially for children.[5] Also it is not clear, if and in what way nano-silver that comes into contact with the skin, e.g. via anti-odor cloth, cosmetics or anti-bacterial wound covers, is influencing the skin flora (Kulthong et al. 2010).

The gastrointestinal tract (GIT) is a reabsorbing organ with a large and permeable surface. Uptake in the GIT 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. For example, 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 and Diel 1980, Kreyling et al. 2002).There are only very few studies available about uptake of MPNs via the 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. Studies with different kinds of nanoparticles showed that translocation rates and amounts are very low (between 1-3 percent; Elder and Oberdörster 2006, Elder et al. 2006). However, the current lack of data prevents a final evaluation (Krug and Wick 2011). But since more and more food and food related applications become available, this field gains importance. For example, titanium dioxide (E171) and silicon dioxide (E551) have been admitted for decades as food additives and in food production (such as anti-caking agents, thickeners and flocculants) - whereby, it is quite possible that they are also present in nanosize.

MPNs that enter the body will be either eliminated by different mechanisms (e.g. by the lung macrophages) – in dependency of size – or can be distributed via the blood circulation and in some cases by the lymphatic system. Subsequent to inhalation 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). Nevertheless, it is not clear 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.

[5]For example: The August edition of C&EN features an article that discusses current controversy surrounding the use of nanoparticles in sunscreens (available at: http://pubs.acs.org/cen/science/89/8932sci2.html); the ABC online article by S. Lauder "Nano sunscreen warnings won't be mandatory" (available at : http://www.abc.net.au/news/2011-07-20/government-won27t-opt-for-nano-labelling/2803276/?site=melbourne); or the recent Friend of the Earth initiative (available at: http://nano.foe.org.au/sites/default/files/Background%20information%20on%20TGA%20attack%20on%20nano%20labelling%20July%202011.pdf).

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).

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). 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 (Elder et al. 2000, Roller and Pott 2006). Up to now, little is known about the metabolism of MPNs. It was suggested that organic/carbon-containing MPNs will be metabolised 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). Also 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 metabolisation and (iii) immune relevant cells (e.g. macrophages; Gormley and Ghandehari 2009).

2.2.3. Methods for toxicity testing and dosimetry

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. It is intended to replace animal experiments in future (Maynard et al. 2006, Xia et al. 2010, Burello and Worth 2011).

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 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.

Currently, it is one of the main aims of many nanotoxicology working groups to adapt the methods to the special need of MPNs and develop high throughput systems to speed up the hazard assessment process (Hirsch et al. 2011). For example Lin et al. (2011) published the successful use of two high content imaging platforms to enhance the ability to screen the toxicological effects in a time- and dose-dependent fashion of nanoparticles in zebrafish embryos (Lin et al. 2011).

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 (see figure 10). 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 ultrafine particles.

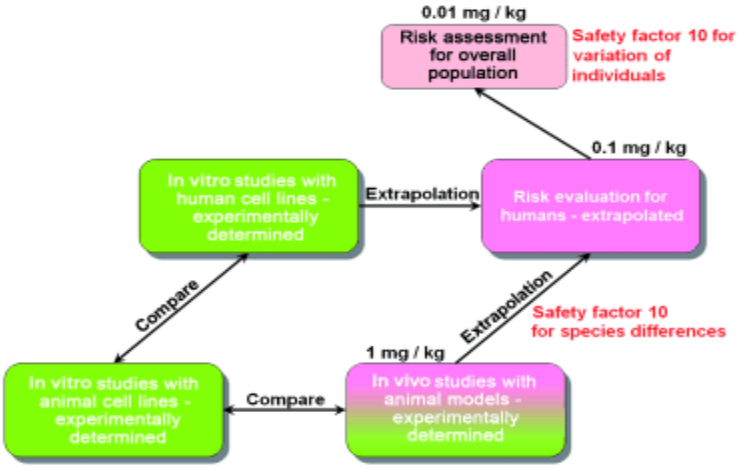

Figure 10: The evaluation process of toxicity of MPNs for humans. The interrelationship between experimentally determined thresholds (assumed here to be 1 $mg\,kg^{-1}$) and the safety factors for the species differences and the inter-individual differences between human beings is shown. This gives a minimum of the factor of hundred for fixing threshold limits for humans. (Taken from Krug and Wick 2011.)

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 and therefore, still very few data are available showing dose-dependent analyses. Recently, Hinderliter et al. (2010) established a computational model which simplifies the dosimetry for in vitro toxicity studies.

2.2.4. Risks to human health and the environment by MPNs

Experts suggest that free nanoparticles might be the greatest at risk for human health. If they find a way inside the body, for example by inhalation, ingestion, or injured skin, then they are potentially able to damage cells and trigger diseases. It seems to be particularly critical, if particles are deposited in a certain area of the lung or body and are (i) neither dissolved and/or metabolised (ii) nor undergoing clearance mechanisms, (iii) or will be enriched in particular areas or even in individual cells causing toxicological effects (Schmid et al. 2009, Geiser and Kreyling 2010).

The mechanisms leading to the toxic effects, however, are quite different for the various MPNs and still not fully understood. One common toxicity mechanism of MPNs is the production of reactive molecules like reactive oxygen species (ROS) (Geiser et al. 2005, Kreyling et al. 2009). At the same time, these so-called "free radicals" are formed as part of the natural metabolism in the human body. Thus, there are cellular mechanisms to scavenge them.

However, if an enrichment of a certain nanomaterial leads to an increased release of these reactive molecules, the organisms might be not capable to remove them. In result, oxidative stress (e.g. lipid and protein oxidation as well as DNA damage) is induced which damage the cell and may lead to cell death or even cancer (Petersen and Nelson2010, Kovacic and Somanathan 2010, Becker et al. 2011). In addition, different intra and extra cellular signal cascades are trigged which inter alia can lead to inflammation, e.g. by the recruiting of immune cells (Elder et al. 2000, Deng et al. 2011). Inflammation is also induced by MPNs that fall under the so-called "fibre paradigm" which means that they behave like hazardous fibres (e.g. asbestos). Macrophages that try to remove those fibres are not able to uptake these structures which finally results in triggering inflammation or inducing genotoxicity (Poland et al. 2008, Bai et al. 2010, Pacurari et al. 2010, Murphy et al. 2011). Chronic inflammation and genotoxicity (damage or changes of the DNA within the cell) leads to fibroses and eventually also to cancer in the lung. MPNs that are able to cross the air-blood barrier of the lung can cause severe cardiovascular effects by a yet unknown mechanism, which was already observed studying ultrafine particles (Oberdörster et al. 2005).

The overarching problem of nanotoxicology, as mentioned above, is the vast number of different MPNs for which – in addition - each size and form of appearance has to be studied individually. Thus, the nanotoxicological community still faces a very limited data basis which allows only preliminary risk assessments, as it was for example stressed by the members of the ENRHES-Team.[6] Thus, conclusions on relative reliable evidence can only be drawn for a small set of abundant materials including carbon nanotubes, fullerenes, nano-TiO_2, nano-Ag and some others (e.g. Aschberger et al. 2011, Hagen Mikkelsen etc al. 2011). The most recent data collection and evaluation is the ENRHES report (2010) and its follow-up publications (Aschberger et al. 2011 and literature therein) which are comprehensive and critical scientific reviews of the health and environmental safety of fullerenes, carbon nanotubes, metal (mainly silver) and metal oxide nanomaterials (mainly titanium dioxide). 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. However, the available studies do not indicate a short term risk from the tested fullerene types, although no extrapolation to all fullerene types and to chronic exposure can be made. It is not clear yet if certain fullerene types may potentially induce genotoxic and/or carcinogenic effects via physiologically relevant routes. Fullerenes of greater water solubility appeared being less toxic. The most relevant exposure seems to be through dermal application of fullerenes present in cosmetics.

[6]See the featured SafeNano-Article "Feasibility and challenges of human health risk assessment for nanomaterials" by Sheone Peters, member of the ENRHES team (July 15, 2011); available at: http://www.safenano.org/KnowledgeBase/CurrentAwareness/FeatureArticles/humanhealthriskassessmentfornanomaterials.aspx

- It was suggested for **carbon nanotubes** that an increasing number of walls, functionalisation and reduced metallic impurities may reduce toxicity, although there are of course other factors to be considered. However, the physico-chemical properties that elicit oxidative stress and inflammation leading to cytotoxicity and disease are still unknown. The genotoxic potential of CNTs is currently inconclusive as well as the possible systemic effects of CNTs that would be either dependent on absorption and distribution of CNTs to sensitive organs or could be induced through the release of inflammatory mediators. Form and suspension of the CNTs also play a critical role. The most relevant exposure seems to be through occupational inhalation.
- The toxicity of **metal nanoparticles** (e.g. nano-silver) is reliant on the entry into the cell 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 general, inhalation seems to cause the most risky exposure to workers and consumers followed by (uncontrolled) drug intake and burn treatments of large parts of the body with nano-silver containing wound dressings.
- In the case of **metal oxides** (e.g. nano-titanium dioxide), it has been demonstrated that its toxicity is of inflammogenic, oxidative, neurotoxic 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. Again, inhalation seems to cause the most risky exposure to workers and consumers (e.g. subsequent to a spray application).

Studying ecotoxic effects of MPNs is rather challenging since environmental conditions have to be either simulated at the laboratory level or have to be investigated within test patches in the environment. But MPNs are hard to measure in biological matrixes and almost untraceable within the environment; thus, investigations of "real life" conditions cannot be performed. Therefore, so called marker organisms are used to test ecotoxic effects under laboratory conditions. Factors that characterise ecotoxicity are similar to those that are identified for human toxicity including biopersistence, chemical or biological reactivity, chemical composition and especially surface functionalisation. However, still 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 in biological matrixes. Also the degradability and the accumulation of MPNs can change the biological effectiveness of the MPNs. Thus, still little is known about fate and behaviour of MPNs in the environment.

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 (Handy et al. 2008a, Handy et al. 2008b, Boxall et al. 2007). For example, it seems that MPNs are passing through the food chain from smaller to larger organisms (Ferry et al. 2009, Zhu et al 2010a,). Within the food chain MPNs can potentially harm already at low concentrations microbes (García-Saucedo et al. 2011, Kool et al. 2011), earthworms (Scott-Fordsmand et al. 2008, Bigorgne et al. 2011) and crop plants (Lin et al. 2009, Foltête et al. 2011, Rico et al. 2011). 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, Barllan et al. 2009), daphnia (Zhu et al. 2009b, Zhu et al. 2010b), 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).

Some attention was put on silver nanoparticles because they are applied to special clothing which prevents odour formation by sweat and bacteria. When washing these clothes, the nanoparticles are released through the waste water into sewage plants and the environment. It is still under discussion whether and to what degree they damage microorganisms there or enter the food chain (e.g. Luoma 2008, Nowack 2010). However, the toxicological principle of nano-silver seems to be the release of silver ions (Choi et al. 2009). Recent ecotoxicological research revealed that these ions as well as the nanoparticles themselves are bound and precipitated by sulfide and other biological ligands effectively (Kaegi et al. 2011). Thus, special wastewater treatment can reduce the ecotoxicity of nano-silver (Kaegi et al. 2011), although nano-silver was classified as "extremely toxic" by Kahru and Dubourguier (2010).

3. CONCERN ASSESSMENT

Concern assessment is a part of the entire risk governance framework and is defined as (see chapter 1):

> "*a social science activity aimed at providing sound insights and a comprehensive diagnosis of concerns, expectations and perceptions that individuals, groups or different cultures may link to the hazard*" (Renn and Walker 2008).

Understanding these different concerns, expectations and perceptions is an important factor in getting to know better how individuals and groups perceive and assess risks, what actions (or non-actions) are perceived as being risky for what reasons and how the different actors risk management and communication are expected to take action. Investigations of the evolving socio-cultural and political context in which research at the nanoscale is conducted, the societal needs that nanotechnology may satisfy and the popular images that experts, politicians and representatives of the various publics associate with nanoscience and nanotechnology (IRGC 2006) are additional elements in improving the societal knowledge about adequate risk management procedures.

3.1. Perceptions, expectations and concerns of the general public

Social science uses different sets of well-established methods to study perceptions of nanotechnology's benefits and risks within individuals, groups or the society as a whole. These methods fall into two distinct categories. The first category covers **quantitative methods,** including surveys which are designed to ascertain large and therefore representative datasets as well as experimental studies using non-probability samples. These methods allow for testing and revising existing hypothesis and making statements about defined groups of people. Typical examples are large, standardised polls within a representative sample of a population. The second category covers rather **qualitative methods** designed to gain insights into individual arguments, ideas or values and to explore new aspects of an issue. Thus, they are designed rather open (not standardised) to capture even unexpected facts. Beside in-depth interviews, focus groups are typical examples of qualitative methods (Fleischer and Quendt 2007).

Generally speaking, the landscape of research into perceptions of nanotechnology and nanomaterials – and the related concerns – among European citizens is somewhat patchy. To our knowledge, representative studies about the familiarity with, attitudes towards and perceptions of nanotechnology covering all member states have only been performed within three Special Eurobarometer surveys in 2002, 2005 and 2010. This research has been complemented with a number of country studies over the last few years (e.g. BMRB 2004, BfR 2008). Since these surveys have used various methodologies and mostly different questions or different question wordings, their results are hard to compare with each other and with the Eurobarometer findings. Notwithstanding these limitations, some general trends have been identified:

- A significant part of the general public (roughly between one quarter and three quarters, depending on country, year and question wording) has never heard about nanotechnology. The temporal change of this situation is still under discussion among scientists. While some researchers claim that the knowledge about nanotechnology is slowly improving over the last few years, others see no change and consider the quantitative results as rather stable.

- Some studies found that the majority of the respondents (numbers range from 60 to 90 percent) have no clear understanding of the terms nanotechnology or nanoparticles.
- Asked about their expectations about the impacts of nanotechnology in general in the future, only a minority (about 10 percent) expect negative effects. However, asked for on a more personal perspective like "effects on you and your family", people tend to be much more worried.
- One reason for this might be the lack of information about risks and benefits of nanotechnology and its applications, as the findings of the qualitative studies suggests. Participants repeatedly asked for more information.

3.1.1. Quantitative results: Eurobarometer Survey 2010

The most recent – and most reliable – representative data on the awareness, expectations and attitudes of the general public towards nanotechnology in Europe can be taken from a 2010 Special Eurobarometer survey on biotechnology (Eurobarometer 2010). This survey covers a representative sample of the population of the respective nationalities of the European Union Member States (plus Iceland, Norway, Switzerland, Croatia and Turkey), resident in each of the Member States and aged 15 years and over[7].

