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Recommendations for Legislation Policy Makers

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IMPART

Improving the understanding of the impact of nanoparticles on human health and the environment

Integrating Activity

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1 Introduction

1.1 The IMPART project, goals and implementation

The influence of nanotechnology on human life is increasing, not only given the fact that nanoparticles are being used as a component of many daily products, but also due to the great amount of materials synthesized for preliminary tests for nano-based devices. Although researchers discover new nanostructures and applications for them almost every day, the impact that nanotechnology can have on the environment, and especially on human beings, is still insufficiently explored. The knowledge gaps considering behavior of nanoparticles and their characteristics create concern in the society. Some groups have demanded a moratorium for nanotechnologies before nanoparticles impact is sufficiently explored and general acceptance is achieved.

In this context, initiatives have been undertaken by scientists, governments and industries. In order to accelerate the growth of knowledge, the co-ordination action IMPART started. IMPART linked a number of regional, national and international initiatives in order to reduce duplication of effort. With the increase of information exchange, through created databases and meetings, it helped understanding the implication of nanoparticles on human health and the environment.

The IMPART project main goals focused on popularization of the knowledge concerning nanotechnology and nanoparticles. Furthermore, this project has also drawn attention to missing standards and regulations. The current knowledge state, initiatives and best practices, in comparison with existing legislation have been extensively analyzed. Several conclusions and recommendations for policy makers have been given along the following chapters, keeping in mind crucial aspects to provide nano-safety. The best practices in this framework as well as intensive measures have been thoroughly analyzed in this context.

1.2 Added value

The greatest significance of the IMPART project in comparison to the existing reports/projects embracing similar considerations regarding nano-impact can be summarized into its inherent goal. In contrary to other projects which map *"what is known"*, IMPART project aims mainly to *“what is missing”*. From this starting point, the further steps focus on broadening the knowledge.

From this kind of searches, some basic gaps have been identified. A very illustrative example is the non-differentiation between "*regular*" and *"nano"* materials (the same "CAS number"). This still keeps outdated nomenclature despite the vast literature describing how "nano" matter differs substantially from "normal" (macro) matter. This is just one of several instances that have been evaluated throughout this project. The sources of these gaps are analyzed in the following chapters.

1.3 Structure of this report

This project is certainly not focused on presenting the state-of-art in nanotechnology but unquestionably concentrates in how these recent developments are taken into account within various entities that are somehow related to the fabrication or use of nanostructured materials. Individual awareness of the effects of nanotechnology in human life has been found. However, it has been detected that the collective procedures still demand special attention. This is the main topic dealt with in this specific document. Existing legislation regarding the hazards of nanostructured materials, and also the regulations currently followed for prevention, are thoroughly reviewed.

This document includes three major sections that give a clear overview of the knowledge acquired, and now provided, by the IMPART project regarding the impact of the production of nanomaterials on human life and the environment. Far from being a purely bibliographic search, this document spots objectively the gaps and divergences that have been identified. All this has given rise to an important outcome, drawing attention to an urgent need to a number of measures regarding legislation policies. With all the assessed data, section 4 has been prepared, with recommendations regarding legislation policies that require urgent attention under a global scope. Additionally, some solutions for immediate implementation have been considered, as well as suggestions for procedures within the further steps.

In particular, the "legislation gaps" chapter is centered around identifying existing gaps in the legislative / regulative systems concerning nano-sized materials. This *"recommendation"* report is mainly based on the material found in previous reports generated by the IMPART project. The gaps encountered in the cited sections were summarized here as a quick reference for policy makers. OECD, EC, Germany, and Canada were reviewed in the full reports. The order here has been considered according to which of these recommend the most elaborate effort for legislation to the case in which nano-sized materials, as considered as regular-size materials, are dealt without any special regulation.

2 Commented overview of current knowledge

2.1 Selection of materials reviewed

The nanomaterials reviewed for the IMPART project are focused on those which have several prominent properties. Novel properties of nanomaterials mean that they are likely to have distinctive transport and accumulation behavior. If exposure assessments and data are still lacking, it is foreseeable that some degree of exposure to engineered nanoparticles, to various segments of the population and the environment, will occur to an increasing extent over the coming years.

A major criterion is the persistence of the material within an organism or within the environment. We have therefore concentrated on stable materials already in use, that are likely to enter the environment in higher concentrations and stay there for months to years. Medical applications of nanoparticles have been excluded because the materials used are very specific, often with biological substances as their backbone, and will therefore require completely different risk governance. These factors have determined the materials that are discussed in this report.

Ceramics and metal oxides are already used in many applications. For instance, sunscreen manufacturers are adding nanoparticles of titanium dioxide and zinc oxide to sunscreens to make sun-blocking ingredients clear instead of white.

Fullerenes are used in cosmetics as a novel free-radical scavenger. Fullerenes are also being investigated for use as drug delivery agents. Several inorganic fullerenes (WS_2 and MoS_2) are used as advanced solid state lubricants in the automobile and aerospace industries and there is also some use in the military. Their spherical geometry enables their use as the best known shock absorbers (Zhu et al. 2005). Manufacture of these particles has recently moved to full-scale industrial production with several tons produced each day.

Carbon nanotubes (CNTs) have a wide range of uses and are already produced in very large quantities. Metal catalysts commonly used in their production are Co, Mo, Fe and Ni. The type and content of residual metal particles is important to the relative toxicity of CNTs.

Quantum Dots (QDs) are manufactured commercially and are generally based upon a CdSe spherical nanoparticle core coated or capped by a thin layer of ZnS as a stabilizing agent (Alivisatos et al. 2005). Recently a number of non-heavy metal based materials have also become commercially available. A point of concern is the decay of QDs, since the core constituents such as cadmium and selenium are toxic. Some evidence exists that the toxicity of QDs is often related to the capping material rather than to the core metalloid complex (Hoshino et al. 2007). In most situations, QDs are surface modified to improve dispersion properties, assist binding and biocompatibility, whilst also minimizing dissolution and reactivity of the metals present in both the shell and the core.

In general, the properties of nanoparticles can be significantly altered by surface modification and the behavior of nanoparticles in the human body strongly depends upon the surface characteristics. Changes of surface properties brought about by the coating of nanoparticles to prevent aggregation or agglomeration using different types and concentrations of surfactants have been shown to change their effects on biological systems significantly. Considering that surface modification is the fastest growing area of nanoparticle technology, the effects of these modifications on the toxicology of nanoparticles must be investigated (Donaldson et al., 2004).