Regarding nanotechnology, respondents had been asked first if they have ever heard of nanotechnology before. **46 % of Europeans have ever heard of nanotechnology, while 54 % have never heard of it.** Looking at the socio-demographic data, they show that gender, education and age are factors. 54 % of men (compared to 39 % of women) have heard of nanotechnology. Most likely to have heard of nanotechnology are managers (76 %), students (60 %) or self-employed people (57 %) as well as persons who left full-time education age 20+ (68 %) and everyday users of the internet (62 %). Least familiar with nanotechnology are house persons (30 %), retired (35 %) or unemployed (38 %) people as well as those who left school at age 15 or below (22 %) and non-users of the internet (25 %). 41 % of Europeans expected a positive impact of nanotechnology on their way of life in the next 20 years, 40 % did not know, 10 % expected a negative effect and 9 % thought that nanotechnology will have no effect.

In order to tap into perceptions of, expectations on and concerns about nanotechnology, respondents were presented ten statements about nanotechnology and asked whether they totally agree, tend to agree, tend to disagree or totally disagree. The statements covered four clusters: perceived benefit, perceived safety/risk, perceived fairness/unfairness with regard to distributional equity and worries related to unnaturalness. Figure 11 presents the results for EU-27.

[7] The survey was carried out between the 29th of January and the 17th of February 2010. All respondents were interviewed face-to-face in people's homes and in the appropriate national language. The sample size (usually around 1000 respondents per country) permits accuracy (confidence interval) of ca. ± 3 percent points.

The original Eurobarometer study provides data by country. For the purpose of this report, we clustered some of the country data into regional data, attempting to present ten regions of roughly comparable population size and similar economic structure and culture in a more accessible graphic. The ten regional clusters were formed as follows: Northern Europe (Iceland, Norway, Denmark, Finland and Sweden), Benelux, UK &Ireland, France, Iberian Peninsula (Spain & Portugal), Central Europe (Germany, Switzerland and Austria), Southern Europe (Italy & Malta), Eastern Europe (Poland, Czech Republic, Slovakia, Hungary, Estonia, Latvia and Lithuania), South-Eastern Europe (Slovenia, Croatia, Romania, Bulgaria, Greece and Cyprus) and Turkey.

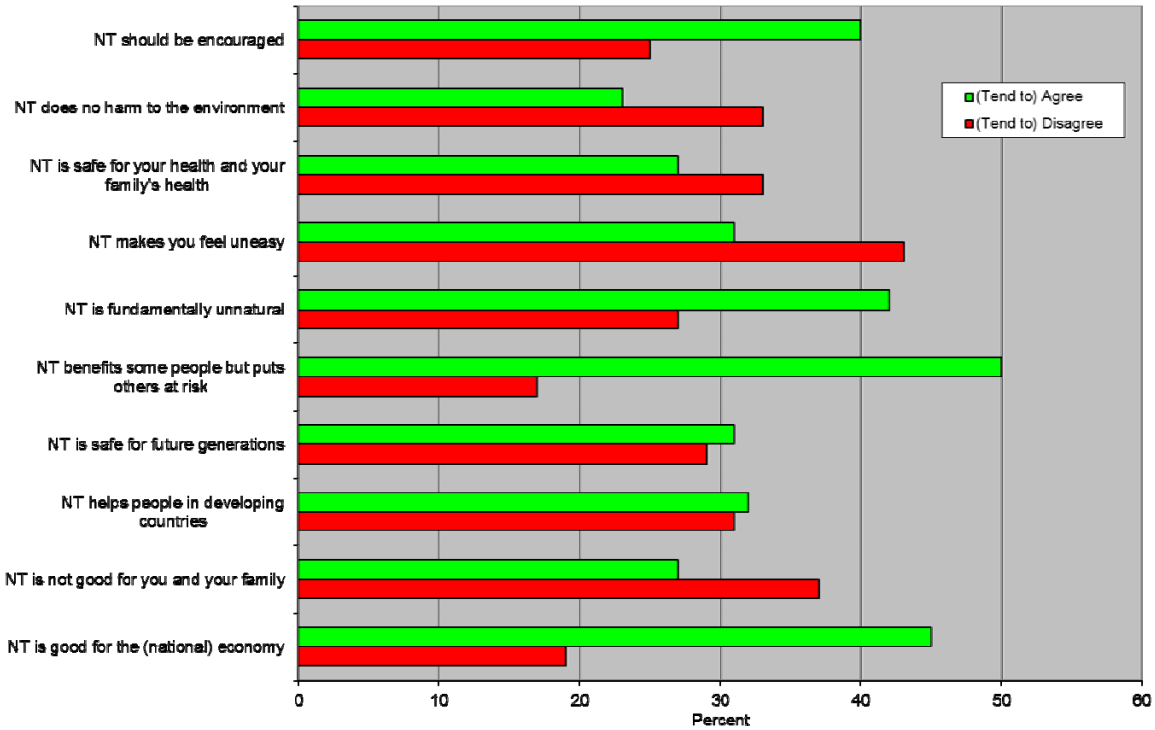

Figure 11: Perceptions of nanotechnology, EU-27, Fieldwork Jan/Feb 2010. Data were taken from Gaskell et al. 2010. For the sake of clarity, we have summarised the answers in two groups (agreement and disagreement). Please also note that – on average – one third of the respondents the numbers answered "don't know", therefore the numbers don't add up to 100 percent.

Of special interest within the context of the NanoSafety project (the environmental, health and safety risks of manufactured particulate nanomaterials) is respondents' perceived safety/risk of nanotechnology[8]. The next two pictures summarise the answers on the two statements "Nanotechnology is safe for your and your family's health" and "Nanotechnology does no harm to the environment." (Figures 12 and 13)

[8] We would like to point out that here a scientific controversy arises. On the one hand, one might argue that large surveys – like this Eurobarometer study - usually ask about statements regarding nanotechnology in general. It remains unclear to which part of the multifaceted concept of nanotechnology the respondents in these surveys refer and how these answers are (or, from a scientist's perspective, can be) related to the more specific perceptions and concerns with regard to manufactured particulate nanomaterials. On the other side, research using qualitative methods (see below) shows that most laypeople do not clearly discriminate between nanotechnology and nanomaterials. More often than not,they link EHS risks of nanotechnology to the application of nanomaterials in various products and areas, therefore "nanotechnology" could be read as a synonym for "nanomaterials" within this context. In addition, to our knowledge, large surveys specifically dedicated to knowledge about and attitudes towards manufactured particulate nanomaterials have not been performed so far among EU member states. We therefore found it allowable to present the Eurobarometer data on safety/risk perception as a concern indicator and to give the reader a general impression of the perception of nanotechnology in the general public.

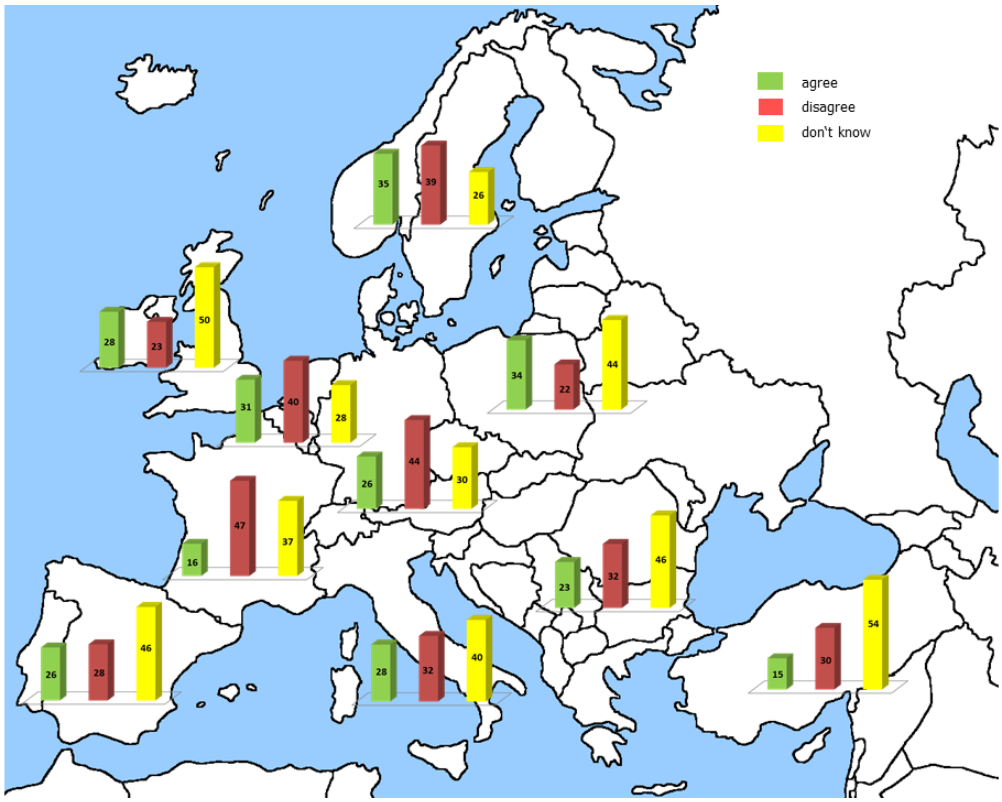

Figure 12: Eurobarometer 2010: Answers on statement "Nanotechnology is safe for your and your family's health" in various European regions in per cent

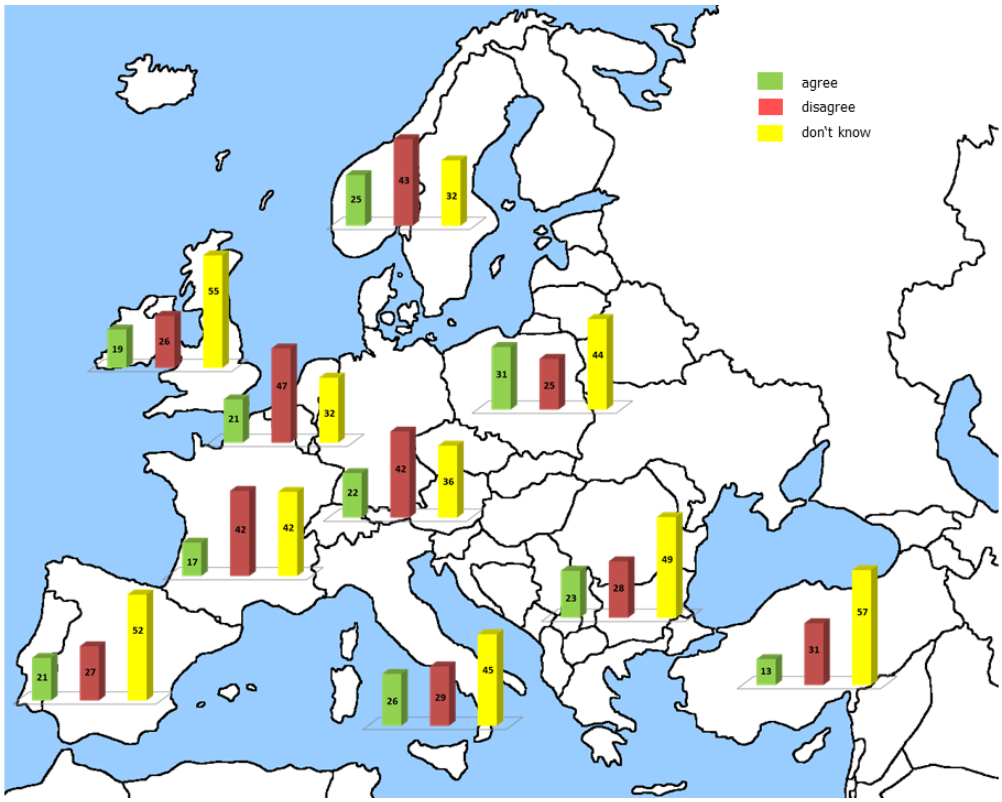

Figure 13: Eurobarometer 2010: Answers on statement "Nanotechnology does no harm to the environment" in various European regions in per cent

As a general impression at the European level, **one third of the respondents believed that nanotechnology may do harm to the environment, is not safe to human health and is not safe to future generations, respectively**. One third expressed an opposite view and one third did not know. A more regional perspective shows interesting differences: The higher the number of respondents that have already heard about nanotechnology is in a certain region, the higher is the number of respondents that don't agree that nanotechnology is safe to their health and agree that nanotechnology will do harm to the environment. On this highly aggregated level, there seems to be a positive correlation between perceived knowledge about and perceived risk of nanotechnology[9], an observation that has to be confirmed by future in-depth research.

Surprisingly, in a number of countries, the percentage of respondents who express an opinion about perceived safety/risk of nanotechnology is even higher (statistically significant) than the percentage of respondents that have already heard about nanotechnology. In other words, the perceptions of some respondents appear to be based on factors other than factual knowledge about nanotechnology.

A more detailed analysis was provided by Gaskell et al. in an accompanying report to the Eurobarometer survey, presenting research from the FP7 project "Sensitive Technologies and European Public Ethics" (STEPE). They found that, across the European public, "*the balance of opinion is that nanotechnology is somewhat more likely to be beneficial than not, to be unsafe rather than safe, to be inequitable rather than equitable, and not particularly worrying (though, equally, not particularly unworrying)*" (Gaskell et al 2010). They also showed that **perceived safety is by far the most influential variable on overall support of or opposition to nanotechnology**, followed by benefit, worries related to unnaturalness and lastly inequity.

3.1.2. Qualitative results: Observations in public engagement exercises and in dedicated focus group studies

Additional insights for studying perceptions and concerns related to nanoparticles can be gained from the results of qualitative methods. Various participatory projects (e.g. NANOBIO-RAISE, DEEPEN, TIME for Nano, German NanoCare, Austrian Risiko:dialog, Danish Survey of 2004, UK "Nanotechnology, Risk and Sustainability", Dutch Nanopodium, or Swiss Publifocus) included qualitative methods such as interviews or focus groups. For details with respect to organisation and special topics of these events see Deliverable 5 of Phase III report (STOA 2011b).

For this report, we attempted to integrate the outcomes of these projects with those of our own focus group exercises (Deliverable 3+4 of Phase III, STOA 2011a) and to present them in an accessible manner. The reader should note that this endeavour faced some challenges. On the one hand, the available material is very heterogeneous with regard to methodological approach, depth of analysis as well as quality of documentation (STOA 2011b). Moreover, only one of the projects that were using qualitative methods was focused explicitly on conceptions and concerns regarding MPNs: the focus groups that were conducted within the German "NanoCare" project (Fleischer and Quendt 2007) while the remainder was dealing with nanotechnology in general. On the other hand, the collection of citizen's expectations regarding improvements gained through the application of nanotechnologies as well as of citizen's concerns provides deeper insights into factors that contribute to their individual risk perception and judgements and – at least partially – shape individual and public acceptance. We have clustered expressed perceptions and concerns of citizens along the following main aspects.

[9] Please note that these observations do not allow for inferences on the level of individuals.

Human health:

- Improvements: disease prevention; early disease detection or medical treatment; benefits of medicinal applications
- Concerns: potentially adverse health effects (mainly due to inhalation);entry of MPN into the human body due to their very small size; scientific uncertainty regarding the behaviour of nanoparticles in the human body; uncertainties with regard to risk assessment

Environment:

- Improvements: energy conservation; pollution prevention and remediation; efficiency gains in production due to miniaturisation effects; cleaner manufacture with less emissions and less waste; nanotechnology-based environmental technology applications; devices for waste water treatment; substitution of classical hazardous chemicals
- Concerns: uncontrolled release of manufactured nanoparticles into the environment; possible occurrence of nanoparticles in ground water and in air; life-cycle impacts; energy and resource intensive manufacturing of nanomaterials; problems in the recycling and disposal phases, especially considering disposal and behaviour in wastewater treatment; possible enrichment in the food chain

Acceptance:

- The vast majority of people still have little or no idea of what nanotechnology is or about its possible implications. Despite this, members of the public have already expressed similar concerns to those associated with other technologies perceived as being risky, particularly around governance structures and corporate transparency. Many citizens were astonished about the broad scope, spectrum and extent of 'nanoproducts' already available. Many discussants arbitrarily mixed their terminology and used nanoparticles, nanotechnology and sometimes also 'nanoproducts' quasi synonymously. They stated that due to the lack of knowledge, a reasonable balancing of chances versus risks is not possible. They were concerned about the transparency of communication, credibility and trust. Almost all refused the application of nanoparticles in the food sector. Concerning food, every manipulation and deviation from natural growth was met with scepticism and even suspicion. The citizens were less reluctant to the use of 'nanoproducts' in cosmetics and other sectors.

Access:

- Concerns: expensiveness of nanotechnology and limiting access to those who could benefit the most (unequal access), widening the divide between the industrialised and the developing world, root causes of the original challenges

Privacy:

- Concerns: the collection of increasingly sensitive data in medical diagnostics is likely to raise serious questions about information provenance and distribution, convergence with information and communication technology could have possible threats to civil liberties from increasingly advanced surveillance capabilities, enabled by nanotechnologies

Liability:

- Concerns: subsequent developments may be as much in the hands of users as the innovators and could be used in ways not originally intended, the complexity of the product life cycle of nanotechnology applications may make it difficult to establish a causal relationship between actions of a company and any resulting impact, questions about sufficient liability frameworks

Regulation and control

- Concerns: whether existing regulatory regimes are robust enough to deal with nanomaterials, or whether new regulation is required; the right balance between a responsible development and safe use of nanomaterials
- Like other emerging technologies that are tightly linked to basic scientific research, nanotechnology generates intellectual property that is perceived as valuable and thus protected by patents. There is an obvious trade-off between the various laws, regulations, and treaties that govern the relationship between the public good and the protection offered by patents.
- The most important measure suggested by the participants in focus groups was labelling, which serves as a basis for deliberation and choice as well as to obtain additional information on their use, risk and appropriate disposal. But they also agreed that the consumer needs information ahead of a purchase decision: information about the (potentially) hazardous nature of a nano-ingredient, enabling the consumer to interpret the label and to allow a risk-benefit consideration. Several participants are worried about the safety of consumer products and the lack of concrete regulations. Few citizens explicitly demanded a definitive ban (a moratorium) of all 'nanoproducts'. Other participants thought of the possibility to subject 'nanoproducts' to a (governmental) permission after they were proven to be harmless. They concluded that an authorisation process and the obligation of long term studies would make a moratorium unnecessary.

Independent, international research:

- research should be organised and performed by international, independent authorities, by universities, or state-run institutions; increase of funding for safety research

The various aspects of concerns and perceptions found in our analysis of the outcomes of qualitative methods support, deepen, and refine the findings of quantitative surveys (like in the Eurobarometer survey), especially with regard to the possible harm to health and environment, safety aspects as well as more general feelings like "uneasiness" and "unnaturalness". Further concerns are dealing with the trustworthiness and credibility of information and measures and desired communication requests. In connection with quantitative results they allow for reliable assessment of the concerns – and their basis – within the general public. They also support the findings of Gavelin et al. (2007) who analysed and discussed the results of dialogues projects dealing with nanotechnology in general, like Nanologue or SmallTalk. Gaining and maintaining public trust under conditions of scientific uncertainty seems to be the key element of the debate on perception and acceptance of nanomaterials. Openness and transparency are factors that have proven to be helpful in achieving this objective. Gavelin et al. found that the general public supports nanotechnologies that are linked to a wider social good and that it is concerned about known and unknown risks as well as the ability of government and private sector to manage those risks.

The public calls for more open decision-making about nanotechnologies. Risk communication strategies should enable a two-way communication. A transparent discussion should make issues ranging from informed opinions of scientific aspects including risks and benefits over clear and transparent description of the approach of regulation and funding up to the information on who has the responsibility to regulate and support nanotechnology available to the public (Gavelin et al. 2007).

3.2. Positions and concerns expressed by Stakeholders

The various stakeholders that took position in the negotiation around "nano" could be divided into the main groups of civil society organisations (CSO), industry and academia. CSO themselves include consumer groups, trade unions and environmental groups. In order to compare the concerns expressed by the general public with the positions and concerns of different stakeholders their statements in the "nanodebate" to ethical and social aspects, uncertainty and regulation as well as transparency and public engagement will be outlined in the following subchapters.

3.2.1. Ethical and social aspects

CSO are concerned that aspects like access, privacy, patenting or equity are not yet addressed appropriate in the debate around nanotechnology and nanoparticles. Especially environmental groups expressed concerns about patenting issues, levels of industrial control and exclusion of those with legitimate interests from the decision making. Also representatives and organisations of the churches feel themselves being responsible to introduce ethical and social aspects into the debate about benefits, risks and the governance of nanotechnology. The justice issues "nano and the poor" play only a tangential role for the CSOs in Europe at this time – in contrast to other parts of the world.

Stakeholders from academia addressed ethical and social issues especially in the area of social science and technology assessment. Representatives from industry consider these aspects in single risk assessment approaches.

3.2.2. Uncertainty and regulation

CSO are concerned about potential effects of MPNs on human health and the environment. In addition, they are worried about existing uncertainties and an insufficient knowledge base on exposure, hazard and life cycle assessment. One of the issues most of the CSO are interested in is an assessment of the actual market situation of nanomaterials and nanoproducts in order to be able to estimate to what extent consumers, workers and the environment are exposed to and potentially affected by MPNs. Some trade unions doubt that workers are sufficiently protected during workplace activities involving nanomaterials and that the labour safety inspectorates have sufficient knowledge on nanotechnology to evaluate this. Moreover, they criticise the missing information on the occurrence and EHS risks of MPNs, e.g. on safety data sheets or by the employer. As a consequence, they call for an increase of safety research and a (partial) moratorium for the marketing of certain products.

With respect to the regulation of nanomaterials, CSO expressed the following concerns:

- current legislatory framework is not sufficient and not nano-specific
- precautionary principle has not been taken into account sufficiently
- a harmonised, clear and sufficiently broad definition is missing

CSO recommend a definition scoped broader with regard to size, also including aggregates and agglomerates. They stipulate mandatory measures, especially a general labelling obligation and a harmonised traceability system. Some even call for a (temporary) moratorium of nanoproducts.

The presentations and statements of **scientists** during dialogue events as well as their publications present single results or overviews of their own work with occasional reference to the results of other groups and colleagues. Some scientists also introduce own risk judgements or even recommendations for regulatory action. The epistemic status of these judgements and recommendations as well as their role in risk communication is controversial. Only very few studies have dealt with individual MPN risk perceptions of scientists – the basis for an analysis of risk judgements – and these empirical studies certainly need further validation and refinement. Scientists' positions show a great plurality due to tacit knowledge on methodological and technical problems, knowledge about research groups and experimental experience. Also disciplinary and individual standards, quality measures and assessment bases of individual scientist vary (STOA 2010).

On the professional side, scientists frequently point out the limitations in current methods of detection and characterisation of MPNs, missing standard methods in hazard and exposure assessment as well as other. One can speculate that the presentation of these results and its potentially "alarming" conclusions also express the concerns of the respective scientists. Notably, those arguments are picked up by other stakeholders groups within the discussions around "nano" if it comes to EHS risks of MPNs and knowledge gaps concerning EHS risk assessment. In consequence, scientists wish a more differentiated picture of nanotechnology and nanoscience in this debate and more funding of the relevant research field to address the uncertainties. They support a science based definition with a narrow size scope and conditional exceptions (inclusion of aggregates and agglomerates). Governance issues are addressed at the utmost by social science and the technology assessment community.

The lack of knowledge concerning the EHS effects of MPNs is also a real challenge for **industry stakeholders**. Due to the enormous potential of nanotechnological applications for new and innovative products, potentials for more sustainability in resource and energy use as well as the substitution of hazardous substances – and therefore the innovation and competitiveness of the companies as well as economic growth, they have invested already large sums into research and development of 'nanoproducts'. The industry wants to take advantage of these potentials and doesn't want to lose those R&D and other investments in their nanotechnological applications. Therefore, there is an urgent need for regulatory reliability and stability. Since it is still under discussion where the burden of proof for the environmental and health safety of nanomaterials and nanoproducts lies – and how this will be translated into regulatory practices -, industry stakeholders urge the politics to establish a reliable regulatory framework.

Large companies and industry associations are well aware of the potential EHS risks and uncertainties of their nanotechnological applications, although they only rarely express EHS concerns in their public communication directly. In stakeholder dialogues, they sometimes touch this field briefly – usually in order to introduce their approaches on safe handling of MPNs or their risk assessment procedures. In any case, they don't contradict the findings of the toxicologists – although they are sometimes questioning the adequacy of certain test procedures and systems and the evidence of the findings.

A support of this observation might be seen in the fact that several companies (e.g. BASF, Degussa, Bayer, Coop, Unilever) and industrial associations (e.g. IG DHS, NIA, VCI) developed – or were involved in the development of – codes of conducts or guidelines for the responsible production, handling and use of nanomaterials as well as risk management systems.[10]

Members of the industry claim that all products are assessed appropriately and judged to be safe before entering the market if "standard working hygiene" is applied[11]. They highlight the high standards of worker and environmental protection and the development of practical risk assessment approaches and safe handling guidelines. They emphasise the importance of regulatory stability and a narrow scope of the definition of the term "nanomaterial" with regard to size and without a general inclusion of aggregates and agglomerates.

In contrast to manufacturing companies, **third-party economy actors** like (re)insurance companies are rather able to be much straighter in naming potential risks of nanotechnology and MPNs. They cannot afford to ignore potential EHS risks for workers, consumers or the environment since in the case of damage they would lose a lot of money. Thus, they request politics to work out a binding regulatory framework and their customers to act responsible in order to avoid any risks of damage and loss.

3.2.3. Transparency and public engagement

Representatives of the CSO are concerned that available information about risks and benefits is often unbalanced and that it is unclear whether products contain MPNs or not. Especially the consumer CSOs advocate informed and free decisions based on an individual risk-benefit-calculation. In addition, the communication of the industry is perceived as being insufficient. They even mistrust some claims of the industry (e.g. "green nano" and safety claims) and call for more transparency and information as well as product labelling and registries. CSO foster dialogues involving all stakeholders for equity of decision making and public participation. They prefer a participatory process of decision making to be put in place that allows for citizens to engage in decisions which will have an impact on their everyday life.

Academia expressed concerns with respect to a precautionary-oriented transparency, especially in the area of social science and technology assessment. The decision making process should be based on scientific arguments. Participatory events involving all stakeholders are interesting from the scientific point of view and may make a valuable contribution to the process.

Corporate social responsibility (CSR) reports addressing nanotechnology specifically, a corporate nanotechnology policy communication, or contributions to stakeholder dialogues were only found by a small number of companies of the chemical industry or industrial goods supply (e.g. BASF, Degussa, DuPont).[12]

[10] For Germany, a summary can be found in the Report of the Issue Group 1, Annex 3, 2011. See also ObservatoryNano First Annual Report Chapter 3, available at: http://www.observatorynano.eu/project/filesystem/files/annrep1responsibility1.pdf.

[11] Discussions in stakeholder dialogue events, e.g. the Nanosafety for Success Dialog of the European Commission in 2011.

[12] According a quick and non empirical scan of Volker Türk (Wuppertal Institute) in spring 2007 (Türk et al. 2007). Available at: http://www.nanologue.net/custom/user/Allgemein/0703_ENTA_CSR-Nanotech_website.pdf (accessed July 2011). See also Chis Groves (Brass) "Nanotechnology in the UK, 2011-2020: A Delphi Exercise" (2011). Available at: http://www.brass.cf.ac.uk/uploads/NanotechnologyintheUK_ChrisGroves.pdf (accessed July 2011).

While those companies seem to identify nanotechnology as a challenge for their communication with the public and for their aim to be recognised as a company that handles EHS issues responsibly, most producers of consumer products market their 'nanoproducts' with only very little communication on nanotechnologies in general and especially without any specific information on the potential risks of the materials used in their products. Especially a number of food sector representatives insist in claiming that there are no MPNs used in food available on the European market, while others state that nanoparticulate food additives are used only "to a minor degree". Industry groups claim that consumer information is sufficient and their communication proactive. They emphasise that their intellectual property rights and patents might be violated if more transparency becomes mandatory. Transparency and labelling would only be necessary for hazardous substances. They support public 'participation' but prefer stakeholder dialogues[11].

3.3. Summary of positions

Risk appraisal of nanomaterials is a multifaceted step in the entire risk governance framework. It consists of a – more or less - classic scientific risk assessment with respect to hazard or exposure and an assessment of concerns considering risk perceptions, social concerns and socio-economic impacts. These two elements usually include different actors and underlie different systemic views, methodologies and interpretations of the results. The challenge for the entire risk appraisal is the identification and understanding of the relations and mutual impacts of the different approaches.

Chapter 3.1 gives a systematic, but due to only little available research data somewhat limited, analysis of the perceptions, expectations, concerns, opinions and attitudes of the general public with regard to nanotechnology and nanomaterials. From the results of different quantitative and qualitative methods it could be deduced that the main aspects of concerns are related to the possible harm to environment and human health (EHS), the dealing with (scientific) uncertainty and general feelings like uneasiness or unnaturalness. Further, there are ethical and social concerns including access, privacy and patenting, the question of sufficient and adequate information and communication, the possibility of public participation in the decision making process and, after all, concerns about adequate regulatory measures. People in general were open-minded about improvements promised by - and expected benefits of – nanotechnology, as long as the concrete person has no obvious disadvantage.