2.2 Health, exposure, environment

Many health and environmental concerns are related to exposure to NPs that are free, rather than fixed to or within a material. Most ENPs are fixed within materials (e.g. composites). However, these particles may become free in the environment due to damage, degradation and recycling following disposal. Currently, exposure to free nanoparticles is mostly limited to workplaces of manufacture and research, and a number of cosmetic uses, including sunscreens. Health and environmental hazards may occur from the production, use and disposal of nanoparticles. Methods for general exposure assessment are still lacking for workplaces. There are no commercially available personal samplers designed to measure the particle number, surface area, or mass concentration of nanometer aerosols. Also, there are no occupational exposure limits for different types of nanoparticles and no standardized, well-characterized reference standards.

It is also possible that nanoparticles used in consumer products may pose a risk to public health. There are already hundreds of nanotechnology-based products on the consumer market but our understanding of the potential toxicity of nanoparticles is still very poor and there are no labeling requirements for products using nanomaterials. As yet legislation on the use of nanoscale products in personal care products is minimal to non existent. Manufacturers are not obliged to state whether nanoparticles are included in their products. Both regulatory agencies and the industries have resisted the calls for the regulation of the use of nanotechnology in cosmetics and personal care products. However, it is questionable whether non-regulation of the use of nanoparticles will be justifiable in the future. The growing number of nanoparticle-containing products is likely to lead to further calls to regulate the use of this technology in consumer products in the near future.

The central issue is that there has been very little research into the life cycles of products containing ENPs and any possible risks from their potential to release free nanoparticles. An assessment of the risks of ENPs in the environment requires an understanding of their mobility, reactivity, ecotoxicity and persistence (Nowack and Bucheli, 2007) and there is, therefore, a need for a life cycle analysis of products containing ENPs. A product life cycle analysis should consider the processes and materials used in manufacture, the likely interactions between the product, people and the environment during its manufacture and useful life, and the methods used in its eventual disposal (Royal Society Report, 2004).

Nanoparticles have different levels of interaction with biological systems and have different mobility based on their size, shape and chemical composition. It is not, therefore, possible to address the hazards and risks of nanoparticles in a general way, as each type of nanoparticle needs to be evaluated. At this time there is not enough research on engineered nanoparticles to know whether or not they present a serious problem to human health and the environment. In order to prevent a backlash of negative public opinion and a political and regulatory backlash, the nanotechnology industry is keen to accumulate risk data to answer questions and address risks early. This will enable the nanotechnology industry to develop and flourish responsibly and with public support (Hood, 2004).

2.3 Legislation

Existing legislation has been reviewed in the, partially overlapping, fields of chemicals as well as workers, consumer and environmental protection.

2.3.1 Chemicals

The current European legislative framework is being replaced by REACH, the Regulation concerning the Registration, Evaluation, Authorization and Restrictions of Chemicals (Regulation No 1907, 2006). The provisions of REACH apply to the manufacture, import, placing on the market or use of substances on their own, in preparations or in articles, if so stated. REACH abolishes the distinction between existing and new substances and establishes a single legislative system for the marketing of chemical substances in Europe. It replaces Council Regulation 93/793 (1993) as well as Council Directive 76/769 (1976). The existing restrictions will remain in force and will be listed in an annex to the REACH Regulation. Council Directives 67/548/EEC (1967) and 1999/45/EC (1999) (dangerous preparations) are to be amended. The provisions related to the safety data sheets (Directive 91/155/EEC amended by Directive 93/112/EEC and Commission Directive 2001/58/EC, 2001) have been incorporated into the REACH Regulation.

Any substance that is produced or imported in annual volumes of at least 1 ton/year must be registered. If the annual volume is > 10 tones, mandatory preparation of a chemical safety report (CSR) which contains chemical safety assessments (CSA) for each identified use, is required. A CSR should include: human health hazard assessment, assessment of human health hazard by physicochemical properties, environmental hazard assessment, PBT (Persistent, Bioaccumulative, Toxic) and a vPvB (very Persistent and very Bioaccumulative) assessment. If, as a result of these steps, the manufacturer or importer concludes that the substance or the preparation meets the criteria for classification as dangerous according to Directive 67/548/EEC (1967) or Directive 1999/45/EC (1999) or is assessed to be a PBT or vPvB, the CSR should also consider an exposure assessment and risk characterization. The main element of the exposure part of the CSR is the description of the manufacturer's or importer's exposure scenario(s) and the exposure scenario(s) recommended by the manufacturer or importer to be implemented for the identified use(s).

Uses of a substance for product and process oriented R&D are exempt for five years from the obligation to be included in the registration dossier of this substance according to Article 9, No. 1 of the REACH Regulation; this exemption can be extended according to Article 9, No. 7. Other obligations, e.g. for risk assessment, classification and labeling, and occupational health and safety, nevertheless apply. It means, that the manufacturer or importer, or producer of nanomaterials for product and process oriented R&D with volumes of less than one ton/yr after 5 year of uses, according to Article 9, No. 2, shall notify the Agency of the following information: the identity of the manufacturer or importer or producer, the identity of the substance, the classification of the substance, the estimated quantity, and the list of customers.

In the context of nanotechnologies, the REACH Regulation defines a substance as "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…" (Article 3, No 1). A key consideration in this regard is the fact that the nano-equivalent of a substance could have different physicochemical and ecotoxicological properties from the substance itself. If it is considered to be a different substance, then the registrant may submit a different registration dossier for the nano-substance (if produced in volumes greater than 1 ton/yr). This means that the manufacturer would be required to generate hazard information on nanomaterials prior to placing them on the market. On the other hand, if the nano-equivalent is considered to be the same as the registered substance, the hazard information would still be available, although the appropriateness of the data for the risks of nanomaterials would be open to discussion.

The European Chemicals Agency (ECHA) has stated on December 3, 2007 at the European NanOSH Conference in Helsinki, that REACH treats both, the bulk material and the nanosized material, as the same substance. The Agency added that this, however, does not prevent the registrant from identifying dangerous properties of this substance depending on its size and classify the different types accordingly. Requirements for substance identification are specified in Annex VI, section 2 (identification of the substance) of the REACH Regulation.

For the risk assessment of substances, REACH requires a set of physicochemical, toxicological and ecotoxicological information, reflecting the spectrum of all identified uses of the substance, i.e. also the identified uses of the substance in its nanomaterial state. The minimum information requirements for different tonnage levels of the substance according to Article 12 of the REACH Regulation are specified in detail in the Annexes VII – X. The test methods to be used for gathering toxicological and ecotoxicological data may require adaptation according to the physicochemical properties.

The Organization for Economic Co-operation and Development (OECD) produced a list of endpoints to take into account when testing specific nanomaterials for human health and environmental safety (OECD, 2008). Addressing these would ensure consistency between the various tests to be carried out on specific nanomaterials. It would also lead to the development of dossiers for each nanomaterial describing basic characterization, fate, ecotoxicity and mammalian toxicity information. However, it must be noted that the set of endpoints for nanomaterials presented by the OECD is beyond the scope of the REACH requirements for assessment of physicochemical properties of substances (Annexes VI, VII, VIII, IX, X and XI of the REACH Regulation).

The provisions of REACH do apply to nanomaterials, including placing them on the market and controlling any risks. According to the Directive 2006/121/EC Annex V, using testing methods to determine the dangerous properties of substances of the

Directive 67/ 548/EEC, was deleted. The experts of the European Commission preparing regulation on test methods should consider introducing the new and revised test guidelines suggested by the OECD for nanomaterials.

2.3.2 Protection of workers' health and safety

European rules concerning the protection of workers' health and safety do not aim for harmonisation of the different Member States' legislations; the Member States are, therefore, entitled to impose national rules more stringent than the European ones if they see fit to do so. The most important piece of legislation in the area of health and safety at work is the Framework Council Directive 89/391/EEC (1989) "on the introduction of measures to encourage improvements in the safety and health of workers" to ensure a higher degree of protection of workers at work. The model for health and safety management in the Framework Directive places prevention in a central position. Equally important are the provisions regulating the obligations of the employers for planning, organizing and regulating the protection of workers at work. The employer is obliged to make an a priori overall risk assessment, and to undertake measures to prevent occupational risks. In the first instance they should combat risks at the source either by eliminating, avoiding or, if this is not possible, by taking the appropriate control measures in order to reduce them (e.g. selecting personal protective equipment (Council Directive 89/656/EEC, 1989). Methods for risk assessment in relation to worker protection need to be developed and made available to the employers.

In addition to the Framework Council Directive 89/391/EEC (1989), there are two other Directives that could be applied, the second one in case any nanoparticle is shown to be carcinogenic or mutagenic:

1. Council Directive 98/24/EC (1998) on the protection of the health and safety of workers from the risks related to chemical agents at work
2. Council Directive 2004/37/EC (2004) on the protection of workers from the risks related to exposure to carcinogens or mutagens at work.

Current legislation covers, in principle, the aspects regarding protection of workers health and safety against risks due to nanomaterials. The obligations of employers are to carry out a risk assessment and introduce measures to eliminate/minimize the risk at the source. The workers and/or their representatives must receive sufficient and suitable training about the potential health risks, precautions for preventing exposure, hygiene requirements, and protective clothing. The nano-scale substances should be covered by the Materials Safety Data Sheets.

2.3.3 Products containing ENPs

Manufactured products containing ENPs are covered by specific Community legislation, laying down product requirements for safety and health of consumers, but also workers and environmental protection, e.g. plant protection products, biocides, and cosmetics:

- Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market; OJ L 230, 19.8.1991.
- Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market; OJ L 123, 24.4.1998.
- Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products; OJ L 262, 27.9.1976.

Regarding plant protection products, the IMPART opinion is that Directive 91/414/EEC covers nanomaterials. However, some guidance documents need to be amended in order to properly address risks i.e. data requirements, risk assessment.

For regulation of biocidal products, the Directive 98/8/EC covers nanomaterials. However, we suggest that some technical notes for guidance in Annexes II-IV (on data requirements, risk assessment and decision making) should be amended in order to properly address risks of nanomaterials.

The IMPART consortium suggests that the “Cosmetics Directive” 76/768 should be amended. There are large data gaps in the risk assessment methodologies and in regard to data on the nanoparticles in cosmetic products via skin absorption, inhalation and ingestion. The biodistribution (toxicokinetics) of nanomaterials has not been studied in detail. Although the requirements of testing the mutagenicity/ genotoxicity of nanoparticles are similar to those of other materials, the specific characteristics of nanoparticles may require further considerations. The present validated *in vivo* genotoxicity tests, however, do not cover the expected target organs of nanoparticles (particularly the respiratory tract) and have not been validated with reference substances, including nanomaterials of relevance for cosmetics. All *in vivo* and *in vitro* risk assessment methods for nanomaterials are still in the research phase. Although some validated *in vitro* methods do exist they have never been validated with nanomaterials as reference compounds. Although animal testing has been largely reduced for skin penetration studies, they are essential for translocation and accumulation studies as well as for chronic toxicity studies.

The new and revised test guidelines by the OECD Working Party on Manufactured Nanomaterials (WPNM) should be introduced.

2.3.4 Environment

Applicable legislations are:

- Council Directive 2008/1/EC (2008) concerning integrated pollution prevention and control
- Seveso II Directive 96/82 (1997)
- Water Framework Directive 2000/60/EC (2000)

Industries are obliged to make an a priori overall risk assessment and to undertake measures to prevent environmental risks. This is essential to combat risks at source either by eliminating/avoiding or, if not possible, by taking the appropriate control measures in order to reduce them.