In chapter 3.2 it was shown how the different stakeholders pick up the main concerns expressed by members of the groups they represent, and how the various aspects are formed to specific combinations of concerns, considering priorities and abstractions of their specific motivations. They formulate requests and recommendations for further handling of risk and improvement of governance procedures, considering the raised concerns. Other stakeholders from industry and academia enter the negotiation scene actively with additional specific arguments, or are consulted by the stakeholders. In Table 2, we have attempted to summarise the positions of the stakeholders.

Finally, the question remains how these results, which bear controversies and potential conflicts, could be intertwined with the procedures of political decision making and risk governance. Doubtless, there is no simple procedure or even a panacea for the "translation" of concerns into recommendations and concrete measures However, for framing possible aspects and balancing inputs from all actors, the described methods of the concern assessment are a first step and its results are recommended to be included in the decision making process regarding risk appraisal and risk governance of nanomaterials and nanotechnologies.

CSO	Academia	Industry
Call for an increase of safety research and (partial) moratorium for the marketing of certain products	Call for an increase of research funding.	Development of risk assessment approaches and safe handling guidelines
Call for mandatory measures including a general labelling obligation and a harmonised traceability system Some even call for a (temporary) moratorium Call for a broader scoped definition with regard to size, also including aggregates and agglomerates.	Support for definition that is based on a defined narrow size scope with conditional exceptions (inclusion of aggregates and agglomerates)	Support voluntary measures like codes of conduct and guidelines for safe handling. Case by case decisions and assessment by scientific agencies that consider e.g. application conditions may be appropriate instruments.
Foster dialogues involving all stakeholders for equity of decision making and public participation.	Support dialogues involving all stakeholders.	Foster stakeholder dialogues - but public 'participation' only with an informative character

Table 2: Summary of the most prominent positions of different stakeholder groups on the main issues in the "nanodebate".

4. RISK MANAGEMENT

Risk management is a dynamic and complex decision-making process *"involving considerations of political, social, economic, and technical factors with relevant risk assessment information relating to a hazard so as to develop, analyse, and compare regulatory and non-regulatory options and to select and implement appropriate regulatory response to that hazard."* (OECD 2003) Numerous actors are involved like national and international authorities, local communities, businesses, stakeholders and the society as a whole. The process includes the identification, implementation, generation, assessing and monitoring of risk management options (IRGC 2006, Renn and Walker 2008). This report focuses only on the identification of current parliamentary regulation practices in the EU and, in addition, on voluntary measures, discussing efforts, limitations and open gaps in detail.

4.1. Political action in the face of uncertainty

New emerging and innovative technologies like nanotechnology create new challenges for the legislator, not least when the associated products and processes raise concerns about health and environmental hazards and risks. The challenges and problems related to nanomaterials and its applications as well as adequate regulatory needs and approaches are discussed among stakeholders and policymakers for almost a decade. The key issues have been discussed in the scientific literature (see e.g. Hodge et al. 2010) as well as in the previous chapters of this report:

- a wide variety of materials and applications are summarised under the umbrella term nanomaterial or nanotechnologies, without broadly agreed general scientific and/or legal definitions (see also chapter 1.3)
- limited scientific knowledge about EHS risks related to nanomaterials (chapter 2) and the epistemic problem of "unknown unknowns"
- a lack of harmonised specific guidelines and standards and validated test methodologies
- ongoing scientific and stakeholder debates about appropriate existing regulatory instruments and regulatory gaps ("case by case" approach, regulatory triggers, distinction compared to macroscopic variants of the same substances)
- adoption of an adequate 'precautionary approach' that allows to mediate between different expectations on safety standards, scientific uncertainties, knowledge about impacts of the production and use of nanomaterials and commercial exploitation
- balancing innovation and safety, governmental provisions, stakeholder engagement, public participation
- transparency and trust, lack of an inventory of products already on the market, including food, cosmetics, textiles, nanomedicine, electronics, composite materials, coatings, agrochemicals, pesticides and biocidal products (see also chapter 3)
- balancing mandatory and voluntary strategies, increasing the self-responsibility of manufacturers and voluntary safety-standards

Individual and institutional positions with regard to these issues shape the selection and design of risk management measures. The following chapter gives an introduction and overview on selected challenges and concepts in risk management.

4.1.1. General principles and approaches for nanospecific regulation

Precautionary principle:

The precautionary principle is firmly established as a component of the aim of the European environmental protection and the principle of sustainable development in international law. Article 191 of the Lisbon Treaty states that:

"Union policy on the environment (…) shall be based on the precautionary principle and on the principles that preventive action should be taken, that environmental damage should as a priority be rectified at source and that the polluter should pay."

The European Court of Justice explicitly considers the precautionary principle to be a general principle of EU law. The European Commission issued a Communication on the precautionary principle in 2000 (CEC 2000). With that, it adopted a procedure for the application of this concept but avoided to give a detailed or even legal definition of it. According to this document, the precautionary principle basically has the effect of legitimising government measures in any situation where there is **uncertainty**. According to this view, the precautionary principle may be applied particularly in cases where the available scientific evidence is insufficient, inconclusive or unclear, but where there are **indications through preliminary objective scientific risk assessment** that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the high level of protection prescribed within the EU (CEC 2000, p. 10). **The precautionary principle thus makes it legitimate for the government to take action where a risk to the environment or to human health – in other words an abstract concern – is present**:

„Accordingly, the precautionary principle must be applied in practice particularly in cases where, based on impartial scientific evaluation, there is cause for concern that the potential hazards for the environment and for the health of people, animals or plants are not acceptable or could be irreconcilable with the high level of protection."(CEC 2000)

Application of the precautionary principle in risk management

In principle, government institutions must take preventive action if a hazard to human health and life or to the environment is present. A hazard is deemed to be present if, on the basis of the available scientific knowledge, and taking into account forecasts and empirical knowledge, there is sufficient **probability** of harm occurring. **The abstract possibility of harm occurring is not sufficient in itself**, however, for assuming that a hazard is present.

In situations – as is often the case with innovations, including the use of newly discovered or developed substances or materials – where a lack of experimental and scientific evidence does not permit to establish a sound connection between a technology, substance, product or production process and an adverse effect, it is not possible to assume that there is sufficient probability. To enable the state to take action in such situations, the complex task of **risk prevention** has been introduced alongside that of **hazard control**. In this context the precautionary principle plays a key role. Correspondingly, the concept of risk is the focus of attention here rather than that of hazard. This is understood to mean a situation in which harm is merely possible; in other words, **where there are abstract grounds for concern that harm might occur**.

There must therefore be "indications through preliminary objective scientific evaluation that there are reasonable grounds for concern" (CEC 2000).

This means that for the purposes of risk prevention it is legitimate for the state to take measures if there is merely an abstract possibility, rather than sufficient likelihood, of harm occurring. As a result, the point at which intervention becomes permissible is brought forward, enabling the government to take action before the hazard threshold is reached. The threshold for action in cases characterised by uncertainty, or the absence of conclusive evidence, under the law is reached when the possibility of a future adverse event occurring can be ruled out in practice, albeit not with absolute certainty (BMU 2011b).

An unclear outcome due to scientific uncertainty or due to a non liquet situation[13] with contradictory conclusions raises the question with whom the **burden of proof** lies. In these cases, the burden of proof is reversed to enable the legislator to make provisions on the basis of the precautionary principle. Blanket reversal of the burden of proof, however, is not possible on epistemological grounds. It is sufficient if the established and reported facts provide sound indications that there are potential risks and potential hazards. **If there are reasonable grounds for concern on this basis, responsibility for rebutting the presumption of hazardousness and disproving the grounds for concern falls to the originator of the risk**.

Once decision-makers have concluded that there are grounds for recourse to the precautionary principle, they must decide on how to act. If action is deemed appropriate, a wide range of options is available. These include not only **legally binding measures**, but also **research funding, public information campaigns on the potential negative consequences of a product or process, or making recommendations** (CEC 2000 p. 4). Legally binding measures that might come into consideration range from **information, reporting and labelling obligations to rules relating to liability and mandatory prior authorisation requirements**. If a mandatory prior authorisation requirement is introduced, measures under the precautionary principle could include exposure limits. A provision could be included stipulating that the manufacturer or user must provide information relating to any uncertainties concerning hazards associated with a substance, product or process, and elicit or generate the scientific evidence demonstrating that a substance, product or process is non-hazardous (permitted under CEC 2000 p. 25). In all cases, new scientific information concerning the substances, products or technologies in question must be elicited or generated through monitoring as a precautionary measure.

If the public decision-makers take action, any measures must be consistent with the fundamental principle of economic freedom, proportional to the chosen level of protection, non-discriminatory in their application, and consistent with similar measures already taken. In addition, the costs and benefits of action or inaction must also be taken into account in the decision-making process. Any measures taken must be reviewed as soon as new scientific data become available. All interested parties should be involved as fully as possible in the regulatory decision-making process, and the procedure must be as transparent as possible (CEC 200 p. 4f).

[13] In procedural law, "non liquet" describes a situation in taking of evidence in which neither the position of one side nor the position of the other side can be proven, i.e. where cannot be concluded that the ultimate fact is true or not even after giving all available pieces of evidence.

With regard to the application of the precautionary principle in the regulation of nanotechnologies (and nanomaterials), the German NanoKommission found that *"the precautionary principle plays an important role in the introduction and use of nanotechnologies, especially as knowledge is largely lacking with regard to any hazards they may pose. The principle is useful for the identification and assessment of both opportunities and risks posed by this technology. Applying the precautionary principle is both necessary and justified in the context of regulating nanomaterials, as there are scientific indications (grounds for concern) that the use of nanomaterials may have adverse effects on human life and on the environment. This gives grounds for an abstract concern with regard to nanomaterials."*

4.1.2. The challenge of a regulatory definition for the term 'nanomaterial'

The public and political debate on the regulation of nanomaterials is struggling with the challenge of defining its own subject. Over the last ten years, a number of definitions of the term 'nanomaterial' have been proposed by various institutions in different contexts, but they vary between each other[14], some partially conflict or are inconsistent. It proved to be difficult to reach a general consensus among the different parties involved in the process. Not least because of this situation, the European Parliament in its resolution of 24 April 2009 called, inter alia, 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). In reaction to that, two almost parallel procedures have been started at the European level: one by SCENIHR that provided its scientific opinion for a definition and the other by JRC. The different positions could be summarised as follows:

Position: JRC

The European Commission's Joint Research Centre (JRC) has published a report in July 2010 (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 in chapter 1.3 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. 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,

[14] This also holds true for existing or proposed European regulation: The regulation for cosmetic products (EC/1223/2009) defines nanomaterials as "*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*." In the – recently failed – recast of the Novel Foods Regulation as well as in the new Food Information Regulation, 'engineered nanomaterials' mean "*any intentionally produced material that has one or more dimensions of the order of 100 nm or less or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic of the nanoscale*." Future regulations – like the one on biocidal products – will most likely refer to the Commission Recommendation concerning the definition of nanomaterial (see box).

- enforceable,
- and in line with other approaches worldwide (e.g. ISO, OECD).

JRC proposed an upper size-limit of 100 nm. This would include all primary nanoparticles but not the possible agglomerates, complex nanomaterials or nanoparticles with coatings. JRC also proposed the use of the term "particulate nanomaterial" instead of "nanomaterial". 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.

In a reply to an article recently published by Andrew Maynard - Director of the Risk Science Centre at the University of Michigan - in which he argues that basing regulations on a term with no scientific justification will do more harm than good (Maynard 2011), JRC has defended its position regarding the need to define the term 'engineered nanomaterials' for regulatory purposes (Stamm 2011). **JRC concludes that there is an urgent need for a definition of nanomaterial, more specifically "particulate nanomaterial",** which can be used in a regulatory framework. Such a definition should not seek to identify hazardous materials, but should assist industry and regulators in identifying where specific safety assessments might be necessary.

Position: SCENIHR

In March 2010 SCENIHR had received a mandate to provide advice on the essential scientific elements of an overarching working definition of the term "nanomaterial" for regulatory purposes. In the final opinion on the 'Scientific Basis for the Definition of the Term "Nanomaterial"' SCENIHR concluded that (SCENIHR 2010).

- Whereas physical and chemical properties of materials may change with size, there is **no scientific justification for a single upper and lower size limit** associated with these changes that can be applied to adequately define all nanomaterials.
- There is scientific evidence that no single methodology (or group of tests) can be applied to all nanomaterials.
- Size is universally applicable to define all nanomaterials and is the most suitable measure. Moreover, an understanding of the size distribution of a nanomaterial is essential and **the number size distribution** is the most relevant consideration.

In order to define an enforceable definition of 'nanomaterial' for regulatory use it is proposed to set an upper limit for nanomaterial size and to add to the proposed limit additional guidance (requirements) specific for the intended regulation. Crucial for the guidance is the extended description of relevant criteria to characterise the nanoscale. Proposed important criteria should be:

- 0.15 number % (=3 x standard deviation) of nanoobjects (< 100 nm)
- Distinction between intentionally manufactured, engineered manufactured, man induced or naturally occurring nanomaterials
- VSSA (volume specific surface area) > 60 m^2/cm^3 (only for dry powders)

In addition, one has to take into account that solely referring to size as "one or more external dimensions" will not capture aggregates and agglomerates of primary particles. On the other hand, a possible inclusion of a reference to "internal structure" would also include multicomponent assemblies or nanoporous and nanocomposite materials. In order to specifically designate purposely made nanomaterials within regulation, the term 'engineered' or 'manufactured' may be used. On the question of a single upper limit, the SCENIHR opinion differs from the suggestion of the JRC (JRC 2010). SCENIHR concluded, that "there is no scientific evidence to qualify the appropriateness of the 100 nm cut-off, it is important to consider the whole nanoscale metric (1 – 999 nm)".

In a statement on the SCENIHR opinion, the Nanotechnology Industry Association noted that the implementation of this definition would result in up to 90 % of the current commercial materials to be defined as 'nanomaterials'. Moreover, the threshold would not represent a readily provided technical specification criterion of a commercial material[15].