2.3.5 Incremental approach

The European Commission has adopted a so-called "incremental approach", which focuses on adapting existing laws to regulate nanotechnologies, and Franco et al. (2007) aimed to test the effectiveness of the approach. The authors used three commercially available products containing fullerenes and carbon nanotubes that were analyzed in a life cycle perspective in order to: (1) map current applicable regulations; (2) analyze their applicability to nanomaterials; (3) identify their gaps, and; (4) suggest proper solutions. After mapping the life cycle of the three products, Franco et al. (2007) analyzed applicable regulations in the order in which they became relevant in their life cycle, i.e.:

- The Safety at Workplace Directives
- Council Directive 96/61 (1996) on the Integrated Pollution Prevention and Control
- The European Union's Directive on the Registration, Evaluation, Authorization and Restriction of Chemicals (Regulation No 1907, 2006)
- The Waste Management Directives: Council Directive 2006/12/EC (2006), Council Directive 91/689/EEC (1991), Council Directive 75/439/EEC (1975), Council Directive 2000/53/EC (2000)

It was found that the applicability of environmental laws is limited, due to difficulties in generating sufficient data on the nanomaterials within the products according to their life cycles. The authors pointed out that metrology tools are unavailable; thresholds are not tailored to the nanoscale; and toxicological data and occupational exposure limits cannot be established with existing methodologies. The conclusion of this paper is that the "incremental approach" would only be applicable with the implementation of due amendments. Based on the findings, the authors concluded that the European "incremental approach" could work. In the short-term, they specifically have six recommendations for amending current rules and regulations:

1. Define standards for labs and other workplaces handling nanoparticles
2. Actively promote research and development of usable metrological tools
3. Establish a Technical Working Group within the EU Bureau of Integrated Pollution Prevention and Control to organize an exchange of information
4. Adapt the Chemical Abstract Service (CAS) to properly classify nanoparticles
5. Establish a specific regime for nanoparticles within REACH requiring industry to submit information on Nanoparticles characteristics and health, safety and environmental information
6. Add free nanoparticles to the list of Annex II in Directive 1991/689 on hazardous wastes

A study by Crane et al. (2008) concluded that the types of test species and biological endpoints used within standard environmental hazard assessment frameworks are generally appropriate. However, there are areas of considerable uncertainty associated with characterization of nanoparticle exposure in test systems that apply to all ecotoxicity testing guidelines, except those in which dosing of nanoparticles is oral. These include the way in which the substance is dosed into, and maintained within, the test medium; measurement and characterization of nanoparticles in the test system; better understanding and reporting of abiotic factors that influence behavior of nanoparticles in the test medium; and agreement on how dosimetric data should be reported.

3 Assessment of existing data

3.1 Important factors in assessing the safety of nanomaterials

Risk assessment in general comprises several components including:

- Hazard identification
- Hazard characterisation
- Exposure assessment
- Risk calculation

On the basis of a reliable risk assessment, measures for risk management have to be undertaken, comprising preventive measures, standardisation and regulation activities. The following figure (Fig. 1) gives an overview of different aspects and components, which have to be taken into account for the assessment and management of risks associated with industrial nanoparticle production and use.

1. Hazard identification

Particle characteristics
- Aspect ratio
- Diameter
- Surface area
- Water solubility
- Chemical composition

Emission
- Production volume
- Material flow
- Potential release

Health effects
- Humans
- Experimental animals

Environmental effects
- Persistence
- Biomagnification
- Long range transport

2. Hazard characterization

Epidemiological Studies
- Workers
- Consumers
- Exposed population

In vivo studies
- Acute/chronic
- Different species

In vitro studies
- Human/animal, different cell types
- Models (lung, skin, systemic effects)

3. Exposure Assessment

Exposure routes
- Inhalation, dermal ingestion

Environmental monitoring
- Biological uptake

Occupational monitoring
- Personal exposure

4. Risk calculation

Susceptibility extrapolation models
- High dose – low dose
- Animal – human

Threshold value calculation
- Intake emission concentration
- Maximum workplace concentration

5. Risk Management

Preventative measures
- Personal protection equipment
- Modification of processes

Standardization
- Measurement techniques
- Toxicological assessment

Regulation
- Exposure/emission schedule
- Production standards/restrictions

Fig. 1: Components and aspects of risk assessment and management (adapted from "Industrial application of nanomaterials - chances and risks, Technology analysis, VDI-TZ, W. Luther (ed.), 2004)

In view of the fact that data on exposure assessment are lacking, a full risk assessment of nanoparticulate materials in most cases is not feasible at present. However a ranking of potential risks can be achieved by applying hazard trigger algorithms. Relevant factors which can give a first estimation of potential risks of nanoparticles are:

- Production volume
- Potential exposure to customers, workers, environment
- Potential aerosol release during production, handling, processing
- Solubility

- Aspect ratio (to distinguish between fibers and particles)
- Particle diameter (taking into account a potential deagglomeration in body liquids e.g. in the lungs)
- Toxicological and ecotoxicological parameters

It can be assumed that many parameters of nanoparticulate materials with regard to toxicological and ecotoxicological properties will be unknown. Here, standardised screening tests would be of great use for giving a first assessment of potential risks. Nanoparticulate materials which are assigned a high priority by such an estimation should be subject to further investigations and/or regulatory measures.

Knowledge gaps in the assessment of existing data:

Knowledge gaps, some of which have been identified by the NIOSH Nanotechnology Research Center, include:

- The application of risk assessment methods in using existing data to provide a framework for developing preliminary risk management strategies.
- Biomathematical modelling approaches to fill data gaps concerning occupational health risks of exposure to non-spherical nanoparticles
- Standardized high-throughput methods of *in vitro* screening which reliably reflect *in vivo* toxicological potential

3.2 Toxicology, hazards, risks, environmental issues

3.2.1 TiO_2 (and accordingly SiO_2) particles

- We have to examine to which concentrations of TiO_2 humans are exposed and these doses have to be used in toxicity studies. *In vivo* studies with TiO_2 doses causing an overload are not relevant for assessing their health effects on humans
- Further investigations are also required to establish the role of the crystal form and surface chemistry and the mechanisms of photoactivity of nanoscale TiO_2
- The effects of coatings on TiO_2 particles have to be further clarified because surface treatments can influence its toxicity. Impurities linked to the synthesis of the TiO_2 particles seem to be very important
- From an environmental viewpoint, the long term stability of these coatings needs to be characterized
- Ultrafine TiO_2 is frequently used in sunscreens. However, the fate of ultrafine-TiO_2 applied to skin is uncertain. Whether nanoparticles can penetrate trough the skin has to be investigated further, because TiO_2 has the ability to form ROS such as hydroxyl radicals that can cause damage to cells and DNA
- Further research is needed to clarify the genotoxic effects of nanoparticles. It is not clear whether they can cause only single-strand breaks or both single- and double-strand breaks