Resulting Commission Recommendation on the definition of the term "nanomaterial":

In autumn 2010, the Commission introduced its Draft Commission Recommendation on the definition of the term "nanomaterial" and invited the public to comment upon it. The consultation was for 30 days, finishing on the 19 November 2010. It has drawn considerable interest and collected almost 200 contributions from stakeholders from all spheres (132 business, 8 NGO) as well as from public bodies (14) and academia (19). The final version of the recommendation was adopted by the Commission on 18th October 2011. Comments from many sides as well as additional discussions within the commission obviously have triggered substantial alterations[16] of the original proposal, including focussing the definition on nanoparticles while disregarding nanostructured materials, explicitly including some materials with dimensions below 1 nm and adding agglomerates and aggregates.

[15] NIA, www.nanotechia.org/global-news from 12.1.2011

[16] In the draft recommendation, a nanomaterial means a material that meets at least one of the following criteria: (a) consists of particles, with one or more external dimensions in the size range 1 nm - 100 nm for more than 1 % of their number size distribution; (b) has internal or surface structures in one or more dimensions in the size range 1 nm – 100 nm; (c) has a specific surface area by volume greater than 60 m^2/cm^3, excluding materials consisting of particles with a size lower than 1 nm.

Commission Recommendation on the definition of the term "nanomaterial" as adopted on 18th October 2011

1. Member States, the Union agencies and economic operators are invited to use thefollowing definition of the term "nanomaterial" in the adoption and implementationof legislation and policy and research programmes concerning products ofnanotechnologies.

2. "Nanomaterial" means ***a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm.***
In specific cases and where warranted by concerns for the environment, health,safety or competitiveness ***the number size distribution threshold*** of 50 % may be***replaced by a threshold between 1 and 50 %.***

3. By derogation from point 2, ***fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials.***

4. For the purposes of point (2), "particle", "agglomerate" and "aggregate" are defined as follows:
(a) "Particle" means a minute piece of matter with defined physical boundaries;
(b) "Agglomerate" means a collection of weakly bound particles or aggregateswhere the resulting external surface area is similar to the sum of the surfaceareas of the individual components;
(c) "Aggregate" means a particle comprising of strongly bound or fused particles.

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

6. By December 2014, the definition set out in points (1) to (5) will be reviewed in thelight of experience and of scientific and technological developments. The reviewshould particularly focus on whether the number size distribution threshold of 50 %should be increased or decreased.

7. This Recommendation is addressed to the Member States, Union agencies andeconomic operators.

Additional reflections about legal definitions for nanomaterials

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. This finding also may help to understand the large variety of all past and recent stakeholder positions about legal definitions of nanomaterials. They include – at least implicitly – a "regulatory impact assessment" that reflects their respective interests and values and shapes the scope and elements of the definitions they propose.

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 and could be variable, depending on the subject of regulation.

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.

f) that the state of agglomeration or aggregation needs to be addressed specifically.

4.2. Overview of current parliamentary regulation practices and their open gaps

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

The major trends in European regulation of nanotechnologies are currently 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.

Over the last years, Directorates General (DG) have prepared a number of proposals that include provisions for the regulation of nanomaterials in different contexts. 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 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 did not agree with the Commission's conclusions as quoted above. Given the lack of appropriate data and assessment methods, the Parliament stated that regulatory change is necessary to address risks in relation to nanomaterials in an appropriate way. The Parliament called, inter alia, for a review of all relevant legislation, to promote the adoption of a harmonised definition of nanomaterials and to adapt the relevant European legislative framework accordingly. Precise revisions were demanded, especially concerning REACH and worker protection legislation. The Parliament's opinion also included 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 will 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. This second regulatory review is expected to include specific information on nanomaterial types and uses and relevant safety issues (CEC 2009a). In the remainder of 2011, also an updated action plan 2011-2015 for nanotechnologies of the European Commission is expected.

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.

4.2.2. Regulation of chemicals

Scope and general principles of REACH:

European chemicals regulation has been adopted with a new over-arching Regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH EC/1907/2006). REACH explicitly states in Article 1 (3) 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 also applies a "**no data, no market" principle** (Article 5) to the commercialisation 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). After registration, the European Chemicals Agency ECHA performs dossier evaluations or substance evaluations in a minimum of 5 % of the dossiers in the so-called *Evaluation process*. Substances of very high concern may be subject to an *Authorisation process*. Producers or importers of such substances must apply for authorisation 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 be subject to conditions or prohibited.

In addition, the 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.

Regulation of nanomaterials under REACH:

In principle, the regulatory instruments of the REACH regulation are suitable for regulating substances on the nanoscale. For the implementation of the precautionary principle, however, the regulation needs to be amended. Especially nano-specific guidance for registrants have to be provided to fulfil their responsibilities in relation to substances and thereby also establishing criteria by which the authorities can monitor compliance. **To facilitate the implementation of REACH and CLP concerning nanomaterials** the REACH Competent Authorities created in March 2008 a subgroup on nanomaterials composed of Member States and stakeholder experts (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.

To support these activities, three so-called RIPoNs (REACH Implementation Projects on Nanomaterials) were established in June 2009, dealing with substance identification (RIPoN 1), information requirements and testing of nanomaterials (RIPoN2) and chemical safety assessment (RIPoN 3). The RIPoNs will provide advice on how the current REACH guidance documents could be updated with regard to nano-specific challenges. The final output of these projects will be considered by ECHA for inclusion in its further guidance updates.

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[17]". The CASG Nano report of December 2008 states that "the question needs to be clarified in which 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). Evaluation of the data published so far by the ECHA on the substances registered to date reveals that some nanomaterials have been classified by the registrant as substances in their own right, as separate substances "in nanoform" (BMU 2011b).

Another point in the discussion, linked to problem discussed above, is the **categorisation 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 categorisation 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).

[17] 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."

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

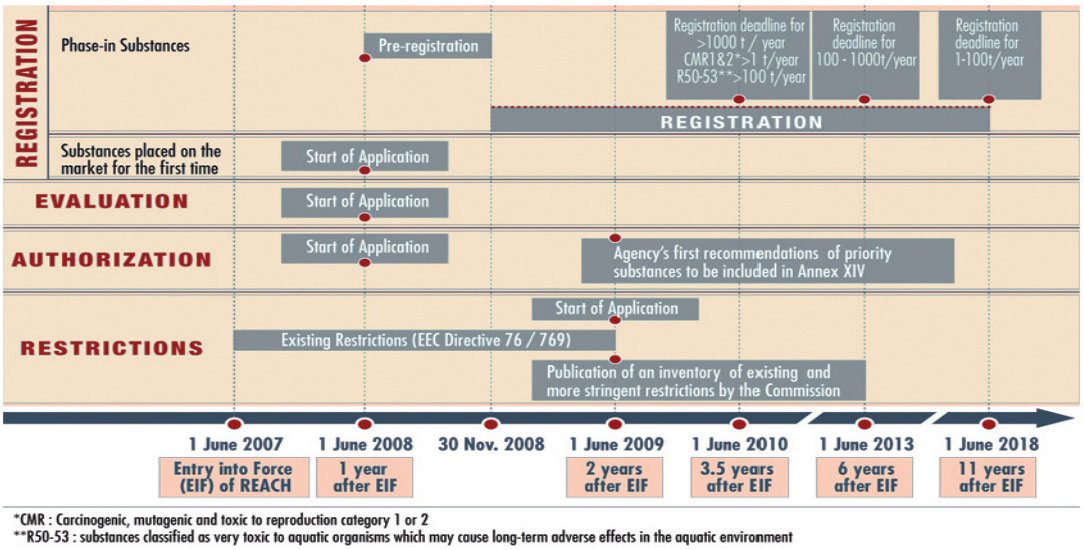

Figure 14: Timeline of REACH Procedures (CRTE Luxembourg)

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 3 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 3: 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 recognised 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 recognised 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. In close co-operation with CASG Nano, the Commission and its agencies are preparing advice on how to manage nanomaterials in accordance with REACH and the CLP Regulation. The first guidance document (Nanomaterials in REACH) provides an overview of how the provisions of REACH apply to nanomaterials. The second paper (Classification, Labelling and Packaging of Nanomaterials in REACH and CLP) focuses on the classification of nanomaterials in accordance with REACH and the CLP Regulation. A third paper deals with Nanomaterials' information in IUCLID[18] 5.2. Additional papers are planned on registration, communication in the supply chain, substance identification, information requirements and chemical safety assessment. Most of the results are expected to be published during 2011. Outcomes of these activities will be taken into consideration in the extensive review of REACH which is expected in 2012 (BMU 2011a, Mantovani et al. 2011, CEC 2011b).

ECHA is also preparing a Nano Inventory from REACH and CLP Submissions, and intended to deliver the inventory by the end of June 2011. The EC requested the inventory in response to the 2009 European Parliament resolution on nanomaterials. An ECHA spokesperson stated that detailed results from the inventory would be available towards the end of 2011, and the inventory may be disseminated at a later date, but this has not yet been discussed. According to the spokesperson, ECHA so far has received ***three registration dossiers and 14 CLP notifications in which "nanomaterial" was selected*** as the form of the substance. The spokesperson stated that **ECHA will be able to identify 50-60 REACH registration dossiers that include information on nanomaterials that will be sent to the Joint Research Centre for assessment under a separate project to address if and how information on nanomaterials is included in REACH registration dossiers**[19].

[18] The International Uniform ChemicaL Information Database.

[19] Lynn L. Bergeson Law Blog 17.5.11, available at:

http://nanotech.lawbc.com/2011/05/articles/international/echa-preparing-nano-inventory-from-reach-and-clp-submissions/

A brief summary of open gaps and issues referring to REACH regulation:

- Introduction of a definition for the term "nanomaterials"
- Consideration of nanomaterials as "stand alone" substances or as a nanoform of existing substances
- Adjustment of nano-specific information and notification requirements (the problem of epistemic uncertainty and endpoints)
- Review and adjustment of the OECD testing methods, standards and strategies
- Adaptation of the threshold concept for a nano-specific assessment, chemical safety reports for all registered nanomaterials
- Adjustment of transitional deadlines for registration of substances in the nanoscale (not compatible with the precautionary principle)

4.2.3. Food regulation

General food law framework:

The *Regulation EC/178/2002* establishes the general principles of food law at EU level. The legal responsibility for ensuring food safety lies with food business operators, but EU law authorises 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, EFSA performs two functions, which are the provision of independent scientific advice to risk management and the communication of food-related risks. In addition the framework mentions two regulatory principles for food regulation:

- Precautionary principle: Article 7(1): „specific circumstances where, following an assessment of available information, **the possibility of harmful effects on health is identified but scientific uncertainty persists**, **provisional risk management measures** necessary to ensure the high level of health protection chosen in the Community may be adopted, pending further scientific information for a more comprehensive risk assessment"
- Traceability principle: It puts all players in a position to remove products from the market, should they, after approval, turn out not to be safe– based on new scientific findings.

Food safety requirements according to the precautionary principle are specified in Article 14, which states that "food shall not be placed on the market if it is unsafe. Food shall be deemed to be unsafe if it is considered to be:

(a) injurious to health;
(b) unfit for human consumption."

"In determining whether any food is injurious to health, regard shall be had:

(a) not only to the probable immediate and/or **short-term and/or long-term effects** of that food on the health of a person consuming it, but also **on subsequent generations**;
(b) to the **probable cumulative toxic effects**"

Nano-specific food safety requirements were regulated by means of secondary acts for novel foods, food contact materials, food additives, food supplements and others. The specific tools differ in terms of the use of positive lists of authorised 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).

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).

Novel foods:

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). The provisions are also applied forfood ingredients which are intended to be used for non-technological purposes, for example nutritional purposes. This is the case where a food or food ingredient is modified by a new production process, and that process gives rise to significant changes in the composition or structure of the foods or food ingredients. Several categories are listed under which a food can be considered as "novel". In its existing formulation 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 urged the Commission to introduce mandatory labelling of nanomaterials in the list of ingredients, and to include a definition of the term "engineered nanomaterial" (European Parliament 2009b). In addition, the European Parliament stipulated an approval of nano-specific test methods for assessing foods produced with nanotechnologies (European Parliament 2010a). The Council position was adopted at first reading in March 2010 (CEC 2010a). Not all proposed amendments of the parliament were accepted in the second reading of the Novel Food Regulation recast (CEC 2010b). The Commission was considering the EP's request for the systematic labelling of all food containing nanomaterials with a favourable disposition. But it was not agreed that food with nanomaterials should not be put on the EU market until specific test methods for nanomaterials are developed. In March 2011, after three years of debate, the amendment of the Novel Food Regulation was not approved. The conciliation process collapsed as Parliament and Council were unable to reach an agreement[20]. Hence, the current Novel Foods legislation adopted in 1997, which does not adequately address nanospecific aspects, remains in force without any modification.

[20] The reasons for disapproval were not related to issues on nanotechnologies or nanomaterials. The regulation also included issues linked to cloning which raised many difficult questions. Parliament had called for a commitment to label all food products from cloned offspring, whereas the Council would only guarantee its support for labeling one type of product: fresh beef.

As a possible future step, in the proposal for a Food Information Regulation a reference to nanomaterial definition has been included, as well as an indication that these will be included in the list of ingredients for food products (Mantovani et al. 2011). During the 4th 'Nanotechnology Safety-of-Success'-Dialogue, held in Brussels in March 2011, it was confirmed that the Commission intends to make a new proposal for the Novel Foods Regulation recast as soon as possible, focusing on those aspects that had already been agreed during the negotiation process.

A brief summary of open gaps and issues referring to Novel Food regulation:

- Lack of explicitly mentioning 'nanotechnology'
- Lack of a definition for the term 'engineered nanomaterials'
- Lack of details for nanospecific methods for assessing Novel Foods
- No provision for a nano-specific labelling

Food additives, enzymes and food flavourings:

The regulation on a *common authorisation 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 authorised substances".

According to the *food additive regulation (EC/1333/2008)*, food additives for technological purposes must not be placed on the market in the EU unless they have been authorised for a given technological purpose following a comprehensive safety assessment (case-by-case authorisation procedure along with conditions for use and labelling requirements by EFSA). There are also provisions for re-evaluation of safety and, where appropriate, re-authorisation of food additives used in a form that differs from the form previously used and assessed by the relevant authority, for example the **nanoscale form**. Article 12 explicitly mentions nanotechnology:

*"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 authorisation 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.