3.2.2 Carbon materials

- Non purified, iron-containing CNT can produce cellular oxidative stress, whereas purified CNT don't to such an extent
- DNA damage (probably linked to oxidative stress) is linked to internalized CNT
- Cytotoxicity of CNT is dependent on the presence of metal impurities, surface reactivity and formation of agglomerates. Purified and water soluble CNT seem to be less cytotoxic than non-purified, water-insoluble materials
- For nanomaterials (CNT and non-fibre metallic and non-metallic materials) oxidative stress appears to be the common mechanism involved in cytotoxicity
- Role of internalisation on the cytotoxicity and the biocompatibility of surfaces containing CNT
- The comparison with asbestos is an important issue, certainly since a recent publication showing that very thick and rigid MWCNT induced length-dependent pathology in the mesothelial lining of the mouse body cavity (as a model of the chest mesothelial lining), (Poland et al., 2008). The *in vitro* study by Wick et al. (2007) also reported similar effects of SWCNT agglomerates and asbestos on cytotoxicty and cell proliferation in a human mesothelioma cell line

3.2.3 Engineered quantum dots

In addition to their potential toxicological properties arising from their nano-particulate nature, some of these quantum dots are composed of elements such as Cd, which are toxic. To prevent toxicity, they are coated with a protective layer, however, the stability of the coating over the long term is a matter of concern, especially if the materials diffuse into the environment.

3.2.4 Knowledge Gaps concerning toxicology and internal dose

Uncertainty remains about many toxicological aspects of nanoparticles in general, including:

- The nature and severity of effects on the lung from inhaled nanoparticles
- Whether exposure to nanoparticles has any effect on the immune system
- Which unique physical and chemical properties of nanoparticles affect the body's response when exposed to these particles
- The relative importance of particle size as a cause of observed health effects
- Whether nanoparticles move throughout the body and affect organs other than the one through which they entered the body
- Persistence in the body
- Long-term stability of coatings

3.2.5 Environmental issues

A number of recent, comprehensive reports outlining the risk associated with the manufacture, modification, formulation and employment of nanomaterials have been placed in the public domain (Singh 2007, Aitken 2006 and NIOSH 2006). Other reports have examined the environmental risks associated with such materials (Guzman 2006) or examined occupational exposure (Aitken 2004), potential health concerns (Powell 2006), risk assessment approaches (Kuempel 2007) and precautionary measures (NIOSH 2006), including suggestions of best practice in this field. Indeed precautionary measures are warranted in the current uncertain climate. Many practitioners, including respiratory experts, toxicologists, environmentalists and meteorologists have argued strongly for the adoption of a uniform set of references and standards (Aitken 2006). Furthermore by considering risk at an early stage in the development of a technology, the potential (detrimental) impact on the environment and public health can be minimized. An account of EU-funded initiatives in research and development in this area of nanotechnology has recently been published by Aguar (2008).

Health and environmental hazards may occur from the production, use and disposal of nanoparticles. Workers in nanotechnology industries are particularly at risk, as it is possible that they could be exposed to high concentrations of nanoparticles that may enter the body through ingestion, inhalation, or skin exposure.

Despite evidence suggesting that we should be concerned about the potential impact of nanomaterials on the health and safety of both humans and ecosystems, there is still a significant amount of uncertainty as to how nanomaterials differ in properties from their bulk counterparts and the corresponding risks. Little is also known about the environmental persistence or impact of engineered nanoparticles. It is difficult to predict which of these new materials may bioaccumulate and persist, as there have been no long-term studies observing the unique physiochemical characteristics of these new materials. Given the complexity of aquatic systems with their suspended sediment particles and natural colloids like humic acids and the water microlayer, predicting the behaviour of nanoparticles is likely to be much more difficult than predicting the behaviour of conventional chemical pollutants, which is still often a major challenge. We may be able to use the known behaviour of natural nanoscale or microscale particles, such as colloids, viruses and bacteria; and how these adsorb to or associate with larger biotic and non-biotic particles in the suspended and deposited sediment.

There is a serious lack of life-cycle analyses that look at the possibilities for environmental release of ENPs from production through to disposal of nanomaterials. There may be direct inputs into the aquatic, marine and terrestrial ecosystems and into the atmosphere from initial and downstream manufacturers. There may also be non-industrial inputs, e.g. consumer products including sunscreens and cosmetics from direct and indirect sources, leaching from landfill or soil-applied sewage sludge, and atmospheric sources of nanomaterials from waste combustion. It is certain that further use of nanomaterials will result in their introduction into environmental systems and ecosystems in greater quantities (Helland et al., 2008). Understanding what happens to nanomaterials during their journey from manufacture to waste disposal will help to focus studies that can tell us about transport pathways, biogeochemical cycling and environmental fate. Such work will help us to identify which, if any, environmental compartments are at risk of contamination by nanomaterials (Owen and Depledge, 2005).

Fortner et al. (2005) are currently conducting studies on how C_{60} (fullerene) affects bacteria and simple organisms like worms. They are also exploring whether these fullerenes tend to move up the food chain. Initial results show that NPs accumulate in living cells over time, with ever-increasing concentrations in microbes, in the worms that eat those microbes, and in animals higher up the food chain. It is possible that these NPs reach humans. NPs have been shown to inhibit the motility and phagocytosis of macrophages in the lungs, which suggests that similar effects might be expected in simple soil organisms (Lam et al., 2004). Lovern and Klaper (2006) recently found that exposure of Daphnia magna to filtered C_{60} and filtered TiO_2 caused an increase in mortality with increasing concentration.

There are several ongoing studies evaluating fullerene toxicity in aqueous systems. Due to the possibility of C_{60} solubilisation through colloid formation under environmental conditions, many studies have focused on the effects of n-C_{60} (highly stable colloidal aggregates of C_{60}). The possibility of n-C_{60} formation following extended contact with water suggests that n-C_{60} could be a significant form of C_{60} if these fullerenes were introduced to aquatic systems. The first interest attracting published work on n-C_{60} toxicity to organisms concluded that n-C_{60} produced oxidative damage in the brains of exposed largemouth bass (Oberdörster, 2004). Nevertheless, the same group has to correct these results as the tetrahydrofuran (THF) solubilised fullerenes are toxic through the peroxides coming from the solvent THF (Oberdörster et al., 2006). The tendency of n-C_{60} to aggregate and deposit will play a key role in determining its longevity in aquatic systems and, therefore, provide key information on the exposure risk presented by these colloids. In one case, it was shown that hydrophobic contaminants can irreversibly interact with fullerene aggregates in water, and these species showed a high capacity for concentrating a model aromatic hydrocarbon (Cheng et al., 2004).