A brief summary of open gaps and issues referring to food additives, enzymes and flavourings regulation:

- Absence of a definition of 'nanoscale'
- Lack of provisions on specific testing procedures for additives, enzymes and food flavourings in the nanoscale
- No provision for specific labelling of nanomaterials

Food contact materials:

A variety of food contact materials containing nanoscale materials are already on the market. These include packagings that act as a barrier, or coatings to block out moisture, oxygen or UV light. In addition, materials with antibacterial properties or indicator functions are used. 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 subjected to an authorisation 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. Additional important provisions are inter alia:

- the business operator have to inform the EC of any new scientific or technical information that might affect the safety assessment of authorised substances (criterion "particle size")
- testing requirements are the EFSA Guidelines for the safety evaluation of substances in food contact materials
- a prior development of nanospecific testing methods as a prerequisite for authorisation is not required in principle
- food contact materials must be labelled with special instructions for their safe and appropriate use
- substance-specific authorisation procedures (preventive ban with authorisation option by EFSA) are specified in directives and regulations from the European Commission:

  Components in food contact materials made from regenerated cellulose film (*Directive 2007/42/EC*), substances in so-called active and intelligent materials and articles (Regulation *EC/450/2009*). The Commission Regulation on plastic materials and articles intended to come into contact with food was published in January 2011 (*EU/10/2011*) and repeals the *Directive 2002/72/EC on* food contact materials made from plastics since May 2011. **This regulation stipulates an authorisation of nanoparticulate titanium nitride (TiN) for the use in food contact materials made from plastics and a restriction for the use in polyethylene terephthalate (PET) bottles. In addition, this new regulation clarifies that the nanoform of a substance is not covered by an authorisation applied for the macroscale form of the same substance.**

A brief summary of open gaps and issues referring to food contact material regulation:

- EFSA Guidelines on safety evaluation at present do not contain provisions for additional nano-specific testing procedures for the authorisation of NM
- Lack of labelling, making it difficult to ensure traceability down the supply chain

Food labelling requirements:

Labelling of food products is an example for a post-market regulatory tool. The *presentation, advertising, and labelling of foodstuffs* is regulated in *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.

The new **provision of food information to consumers** will repeal Directive 2000/13/EC. The proposal consolidates and updates two important areas of labelling legislation, the general food and nutrition labelling. **The objectives** of this new regulation are to pursue a high level of protection of health, transparency and comparability of products, in the interests of consumers, and shall provide a basis for informed choices and safe use of food. Food labelling must be easily recognisable, legible and understandable for the average consumer. Some of the main objectives of the proposal were:

- The creation of a single instrument for principles and requirements for horizontal labelling requirements regarding general and nutrition labelling;
- To include specific provisions on the responsibilities along the food chain with respect to the presence and accuracy of food information;
- To establish measurable criteria for certain aspect of legibility of food labelling;
- To introduce mandatory nutrition labelling in the principal field of vision for the majority of processed foods.
- To avoid misleading consumers by the presentation of food packaging with regard to its appearance, description of pictorial presentation

The principles governing mandatory food information include information on the identity and composition, quantities, properties or other characteristics of the food, and on durability, storage, conservation requirements once the product is opened and safe use. However, they will not include the health impact.

In June 2010, the European Parliament voted in first reading on a consolidated text which contains a number of amendments (European Parliament 2010c). Amendment 130 accounts for the indication of nanomaterials in the list of ingredients. After second reading, Article 18 (List of ingredients) in the consolidated text was amended as follows (European Parliament 2011):

"(...) **3. *All ingredients present in the form of engineered nanomaterials shall be clearly indicated in the list of ingredients. The names of such ingredients shall be followed by the word 'nano' in brackets. (…)***

5. *For the purposes of achieving the objectives of this Regulation, the Commission shall, by means of delegated acts in accordance with Article 51, adjust and adapt the definition of engineered nanomaterials referred to in point (t) of Article 2(2) to the technical and scientific progress or to definitions agreed at international level.*

4.2.4. Cosmetics regulation

In December 2009, the new *Regulation EC/1223/2009 on cosmetic products* was published. The regulation will take effect in 2013. In contrast to the former cosmetic directive, the regulatory authority over cosmetics was centralised at the EU level, because the regulation is directly applicable in and legally binding for the Member States. **The Cosmetics Regulation is the first EU legislation that dedicates an entire article (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 attention 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, the regulation requires 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. Article 2 provides a definition of nanomaterials (see also chapter 4.1.2). 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." The general provisions of the cosmetic regulation could be summarised with the following points:

- Legal definition of the term „nanomaterial" (according to SCCP Scientific Committee on consumer products)
- Nanospecific notification (Pre-market control, procedure by EC, provisions for information like particle size, toxicological aspects, tonnage)
- Obligations for manufacturers
- Exposure evaluation
- Nanospecific guidelines on safety assessment
- Product safety report
- Nanospecific labelling (Post-market control)
- Publicly available catalogue of NM in cosmetic products (market surveillance)

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.

A brief summary of open gaps and issues referring to cosmetic regulation:

- Relatively narrow definition of nanomaterials: only biopersistent or insoluble ingredients and materials with size-dependent properties which are larger than 100 nm are addressed
- Colorants, UV filter or preservatives are exempted from notification requirements under Article 16 (a positive list of permitted substances already exists)

4.2.5. Pesticides and biocidal products regulation

Pesticides fall under the new *Regulation EC/1107/2009* concerning the *placing of plant protection products on the market*, which is in force since November 2009 and took effect on 14 June 2011. This regulation includes a positive list of approved substances. Substances can be included on this list if they were subjected to toxicological and ecotoxicological tests. Nanomaterials are not explicitly mentioned. In addition, there are no specific labelling provisions besides the general regulations for chemicals. Nanoscale forms of plant protection products do not need an update of the authorisation 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 authorised for use.

The general provisions of the biocidal and plant protection products regulation could be summarised with the following points:

- Preventive ban with an authorisation option:

  Products must not be placed on the market unless they have successfully undergone authorisation procedure. In the context of the authorisation procedure, applicants must submit research studies as evidence to prove that there are no potential harmful effects (shifting of the burden of proof)

- Implementation of a two-tier authorisation process:

  1. Assessment of active substances and inclusion in a positive list valid throughout the EU
  2. Authorisation of substances or products at national level; as a minimum requirement for authorisation, a product must contain only substances included in the relevant positive list.

- Risk-assessment based on precautionary principle

  "Realistic worst case" scenarios where exposure data are lacking, while lack of data on the impact side are compensated for using weighting factors.

  Under the Regulation on Plant Protection Products, the precautionary principle is supplemented in a specific way by an additional legislative tool – exclusion criteria – in the interests of hazard prevention. Exclusion criteria means that where a substance is found to possess particular intrinsic properties which give cause for concern regardless of potential exposure or other risks, then that substance is automatically excluded from the Community list (Annex I);

- Both the Biocidal Products Regulation and the Regulation on Plant Protection Products provide for "**comparative assessment**": substances or products having effects that are on the **borderline between acceptable and unacceptable** may be granted **provisional authorisation** with the note that **"concerns remain"**, but must then undergo comparative assessment. The aim of this provision is to substitute them with active substances or products of less concern.

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). In contrast to the Commission's proposal, which did not provide specific regulations for nanomaterials, the 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". 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). On 21st June 2011, the European Council adopted its position on the 1st reading of the proposed new Biocidal Products Regulation (CEC 2011a).

The Council position includes the following provisions on nanomaterials: *"There is scientific uncertainty about the safety of nanomaterials for human health and the environment. In order to ensure a high level of consumer protection, free movement of goods and legal certainty for manufacturers, it is* ***necessary to develop a uniform definition for nanomaterials****, if possible based on the work of appropriate international fora, and to specify that* ***the approval of an active substance does not include the nanomaterial form*** *unless explicitly mentioned. The Commission should regularly review the provisions on nanomaterials in the light of scientific progress."*

In article 3 an adapted definition was given: ***"nanomaterial" means nanomaterial as defined in Commission Recommendation 20../.../EC of ... ... concerning the definition of nanomaterials;***

The Council position supports the European Parliament's proposal in regard to the need for nanospecific provisions in the new Biocidal Products Regulation, but differs from the latter in demands for nano-specific labelling or for an exclusion of any biocidal product from being 'considered a low-risk biocidal product if [...] it contains a nanomaterial'. The European Parliament's Environment Committee is expected to publish its report on the 2nd reading in October 2011, with view to a vote in plenary session in January 2012.

A brief summary of open gaps and issues referring to biocidal and plant protection products regulation:

- no separate provisions concerning plant protection products which contain nanoscale substances
- labelling of nanomaterials in biocidal products

4.2.6. Restriction of hazardous substances in electrical and electronic equipment

In 2008, the Commission proposed a recast of the Directive on the restriction of the use of certain Hazardous Substances (RoHS) in electrical and electronic equipment, which should repeal the Directive EC/95/2002. General provisions of the RoHS regulation could be summarised with the following points:

- Protection of human health and the environment
- Environmentally sound recovery and disposal of waste electrical and electronic equipment
- Proposed hazardous substances with regard to waste treatment according Annex IV: certain heavy metals and two groups of brominated flame retardants

The aim of the proposal was the elimination of certain hazardous substances from electrical and electronic equipment like heavy metals and two groups of brominated flame retardants (CEC 2008e). Important points were inter alia:

- Harmonisation of the scope of the regulation and the definition of "electrical and electronic equipment"
- Adaptation to the REACH Regulation: for the purposes of adapting Annexes of RoHS to scientific and technical progress, the Commission shall adopt measures such as the inclusion of materials and components of EEE for specific applications on exemptions if such inclusion does not weaken the environmental and health protection of Regulation EC/1907/2006 (REACH)
- Substance ban (review and amendment of the list of restricted substances)

In June 2010, the European Parliament's Committee on the Environment, Public Health and Food Safety has voted on the adoption of suggested amendments to the current regulation, considering the following nanospecific aspects:

- Definition of the term „nanomaterial" according to a definition originally drafted for the Novel Foods Regulation recast
- Ban on the use of nano silver and long, multi-walled carbon nanotubes in electronic equipment

- Labelling of electrical, electronic material that contains nanomaterials

The first reading in November 2010 has led to a compromise between the European Parliament and the Council, rejecting these nanospecific measures. The European Council had adopted the revised Directive on the 27th May 2011. The Commission had repeatedly stated that the current provisions in the RoHS Directive covered different forms (including 'nanoforms') of those substances, which are currently banned, and those which will be in the future subject to a priority review under RoHS.

The recast of the Directive 2011/65/EU on RoHS was published on 1st of July 2011 and entered into force on 21st July 2011. The notice calls for the restriction of other hazardous substances (like nanomaterials) and their substitution by more "environmentally friendly alternatives" as soon as scientific evidence is available, and taking into account the precautionary principle:

"*As soon as scientific evidence is available, and taking into account the precautionary principle, the* ***restriction of other hazardous substances****,* ***including any substances of very small size or with a very small internal or surface structure (nanomaterials) which may be hazardous due to properties relating to their size or structure****, and their substitution by more environmentally friendly alternatives which ensure at least the same level of protection of consumers should be examined. To this end, the review and amendment of the list of restricted substances in Annex II should be coherent, maximise synergies with, and reflect the complementary nature of the work carried out under other Union legislation, and in particular under Regulation (EC) No 1907/2006 while ensuring the mutually independent operation of this Directive and that Regulation. Consultation with the relevant stakeholders should be carried out and specific account should be taken of the potential impact on SMEs."* (paragraph 16).

The new text provides for transitional periods for the inclusion of monitoring and control devices and medical devices, in vitro medical devices and industrial control appliances, which will fall within the scope of the RoHS ban in three, five and six years' time respectively.

4.2.7. 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.

The MDD is a 'New Approach' Directive. Products conforming with the MDD must have a CE mark applied. The Directive was most recently reviewed and amended by the Directive 2007/47/EC and a number of changes were made. Compliance with the revised directive became mandatory on March 21, 2010. The Directive is currently under review and is expected to be published by the end of 2011. Important general provisions of the medical device regulation are:

- The solutions adopted by the manufacturer for the design and construction of the devices must conform to safety principles, taking account of the generally acknowledged state of the art.
- Medical devices are classified into one of Classes I to IV by means of the classification rules [...], where Class I represents the lowest risk and Class IV represents the highest risk.
- Labelling and notification requirements

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).The New & Emerging Technologies WG is currently developing a guidance document (Mantovani 2011).

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 to 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).Some medicinal products based on nanotechnologies have already been approved by EMA (Mantovani et al. 2011).

A brief summary of open gaps and issues referring to medical device regulation:

- Nanomedical products challenge the current criteria of classification between medicinal products and medical device
- A classification rule for free nanoparticles in medical devices is proposed (Class III)

4.2.8. Worker protection and environmental protection regulation

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.

Regarding occupational health and workers safety, most efforts are devoted to evaluating and adapting the existing risk management methods, and to develop appropriate guidance for the handling and disposal of engineered nanomaterials. The need to define and agree on specific testing procedure for nanomaterials and to have a better view of concrete exposure scenarios remains amongst the highest priority. As from the EC mandate, an increasing commitment on the matter is expected by the European Agency for Safety and Health at Work (EU-OSHA, Mantovani 2011). OSHA is developing several guidance documents including best-practices for R & D laboratories.

In its 2009 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).

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).

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)

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 display 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).

4.3. The role of voluntary measures for a responsible handling and regulation

Voluntary approaches are important for risk management while mandatory measures are under development due to their flexibility and their adaptive properties. They are most helpful for dynamic and complex issues.

Voluntary nanotechnology initiatives could be classified according to the actors and sponsors (government-sponsored programs, business initiatives and NGO-business partnerships) or according to their type and instruments (register, codes, certification). Table 4 gives an overview of different voluntary measures. In general, the role of voluntary initiatives could be summarised as follows:

- To inform and prepare regulation due to data collection
- To help provide a firmer scientific foundation for regulatory decisions
- To complement existing and future regulatory capacities as one component in a larger system (Fiorino 2010)

In addition, there are different possible roles of voluntary initiatives with regard to regulatory strategies: they can support the preparation of a regulation, complement of existing regulations or serve as independent systems. In this chapter voluntary measures are classified according to their instruments and goals. Disadvantages and problems will be discussed for different initiatives in detail.

Type of initiative	Actors	Examples
Register	Governmental agencies	UK Voluntary Reporting Scheme for engineered nanoscale materials by DEFRA
	Governmental agencies	Nanoscale Materials Stewardship Program by EPA (NMSP)
	Governmental agencies	Swiss Nano-Inventory – an assessment of the usage of nanoparticles in the Swiss industry by IST
Codes of Conduct	Governmental agencies	EU-Code of Conduct for Responsible Nanoscience and Nanotechnologies (N&N) Research
	Business-NGO Partnerships	Responsible Nano Code
	Business-NGO Partnerships	IG-DHS Code of Conduct Nanotechnology
	Collective Business Initiatives	Responsible Care (RC)
	Business Initiatives, Private enterprises engagement	BASF Code of Conduct Nanotechnology
Risk Management systems	Business Initiative	Cenarios
	Business-NGO Partnerships	NanoRisk Framework
	Governmental initiative	Criteria for a preliminary assessment (NanoKommission)
	Governmental initiative	Precautionary Matrix for Synthetic Nanomaterials

Table 4: Types and examples of voluntary initiatives

4.3.1. 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 harmonised 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[21] (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 be 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 sufficiently simple and well understandable. Databases for that purposes generally do not need to contain detailed physical or chemical properties of the materials used.