The mobility of eight particulate products of nanochemistry in a well-defined porous medium were evaluated by Lecoanet et al. (2004) to assess their potential for migration in porous media, such as groundwater aquifers and water treatment plant filters. Their results showed that nanomaterials exhibit widely differing transport behaviours, and consequently, they suggest that the potential for exposure to n-C_{60} through groundwater transport may be less than that of other fullerenes. Observations made by Brant et al. (2005) suggest that, under some conditions present in natural aquatic systems, these materials have limited mobility as they form large aggregates that may settle out of suspension or deposit on surfaces. These phenomena may, at least partially, offset any risk presented by n-C_{60} toxicity due to a reduced potential for exposure (Brant et al., 2005). Such investigations will increase understanding of the potential uses of such NPs to clean-up groundwater pollution, as well as aiding in the assessment of any environmental risks the materials may present.

More recent data have shown for the first time how multiwalled carbon nanotubes might behave in natural aquatic environments (Hyung et al., 2007). This research suggests that natural organic matter present in river water could aid the dispersion of carbon nanotubes by stabilizing the nanotubes and increasing their potential for dispersal dramatically. In fact, their experiments showed that natural organic matter stabilizes the model carbon nanotube in the aqueous phase more efficiently than a surfactant. They also found that the nanotubes remain as discrete units. However, the toxicity of the new materials in natural environments remains relatively unknown. The paper on the occurrence, behaviour and effects of NPs in the environment by Nowack and Bucheli (2007) is a comprehensive and useful review of this area.

There is still currently very little evidence on which to determine the risks posed by engineered nanoscale materials. It is, therefore, difficult to assess the additional measures that may be necessary to control potential risks. To address this, the UK Government has developed a comprehensive programme of research on potential risks and a Voluntary Reporting Scheme for engineered nanoscale materials. This scheme aims to contribute to the process of gathering evidence on the potential health and environmental impacts of nanomaterials. There are uncertainties about the risks of nanoparticles currently in production that need to be addressed immediately to safeguard workers, consumers, and the environment, and to support regulatory decisions that may be necessary. The report produced by the Royal Society and Royal Academy of Engineering in 2004 recommends that, until more is known about the environmental impact of NPs, their release into the environment should be avoided as far as possible. They also recommend that NPs should be treated as hazardous and be reduced in waste streams and that the use of free NPs in environmental applications such as remediation of groundwater be prohibited (Royal Society Report, 2004).

More research into the hazards and exposure pathways of NPs and nanotubes is required to reduce the many uncertainties and knowledge gaps related to their potential impact on health, safety and the environment. Current funding and hence research is inadequate. Zhang (2003) suggests that more attention should be directed to the fundamentals of nanochemistry in the environment, such as the process of contaminant transformation at the nanoparticle-water interface. An interdisciplinary approach is necessary for an appropriate risk assessment. There are many opportunities for collaboration between the different centres of expertise in nanotechnology, environmental science, pharmaceutical science and toxicology within the European Community. It is important to appreciate that environmental scientists and engineers already investigate nanostructures and nanoscale systems, as in studies of the natural weathering of minerals or the production of nanoscale colloids by microorganisms that are important in the fate, transport and transformation of potentially toxic substances (Masciangioli and Zhang, 2003).

Knowledge gaps in environmental risks:

- Environmental persistence, mobility through the food chain and bio-accumulation of ENPs
- Environmental release profiles through the entire life cycle of ENP-containing products

3.3 Best practices

Best practices in dealing with potentially dangerous materials of any type involve the following steps:

- Hazard identification – is there reason to believe the material could be harmful?
- Hazard characterization – how and under what conditions could it be harmful?
- Exposure assessment – will there be exposure in real world conditions?
- Risk characterization – is the substance hazardous and will there be exposure?
- Risk management –develop procedures to minimize exposure.

Best practice protocols specifically dealing with nanoparticle production and handling have been drawn up by various companies and government organizations and address the issue in varying degrees of detail. (See “Best practices” in the reference list). Once the hazard posed by the nanomaterial has been evaluated, based on available, physical and chemical property data and toxicology or health effects data, and the potential worker exposure has been assessed to determine the degree of risk, the issue of “best practice” becomes one of risk management. It is generally accepted that risk management involves:

- The education and training of workers in the proper handling of nanomaterials (e.g., good work practices). This activity is not restricted to those producing nanoparticles but applies also to customers handling the materials in downstream applications. Part of the education includes instructions and safety data sheets to be provided, along with the raw materials, to the customers
- The establishment of criteria and procedures for installing and evaluating engineering controls (e.g., exhaust ventilation) at locations where exposure to nanoparticles might occur
- The development of procedures for determining the need for- and selection of personal protective equipment (PPE) (e.g., clothing, gloves, respirators)
- The systematic evaluation of exposures to ensure that control measures are working properly and that workers are being provided the appropriate PPE
- Routine health surveillance programs to ensure that any work-related change in health status is quickly determined and steps taken to identify and address the causes

3.4 Legislation

Current European legislation covers, in principle, the important aspects regarding workers’ and consumers' health and safety as well as protection of the environment.

The most important gaps found with an impact on legislation can be listed as follows:

- With regard to cosmetics several alternative tests have not been validated with reference substances including nanoparticles/nanomaterials
- In addition; there are some knowledge gaps regarding toxicology and the internal dose, fire and explosion safety, engineering controls and personal protective equipment and measurement etc. Regarding legislative aspects it is thus important

to develop and validate methods for evaluating the health, safety and environmental impact of engineered nanomaterials. Without such a validation it will be difficult to develop a solid basis for adapting current legislation and regulation

- good occupational hygiene practices and existing knowledge on how to work with hazardous substances provide a useful basis for working in a safe way with nanomaterials. These practices are not sufficiently communicated and fostered
- a standardized and trust-based framework for the risk assessment (health, safety and environment) of nanoparticles/nanomaterials (which includes for instance standard reference samples and toxicology protocols) is missing, to adapt current legislation, regulation and its implementation to match the requirements for a responsible industrial use of nanoparticles/nanomaterials where necessary.