[21] "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."

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 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, **thirteen forms** have been submitted, eleven from industry and two from academia[22]. In June 2009, DEFRA announced that it is "currently reviewing the scheme in order to take a decision on a suitable way forward." Plans regarding the future of this scheme have not become known yet.

Nanoscale Materials Stewardship Program by EPA (NMSP)

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". EPA aimed "to complement and support its regulatory activities on nanoscale materials" under the Toxic Substances Control Act (TSCA), the U.S. law that regulates the introduction of new or already existing chemicals (Fiorino 2010). Within this programme, US enterprises producing, importing or using nanomaterials are requested in the Basic Program 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**. The In-Depth Program asked for a commitment to work with EPA and develop test data for selected nanoscale materials.

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 referring to the Basic Program. 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 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.

Participation in the In-Depth Program was much more limited. As of December 2008, only four companies had offered to develop test data on materials (Fiorino 2010). Thus information on toxicity, exposure and fate were limited. From these results it can be deduced that the NMSP provided only limited data for regulatory decisions but it was helpful as a preparation for a mandatory data collection (Fiorino 2010).

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

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.

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.

Especially b) and d) are significant extensions of the 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.

Discussion:

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 be 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 challenges on existing and future regulations of nanomaterials similar to those which have already been discussed in chapter 4.2. 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 harmonised 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.

In June 2011 the European Trade Union Institute (ETUI) published its recent policy brief entitled 'Nano governance: How should the EU implement nanomaterial traceability?' ETUI urges the EU to adopt a centralised registry of nanomaterial-containing articles. The document argues that states like France, The Netherlands, Italy and Belgium already have voluntary reporting schemes for nanomaterials, but the ETUI proposes to make them mandatory. The document describes the pressure from civil society to find out what is already on the European market in terms of nano-enabled products. The communication brief also points out that 'voluntary schemes have too little take-up among firms, lack control, and tend not to disclose negative information'[23].

In 2011 the **German NanoKommission** also **recommended a mandatory product register** which should be managed by a competent public authority. Persons manufacturing, importing or placing on the market a nanoproduct for the first time should have a mandatory obligation to submit information on the identity of the manufacturer, the product and other information on the nanomaterials contained in the product (BMU 2011a). The purpose of this register is to create transparency and traceability, to support authorities and manufacturers in terms of risk management and to guarantee freedom of choice for consumers. A product register would also be able to collect information for the revision of REACH.

4.3.2. Codes of Conduct

In order to address concerns that handling of nanomaterials bears additional risks which are not sufficiently covered 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 a voluntary basis and have been proven as an 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 committing 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 and social responsibility. In addition, a broadly accepted code might also support the implementation of these principles within the organisation.

[23]http://hesa.etui-rehs.org/uk/publications/files/Policy_Brief_Social_Policy-Issue2-2011_EN.pdf

EU-Code of Conduct for Responsible Nanoscience and Nanotechnologies (N&N) Research

The European Commission developed, and published in February 2008, a Recommendation for a European Code of Conduct (CoC) for Responsible Nanosciences and Nanotechnologies Research which sets out a number of principles aimed at guiding stakeholders towards undertaking nanotechnologies research in the European Community in a safe, ethical and effective framework, so as to support sustainable economic, social and environmental development. The CoC is addressed to Member States, industry, universities, funding organisations, and researchers. 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).

The CoC itself is **voluntary but** is intended to facilitate and underpin regulatory and governance approaches towards nanotechnologies and to help cope with scientific uncertainties. It is also intended to provide a European basis for dialogue with third countries and international organisations. Consultation has shown, however, that not all stakeholders are aware of the CoC and that, due to the general way its principles and provisions are expressed, others had difficulties implementing it in a consistent way. For example, the code does not contain advice, guidelines, checklists, indicators or any other suggestions regarding the operationalisation of the code.

In order to analyse user perspectives in more detail, to develop and provide guidance and tools, and to avoid an unacceptable variety of interpretations of the principles, the Commission launched a research project, NanoCode, in January 2010[24]. The Synthesis Report of the NanoCode Survey was published in 2011. Information from detailed Country Reports of the Consortium partners from seven EU-Member States (Italy, UK, France, Spain, The Netherlands, Czech Republic and Germany) and three Non-EU Countries (Switzerland, Argentina and The Republic of South Africa) were included in this report. All in all, 304 European and international experts contributed to the NanoCode Survey between August and October 2010. Furthermore, about 150 experts had been involved in qualitative interviews or focus groups in the different countries between October 2010 and January 2011. With respect to this large and inhomogeneous sample, the results offer a surprisingly unambiguous tendency[25]:

- there is a broad general support of the EU-CoC principles (about 80% of agreement)
- a two third majority of the participants appraised the EU-CoC as an appropriate instrument for complementing regulation and for encouraging a dialogue about health, safety, environmental, ethical, social and legal issues
- Only 15% thought that the Code is "not useful at all" for them.
- Contrary to the high level of agreement, a very low rate of adaption was observed in practice (only 20% of the participants stated an adaption by their organisation).
- Several principles (e.g. Accountability, Inclusiveness, Precaution and Sustainability) should be revised
- Only 21% of the participants were aware of governmental activities to enforce the EU-CoC.
- It will be fairly difficult to achieve compliance without an improvement of the awareness and appropriate communication strategies for different target groups

[24] http://www.nanocode.eu

[25]http://www.nanocode.eu/files/reports/nanocode/nanocode-consultation-synthesis-report.pdf

The further development and the planned revision of the CoC were discussed on the NanoCode conference in Brussels in September 2011.

Code of Conduct for Responsible Nanotechnology ("Responsible Nano Code")

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** that address broad issues of governance and a series of examples of good practice for each principle. The principles range from stakeholder involvement, transparency and disclosure to worker and public health, safety and environmental risks. 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 has been open to public consultation (Autumn 2007). In an update paper in 2008, examples of best practice were finalised. In 2008, a sub group has developed a procedure for a benchmarking process. Because the code does not include a kind of certification nor 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 because of funding issues (Fiorino 2010).

Responsible Nano Code is an unfinished product due to its general and far less detailed set of principles. One open question is the fit between the Nano Risk Framework and the Responsible Nano Code, both based on the concept of "governance outside of government" (Fiorino 2010).

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 Swiss 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 (RC)

From a regulatory perspective, the Responsible Care[26] initiative could be compared to 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:

- Continuously improve the environmental, health and safety knowledge and performance of technologies, processes and products over their life cycles so as **to avoid harm to people and the environment.**
- Use resources efficiently and minimise waste.
- Report openly on performance, achievements and shortcomings.
- Listen, engage and work with people to understand and address their concerns and expectations.
- Cooperate with governments and organisations in the development and implementation of effective regulations and standards, and to meet or go beyond them.
- Provide help and advice to foster the responsible management of chemicals by all those who manage and use them along the product chain.

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 nanomaterials 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 actively involved in the ongoing development of a scientifically based database for the assessment of potential risks as well as in improving and refining product-based testing and assessment methods.

[26] http://www.responsiblecare.org

In addition, BASF debates the opportunities and risks of nanotechnology with partners and stakeholder from all areas of society. The declared goal is to establish risk-appropriate, solid standards and to support relevant legislation.[27] BASF is still committed to its code.

Discussion:

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 governing 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.** The overall value of such codes depends on the transparency of the process, on the commitments and their implementation in the individual case.

4.3.3. Risk Management Systems

Voluntary risk management systems provide tools, procedures and guidance on how to appropriately and responsibly handle nanomaterials and on how to identify, assess and minimise potential risks under circumstances of high uncertainty. The initiatives are commonly unilateral commitments which complement existing risk management approaches in a company.

Nano Risk Framework:

This kind of risk management framework led jointly by the Canadian CSO Environmental Defence (EDF) and DuPont was begun in 2005 and released in June 2007. The development process was consultative, including workshops with industry and NGO and opportunities for expert and public comment. The goal was to define a systematic and disciplined process for identifying, managing and reducing potential EHS risks of nanomaterials across all stages of the life cycle (DuPont 2007)[28]. The framework defines a six-step process for identifying, characterising and communicating information about potential risks. In addition, options for managing risks and recommending appropriate actions are integrated within this framework concept. The framework adopts a pragmatic approach to the limits in data availability. Reasonable worst-case default values and bridging information should fill in the data gaps as a temporary measure.

[27] http://www.basf.com/group/corporate/en/sustainability/dialogue/in-dialogue-with-politics/nanotechnology/code-of-conduct

[28] http://www.nanoriskframework.com/page.cfm?tagID=1095

The most important critique focuses on the possibility that this voluntary effort could displace regulation and a precautionary government oversight system (Fiorino 2010). On the other hand, EDF has been working with ISO on incorporation the framework as an ISO standard.

Certifiable Nanospecific Risk Management and Monitoring System (CENARIOS)

CENARIOS describes systematic structures and processes to identify, assess, document and manage any potential risk of nanomaterials. For this purpose it relies on existing standards and guidelines for risk assessment and risk management, but also includes new tools, developed by the Swiss consultancy "Innovationsgesellschaft" together with the German "TÜV-SÜD" (Meili and Widmer 2010). CENARIOS uses semi-quantitative state-of-the-art methods to allow subjective assessments to be linked to objective experience in cases of incomplete risk data. Unlike in other risk management systems, not only EHS risks but also "soft risks" such as societal risks, regulatory risks and liability risks are included. Regarding transparency of the system, all requirements are disclosed in the CENARIOS Certification Standard. The certification procedure is performed by the independent TÜV SÜD. It has to be considered that CENARIOS is not a product certificate, certification only refers to the risk management system.

Criteria for a preliminary risk assessment according to the German NanoKommission

Any non-mandatory guideline to support companies in identifying, assessing and managing risk related to nanomaterials could be classified as a voluntary measure in risk governance. One approach was introduced by the German NanoKommission. This stakeholder commission on nanotechnologies was established by the German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) and presented a key dialogue panel within the German Federal Government's Nano-Initiative. The commission worked from 2006 to 2011, comprising two dialogue phases.

A special topic of the first dialogue phase (2006-2008) was the design of a heuristic for a preliminary risk assessment with regard to the precautionary principle (See also chapter 4.1.2), introducing three different categories of 'levels of concern' and linking them to a set of – often only vaguely described – criteria (BMU 2008). It is crucial to note that these criteria are only indicators of potential risks. Their main purpose is to inform decision-makers downstream in the production process and provide orientation for further assessments. In most cases it would be too simplistic if meeting one criterion would automatically imply risk management decisions, for example about manufacturing or termination of production.

The system was intended to serve as a basis for developing appropriate measures in accordance with the precautionary principle in a two-tiered process. Such measures should form an elementary component of an entire risk management concept, considering also aspects of benefits and a scientific risk assessment.

The commission suggested that, until such time as scientific risk evaluations for health and environmental protection become available, nanomaterials should be tentatively ranked in the following three categories:

- Probably hazardous – concern level high:

  Criteria: Exposure occurs; materials have high mobility, reactivity, persistence or toxicity of the materials

  Action: A strategy is required for measures aimed at minimising exposure or avoiding certain applications

- Possibly hazardous – concern level medium

  Criteria: Exposure cannot be ruled out; materials have unknown agglomeration or deagglomeration behaviour; too little is known about materials' solubility and biodegradability; the possibilities for release of nanoparticles from matrices have not yet been explored

  Action: A strategy is required for measures aimed at reducing exposure

- Probably not hazardous – concern level low

  Criteria: Exposure can largely be ruled out; materials are soluble or biodegradable; materials are bound in matrices; materials form stable aggregates or agglomerates

  Action: No procedures are required over and above "good work safety practice" (or "hygiene practice")

It was one of the main tasks of the second phase of the German NanoKommission (2009-2011) to render the criteria for the different categories operational (BMU 2011a). In order to do so, the Issue Group 2 of the second NanoKommission has named and described scientifically accurate, and yet simple and practicable, parameters for identifying the need for precautionary measures/criteria for concern and no cause for concern for uses of nanomaterials. The assessment criteria identified by the first NanoKommission were elaborated further and grouped into four blocks: probability of exposure, physico-chemical properties, behaviour in the environment, and toxicology and ecotoxicology. For each of the criteria, a guiding question requiring a "yes" or "no" answer was formulated. Depending on the criterion in question, a "yes" or "no" response leads to one of the following categories: "No immediate need for precautionary measures/No cause for concern", or "Further consideration/Need for precautionary measures/Cause for concern". In the absence of information to answer the question, the response "data gap" can be given. It is envisaged that the user will check and respond to all of the criteria.

The list of criteria that is aimed at raising users' awareness of potential causes for concern and factors giving no cause for concern as well as at highlighting gaps in the users' information, is freely available as an Excel spread-sheet. If users of this instrument identify potential grounds for concern, they could consider first of all discussing and verifying the result of the assessment with expert help. If the assessment indicates "Further consideration/Need for precautionary measures/Cause for concern", options for conducting scientific risk evaluation of (this use of) the nanomaterial should be explored. In the event of a concern arising with regard to the environment, but no grounds for concern are identified relating to workers and consumers for the use in question of the nanomaterials, the scientific risk evaluation can include a "targeted risk assessment" focusing on the specific protection target. The Issue Group also recommended establishing an advisory service at the level of a federal agency. This service could gather experiences of using the criteria and harness these to develop the criteria further. In addition, it could assist users to interpret the results and, where necessary, to identify relevant information and develop appropriate risk management measures. Finally, the service could organise an exchange of experience among various users (BMU 2011a). Next steps will be elaborated in the follow-up of the NanoKommission, the so-called Expert Dialogues on Nanotechnologies.

The Swiss 'Precautionary Matrix for Synthetic Nanomaterials'

The Swiss Federal Offices of Public Health (FOPH) and for the Environment (FOEN) launched the introductory phase of the Swiss 'Precautionary Matrix for Synthetic Nanomaterials' in December 2008. The approach was introduced as a key element under the Swiss Action Plan for synthetic nanomaterials and was revised on the basis of users' experience at the beginning of 2010.

The precautionary matrix "provides a structured method to assess the "nanospecific precautionary need" of workers, consumers and the environment arising from the production and use of synthetic nanomaterials. The matrix is a tool to help trade and industry meet their obligations of care and self-monitoring. It helps them to recognise applications which may entail risk and to take precautionary measures to protect human health and the environment. In the case of new developments, the matrix can contribute to the development of safer products. It enables users to conduct an initial analysis on the basis of currently available knowledge and indicates when further investigations are necessary. The precautionary matrix is available to a broad circle of users at home and abroad. It will be further developed in close cooperation with trade, industry and science as well as with consumer and environmental organisations."[29]

The precautionary matrix only regards as relevant nano-objects with at least two nano-scale dimensions or products containing these nano-objects. Upon entering a limited selection of nanomaterial-specific and application-specific parameters into an electronic form (size of the particles, reactivity and stability, their release potential, the amount of particles) the matrix provides a simple hazard classification:

Class A: risks specific to nanomaterials are low, no further clarification necessary

Class B: possible risks, further clarification and/or risk reduction needed

The Precautionary Matrix may be regarded as an instrument that supports companies and is to be used in the context of duty of care and industry self-supervision (Hodge et al. 2010). The approach functions simultaneously as a differentiation aid, a detector of gaps in knowledge and an early warning system and should not in any way be compared with a classical risk assessment process.

Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain by EFSA (European Food Safety Authority):

Following a request from the European Commission, EFSA has developed a practical approach for assessing potential risks arising from applications of nanoscience and nanotechnologies in the food and feed chain (EFSA 2011). Guidance is provided on:

- the physico-chemical characterisation requirements of engineered nanomaterials used e.g. as food additives, enzymes, flavourings, food contact materials, novel foods, feed additives and pesticides. The characterisation is needed to identify engineered nanomaterials and decide whether the Guidance is appropriate.
- testing approaches to identify and characterise hazards arising from the nanoproperties which, in general, should include information from in vitro genotoxicity, absorption, distribution, metabolism and excretion and repeated-dose 90-day oral toxicity studies in rodents.

[29] http://www.bag.admin.ch/themen/chemikalien/00228/00510/05626/index.html?lang=en

Prior to a detailed risk assessment of the nanomaterial, exposure scenarios from the proposed uses should be outlined. These exposure scenarios will contribute to decisions on the extent of the hazard characterisation and will provide parameters for the exposure assessment required in risk assessment. However, it was argued that currently it is not possible to routinely determine nanomaterials in situ in the food or feed matrix, which increases the uncertainty in the exposure assessment. In the absence of exposure data, and where it is not possible to determine the nanoform in the food/feed matrix, it should be assumed that all added nanomaterial is present, ingested and absorbed as the nanoform.

The guidance allows for reduced information to be provided when no exposure is verified by data indicating no migration from food contact materials or when complete degradation/dissolution is demonstrated with no absorption of engineered nanomaterials as such.

Six cases are presented which outline different toxicity testing approaches:

1. *No persistence of ENM in preparations/formulation*

   Nanomaterials are completely degraded/solubilised to non-nanoform: testing for non-nanoforms for the specific intended use should apply

2. *No migration from food contact materials*

   No exposure to nanomaterials via food and no toxicological concern: no additional testing required

3. *Complete transformation of nanomaterials in the food/feed matrix before ingestion*

   Testing for non-nanoforms for the specific intended use should apply

4. *Transformation during digestion*

   When nanomaterials completely dissolves/degrades in the gastro-intestinal tract without absorption: hazard identification and hazard characterisation can rely on data for the non-nanoform substance (if available)

5. *Information on non-nanoform of the same substance is available*

   When information on non-nanoform is available and where some or all of the nanomaterials persists in the food/feed matrix and in gastrointestinal fluids: a testing approach which is based on comparing information on ADME, toxicity and genotoxicity of the non-nanoform with ADME , repeated-dose 90-day oral toxicity study and genotoxicity information of the nanomaterials.

   If differences observed indicate increased hazard, then more toxicity testing will be required, beyond ADME, 90-day and genotoxicity tests

6. *No information on a non-nanoform is available*

   When information on a non-nanoform is not available and where some or all of the ENM persists in the food/feed matrix and in gastrointestinal fluids: toxicity tests should follow the relevant EFSA guidance for the intended use with the modifications which take into account the nanoproperties

EFSA concluded that conventional risk assessment paradigm is appropriate in general. However EFSA pointed out that some test models and standard testing protocols used for non-nanoform substances may not necessarily be appropriate or optimal for the testing of ENM, and ongoing efforts in the research community are currently addressing these issues.

4.3.4. Voluntary labelling schemes

Labelling of products that contain nanomaterials or that have 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 labellled: 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 basically serves to provide transparency about products and the ingredients they contain, and enables consumers to alter their purchasing behaviour. Voluntary product labelling is an appropriate instrument for influencing purchasing decisions. 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, 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 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.

5. CONCLUSIONS

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 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 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 socioeconomic interests and the ability to innovate, on the other.

To specify these **challenges** more precisely, a **number of key questions** in the regulatory discourse can be identified. Aspects of these questions have already been discussed in the preceding chapters of this report.

1. Development of a legal definition

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, in many cases 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 sectoral 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.

With the recently published Commission Recommendation on the definition of the term "nanomaterial", an overarching definition has been proposed that could serve as a starting point for developing sector-specific definitions for specific regulatory requirements. Since this recommendation was published only a few days before the end of the NanoSafety project, its comprehensive assessment will be subject to further discussion outside the framework of this report. But a number of arguments might be helpful to assist the process of implementing the Commission's definition in legislative practice:

- Legal definitions of nanomaterials have to describe the object of regulation sufficiently precisely 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 authorities responsible.

- 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 should therefore be science-based but does not necessarily have to be identical to scientific definition(s) of the same term.
- The breadth 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 they may occur in nature including in a number of natural products that are consumed by humans, that they can be incidentally produced as results of various human activities, or that they 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.**
- Since regulatory goals are set as a result of a political process which seeks to balance various expectations and interests, they may vary with different contexts. It is unlikely that this will change in the near future. For that reason, within specific regulatory processes additional clarifications and specifications of a "harmonised definition" will be required that might lead to variations of the "general" definition in the resulting legal documents. The overarching definition here can only provide a general framework.
- 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 and may differ within different regulatory contexts**.

2. Developing an adequate precautionary approach

The second key challenge in the current debates on regulation of nanomaterials originates from a conflict of two different regulatory approaches. One position can - in a schematic way – be summarised as 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 make it possible to predict a certain hazard potential (e.g. when the nanomaterials exist in free form, are known to be insoluble, biopersistent, etc.). The rationale behind this "**hazard control**" approach is to assume that a hazard is present if the **probability of harm is sufficient**.

In situations where there is considerable scientific uncertainty or in a non liquet situation[30] (like it is given for a number of applications of nanomaterials), it is not possible to provide evidence that there is sufficient probability of harm. In these cases, the **concept of risk** plays an important role and therefore "**risk prevention**" was introduced. This means that for the purpose of risk prevention it is legitimate for the legislator to implement measures if there is merely an abstract possibility, rather than sufficient likelihood, of harm occuring. With this second, **strongly precautionary-oriented** regulatory approach, **the burden of proof is reversed**. Nanomaterials are put under **general suspicion** because of their new properties and the limited knowledge about their (potential) environmental, health and safety implications. Proponents of this approach usually define nanomaterials rather broadly and propose a number of strong measures to supervise and control the entire life cycle of nanomaterials or products that contain nanomaterials or that were manufactured using nanotechnologies. 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, assuming they were proven to be "safe"? And how "safe" is safe enough to justify this decision?

3. Handling limitations of risk assessment methodology for regulatory strategies

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 characterisation. Each of these four elements holds a number of limitations that are not easily overcome:

The majority of nanotoxicological work done so far 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. There is evidence that some 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.

[30] In procedural law, "non liquet" describes a situation in taking of evidence in which neither the position of one side nor the position of the other side can be proven, i.e. where it cannot be concluded that the ultimate fact is true, not even after giving all available pieces of evidence.

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. ***Parliament could therefore continue supporting a cross-departmental and interdisciplinary research on safety and risk assessment. In this area, funding for research and development relative to specific measures in the areas of occupational health, safety, protection of public health and environmental protection should be significantly increased. The results of this research should be made available, in a suitably structured form, to society***.

Another problem discussed in this context is that of so-called "no-effect studies", i.e. nanotoxicological studies, which have failed to show effects of MPN on various endpoints, and remain unpublished to a large extent. The reasons for that are manifold and span from methodological challenges to limited opportunities and incentives for publication. Then again, no-effect studies are a valuable repository for hazard characterisation 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 characterisation that builds on hazard and exposure assessment is at this time (and most probably in the 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 inform in a timely manner 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, the role and validity of risk assessment as justifications for regulatory strategies linked to 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 precaution-oriented 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.

4. Handling limitations and gaps of existing regulatory measures

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 adapting the existing legal framework to enable nanotechnology regulation and amending it in order to deal with the unintended implications of this technology. This approach, which includes a number of regulation proposals as discussed in chapter 4, is confronted with various 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 previously in this report, including among others:

- developing a legal definition for nanomaterials; consideration of nanomaterials as "stand alone" substances or as a nanoform of existing substances;
- 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 which regulators have additional uncertainties for the regulatory coverage of emerging nanomaterials risks;
- finding adequate regulatory instruments;
- review and adjustment of specific testing methods, standards and strategies
- labelling of nanomaterials in consumer products of concern (cosmetic products labelling takes effect in 2013, food ingredient labelling takes effect in 2014, no labelling provision for plant protection products, biocidal products and textiles)
- enforcing compliance with existing and emerging regulation.

These – and other – issues 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 conceptualise this idea. Although the European Commission has announced that it is not seeking to develop a separate regulatory legislation for nanomaterials and all necessary regulation will instead be planned under the existing REACH legislation, some experts proposed to merge and further elaborate basic rules for handling nanomaterials in an overall "NanoAct". ***Parliament may want to consider commissioning a study project that develops a concept for 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.

5. Risk communication

Risk communication is a multifaceted term. At first sight, one can distinguish between two understandings that can be described as instrumental or dialogical communication. Only in very rare cases does the Parliament have to deal with instrumental risk communication which can be basically seen as a tool in the hands of risk managers, policy-makers and public officials to prevent critical public responses to serious crises. In the process of anticipatory governance of potential EHS risks (like in the case of manufactured particulate nanomaterials), dialogical **risk communication** plays the dominant role. It should **put people** that are concerned about certain hazards and risks **in a position to redeem their claim to be 'capable of informed risk appraisal'** by making them appropriate offers of information, dialogue and participation**.**

Parliament itself is usually not an active actor in dialogical risk communication. But it **can actively contribute to the implementation of risk communication measures by encouraging voluntary activities as well as by making various risk communication measures mandatory in relevant legislative acts.** This is especially true for the **involvement of concerned parties and representatives** of organised societal groups (like industrial associations, trade unions, environmental organisations, consumer protection associations or other civil society organisations) and the **participation of the general public** in processes of governance of EHS risks of nanomaterials.

6. Market transparency for consumers and traceability

Clear, understandable information about ingredients, functions and effects of nanomaterials in consumer products, and about product safety, are required by many citizens as well as by consumer organisations, not least in order to enable informed choice, a "right to know", on the side of the customer. This information is expected to be provided by industry and made freely accessible. New concepts for such information provision need to be developed. **To achieve transparency regarding the application of nanomaterials in consumer products, a dedicated labelling of consumer products in which engineered nanomaterials are intentionally used could be considered.** Labelling provisions are already adopted for food additives and cosmetics and will take effect in the next years.

Labelling of products that contain nanomaterials or were produced using nanotechnology has proven to be a highly controversial issue in the debate on nanotechnology regulation in the last years. Five main distinctions can be identified:

- Objects to be labelled: nanomaterials and nanointermediates sold for further processing by (industrial) downstream users or consumer products, nanoproducts;
- 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.

In a nutshell, consumer product labelling, especially when mandatory, faces the same terminological and definitional problem as other regulations. 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 should therefore 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 the ultimate design and scope of labelling schemes are the results of political decisions.**

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 enforcing (non-)labelling violations. At present, appropriate measurement 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 threat 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.

Close to market transparency is the principle of traceability. According to the general food law framework, the traceability principle means that all players are in a position to remove products from the market, should they, after approval, turn out not to be safe – based on new scientific findings. **Parliament could therefore examine whether and to what extent the regulations on traceability need to be adapted for nanomaterials.**

Another issue is the improvement of product and market knowledge on the side of regulators, risk assessors and society at large. Currently, in many sectors manufactured nanomaterials can be marketed notwithstanding the substantial scientific uncertainties about the EHS risk related to them. **Parliament could consider supporting the conceptualisation and implementation of a mandatory notification scheme for products containing nanoparticles.** The obligation could lead to a product register either only available to authorities or, if desired, to the general public. This instrument would enable consumers to make their own choices and agencies to react immediately if new indications with regard to concrete hazards become known. The specific design of a possible product register depends on the intentions, goals and the utilisation of different actors.

It should be noted that most industry stakeholders tend to advocate voluntary measures rather than mandatory regulation. They argue that comprehensive legal obligations would lead to increasing bureaucracy and a decrease of their international competitiveness. Especially concerning the call of the general public (and CSO stakeholders) for more information that should be available in registries or in the form of a labelling of 'nanoproducts', industry stakeholders emphasise that voluntary information via public communication and their participation in public events with an informative character are sufficient. They argue that more far-reaching obligations, especially a detailed, obligatory registration of nanomaterials and/or 'nanoproducts' would infringe their intellectual property rights - which is an important issue for the industry stakeholders.

7. Intensifying the dialogue on social and ethical issues

Another important task for politics besides the regulatory measures consists in a social dialogue process, which should include all relevant stakeholders. The primary goal of a dialogue consists in creating trust. Transparent and credible information on nanoproducts will contribute to consumers' trust and freedom of choice. Their need for information with regard to individual concerns and perceived risks should be taken seriously. A prerequisite is the duty of care and the duty of disclosure for manufacturers as well as safety data that contains information on market volume, exposure and toxicological properties. **Parliament may want to consider the important role of concern assessment for the entire risk governance process, broadening public communication of ongoing efforts and current findings and intensifying participation in the relevant international discussion.**

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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).[31]

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: Carbon nanotubes

CoC: Code of Conduct

CSO: Civil society organisations

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

[31] 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).

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

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

ICCA: International Council of Chemical Associations

IRGC: International Risk Governance Council

ISO: International Organisation for Standardisation

JRC: Joint Research Centre

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.

Noxa: (pl. noxae) Latin for pollutant; a toxic substance/chemical that exerts a harmful effect on the human body or any other organism.[32]

OECD: Organisation for Economic Co-operation and Development

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

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

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).

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

VSSA: Volume specific surface area