4 Recommendations with regard to legislation policy

The goal of this section is its use by policy makers and legislators in order to improve safety and health regulations in all cases where nanoparticles are involved.

4.1 Summary of assessment and knowledge gaps detected

4.1.1 General

There is an ongoing debate on whether current laws and regulations need to be strengthened where they relate to nanotechnology. Good occupational practices and existing knowledge on how to work with hazardous substances provide a useful basis for working safely with nanomaterials. But where existing knowledge fails, new research is needed to fill the gaps.

Several studies demonstrate that nanomaterials, which are making their way into the marketplace today, are possibly harmful to consumers and the environment, some studies have already suggested that engineered nanomaterials may be harmful, for instance, causing brain damage in animals.

The health and safety issues related to nanomaterials are in an early phase and, as a consequence, it seems premature to draw far-ranging conclusions regarding the potential hazards and risks related to exposures to these materials, particularly since the inhalation toxicology database on nanomaterials is rather sparse. Similarly, few data exist regarding the health risks of dermal or oral exposures to nanomaterials. It is necessary to develop methodologies and protocols concomitant with the implementation of hazard/toxicity studies, as well as workplace exposure assessments and legislation with the aim to have immediate and medium term impact of nanomaterials on human health.

The following knowledge gaps have been detected:

- some specific characteristic of nanomaterials will necessitate new test strategies to determine the mechanisms of potential injuries that they may cause
- more information about surface energy, reactivity and biological activity is needed
- lack of metrology instrumentation
- need for standardized and well characterized nanomaterial samples
- methods to evaluate dermal and/or injection exposure
- generally methods for exposure assessment are lacking in workplace
- research has to be continued in skin absorption of different composition of nanomaterials as way of occupational exposure and for development of safety measure
- behavior of nanomaterials from manufacture to waste disposal; to identify which environmental compartments are at risk of contamination with nanomaterials

Significant efforts are required in order to collect the large amount of data required to establish the risk assessment of nanomaterials. A standardized framework for the risk assessment of nanomaterials, involving standard reference samples and toxicology protocols, should be developed as soon as possible.

The "REACH" concept, which is currently in its initial phase, is the tool to automatically adjust and broaden the existing legislation according to new information and techniques found later.

4.1.2 Recommended REACH work tools

The OECD WPMN recommends a tabulated set of information, such as NP Id, environmental fate and toxicology, material safety, characterization of NP, Mammalian toxicology, etc. Here it has to be mentioned, that the scope of OECD exceeds the REACH demands.

The IMPART Consortium suggests that in addition to the OECD recommendations, the following principles are essential for the continuing implementation of REACH:

1. Define standards for labs and other workplaces handling Nanoparticles
2. Actively promote research and development of usable metrological tools
3. Establish a Technical Working Group within the EU Bureau of Integrated Pollution Prevention and Control to organize an exchange of information
4. Adapt the Chemical Abstract Service (CAS) to properly classify Nanoparticles
5. Establish a specific regime for Nanoparticles within REACH requiring industry to submit information on Nanoparticles characteristics and health, safety and environmental information
6. Add free Nanoparticles to the list of Annex II in Directive 1991/689 on hazardous wastes

4.1.3 Various NP areas which meet the REACH concept, and those which need refinement

The plant protection products: Besides the two recommendations

- harmonizing the process for considering the safety of active substances at an EC level, and, once safety of the active substance has been established
- allowing product authorizations to be considered at a national level using the established harmonized criteria,

IMPART is satisfied with the NP coverage.

Biocidal products: IMPART is satisfied with the NP coverage.

Cosmetic products: IMPART opinion is that large gaps still exist and must be further assessed.

Protection of workers' health and safety against risks due to chemicals: Current legislation covers in principle the aspects regarding protection of workers' health and safety against risks due to nanomaterials. The obligations of employers are defined:

- to carry out a risk assessment and introduce measures to eliminate/minimize the risk at the source
- The workers and/or their representatives must receive sufficient and suitable training about
- potential health risks, precautions for preventing exposure; hygiene requirements
- protective clothing
- the substances in nanoscale should be covered by the Safety Data Sheets

Environment: Current legislation covers in principle the aspects regarding environmental protection, by including requirements for specific waste materials. Risks of nanomaterials are not explicitely addressed. More restrictive actions are under the responsibility of national policy makers. From the IMPART point of view further legislative and regulatory steps can only be taken when a defined need for actions, based on scientific investigations to be conducted, is available.

4.1.4 International activities

OECD is strongly involved in helping to develop a unified legislation concerning NPs. Although a non-national body, it enjoys active participation of the EC and other countries. The aim is that the end-result will be the development of dossiers for each nanomaterial describing basic characterization, fate, ecotoxicity and mammalian toxicity information. It is also expected that the list of endpoints be refined based on the practical results obtained through the testing programme, which has now started.

ISO has recently issued two important documents, which largely help to clarify the standardisation basis for nanotechnologies in general, and nanoparticles in particular:

- ISO Technical Specification 27687: Nanotechnologies **-** terminology and definitions for nanoparticles; ISO/TS 27687:2008(E)
- ISO Technical Report 12885: Nanotechnologies **-** health and safety practices in occupational settings relevant to nanotechnologies; ISO/TR 12885:2008(E)

USA**:** The National Nanotechnology Initiative (NNI) is the Federal Government's agency for multidisciplinary nanotechnology research and development. The goals of NNI are to advance a world-class research and development program; to foster the transfer of new technologies into products for commercial and public benefit; to develop and sustain educational resources, a skilled workforce, and supporting infrastructure and tools to support responsible development of nanotechnology regulatory decisions regarding Nanomaterials are covered under current statutes. Established in fiscal year 2001, the NNI serves as a focus for communication, cooperation, and collaboration among participating federal agencies and provide a framework of shared goals, priorities and strategies.

However, the main obstacle depends on a fundamental question: "are NPs new materials?" This question is the basis of one of this report's recommendations, since both "regular matter" and NPs have the same CAS numbers. This question, as well as a suggested solution, appear in the next section.

4.1.5 CAS numbers

Discussions held with a leading marketing manager of the largest fine chemical company in the US during the preparation of this documents are stated here. The discussion was centered on the following fact:

No official MSDS mentions any risk or toxic effects which may be inflicted by nanoparticles, or any special recommendation for safer working practices. For example, there is no information as of the cytotoxicity of Gold NPs, or the dangerous nature of nano Aluminum.

The discussion revealed the following problem: No legislative systems tackled with the differences between NPs and "normal"-sized matter. Therefore, they do not differentiate a traditional X compound from X-NP.

Recommandation: Forming a new labeling system for NPs, just by adding to the traditional CAS No. "**-N**", may be a great advance, as manufacturers will have to include the actual health, risks, toxicity information. These steps can be enforced even before any legislation, since manufacturer must modify their MSDSs according to the best published safety data, without the need of appropriate legislation.

A more elaborate division may be that **N** will be accompanied with an identification symbol according to its suitability for different uses

M	(for products in medical & cosmetic uses)	- NM
F	(for products added to food)	- NF
A	(for products used in agriculture)	- NA
I	(for products used in industry)	- NI

4.2 Derived need for actions in the field of legislation

By assessing possible hazards to workers that might be connected with their activities, employers must identify occupational health and safety measures to be taken. These include design and structure of the workplace in its entirety and of individual workstations, as well as measures to reduce exposure to physical, chemical and biological impacts.

One can propose a number of obligations of employers to take measures necessary for the safety and health protection of workers:

- Employers must carry out a risk assessment in relation to nanomaterials related risks for workers health and safety
- Adopt preventive and protective measures for workers

- Worker protection is also achieved by product regulation containing specific rules in order to protect workers, such as personal protective equipment, medical devices etc

In order to determine technical, organisational and personal protection measures, the following points must be examined based on the hazard assessment:

- whether health-endangering substances or technical processes can be replaced by less dangerous substances or processes (e.g. substance variations with reduced emissions)
- technical measures: use contained installations and capture, limit and remove dangerous gases, vapors and dusts, at source if possible
- organisational measures: adequate washing facilities, protected storage of clothing not worn for work purposes, further hygiene measures, time arrangement of operational sequences, training and instruction, access and storage rules etc
- use of protective equipment for personal, additionally to technical and organisational measures
- nanomaterials for which no health-based limit values could be established yet, it is particularly important to document protection measures taken, substances used, working conditions and possibly available measurement data on strains for assessment at a later stage

4.3 Recommendations for immediate and long term measures

4.3.1 Immediate measures

Legislation policy makers should be prepared to adopt and implement several immediate measures necessary if more studies clearly show that NP are harmful for safety and health of humans and the environment.

- it is important to develop new testing methods (especially toxicological testing) in order to evaluate the safety and health risks of engineered NP
- to the extent that nanotechnology is a highly interdisciplinary area, it is recommended that collaboration between lawmakers, scientists, ethicists, economists, and other stakeholders be enforced to account for the complicated issues arising from nanotechnology. Nanotechnology industry should be the one to create and implement these rules, since the industry knows nanotechnology the best and has a direct interest in sustaining this field
- it is necessary to create new protection measures at the workplace for the people that manipulate nanomaterials. Existing threshold values – e.g. general dust limit values for the alveolar and breathable dust fraction or substance-specific limit values – must be observed

Future research should be carried out in order to evaluate the risks for the health and safety of the workers. Methods for risk assessments in relation to worker protection need to be developed and made available to the employers.

The following protection measures should be immediately implemented:

- Substitution options: binding powder nanomaterials in liquid or solid media; using dispersions, pastes or other compounds instead of powder substances, wherever this is technically feasible and economically acceptable.
- Technical protection measures: perform activities in contained installations, wherever this is possible and, if this cannot be done, avoid the formation of dusts or aerosols. To this end, extract possibly forming dusts or aerosols directly at their source (e.g. in filling and emptying processes), depending on the materials produced and production conditions. Ensure regular maintenance and function testing of extraction facilities. Extracted air must not be recirculated without exhaust air purification.
- Organizational protection measures: instruct the workers involved about the specific physical properties of nanomaterials, the need for special measures, and potential long-term effects of dusts formed. Include relevant information in the operating instructions.
- Also, keep the number of potentially exposed workers as small as possible. Furthermore, deny unauthorized persons access to the relevant work areas. Ensure clean work wear. Work wear must be cleaned by the employer. Work wear and private clothing must be stored separately. Ensure the regular cleaning of workplaces. The only way to remove deposits or spilled substances is with a suction device or to wipe them up with a moist cloth; do not remove them by blowing.

Personal protection measures:

- Where technical protection measures are not sufficient or cannot be put into place, personal protection measures – such a respiratory protection (e.g. filters of protection levels P2, FFP2, P3 or FFP3, to be selected in the hazard assessment) – are a suitable step. Depending on substance properties, it might be necessary to wear protective gloves, protection goggles with side protection and protective clothing. Where respiratory protection equipment is used, limited wearing times and preventive occupational medical checks must be observed.
- In the selection of protective gloves, it must be ensured that the glove material is suitable. The glove material must fulfill requirements for maximum wearing time under practical conditions. An important relevant criterion is the permeation time (break-through time depending on glove material and material strength). Additionally to hand protection, it can be necessary to protect further parts of the skin with protective equipment. This includes in particular protective suits, aprons and boots.

The effectiveness of applied protection measures (e.g. personal protective equipment) must be reviewed.

4.3.2 Long term measures

At the moment, issuing a specific long-term regulation on nanotechnology seems technically problematic and politically improbable. It is therefore necessary to make a consistent use of existing legislation when this can be easily applied as such or suitably amended.

But still it is recommended to establish some general long-term strategies for:

- *in vivo* long term toxicity assays for inhalation, oral, skin and injection exposure with the evaluation of markers for inflammation, cell proliferation in remote organs (e.g. liver, bone marrow, kidney)
- chronic nanotoxicity assay
- extended immunotoxicity studies
- development of new technologies for effective health and safety management in workplaces
- further epidemiological and toxicological data are required to determine the properties of nanomaterials in humans
- more measurements are needed in order to establish that will be no reason for concern at workplaces
- establishment of a standard guideline for workplaces and laboratories
- identification of protection measures and development of efficient metrology infrastructure

We have to keep in mind that new knowledge becomes the critical factor for legislation and regulation. From our point of view specific measures with a long term impact could be:

- assessment of a “nanotechnology product” should be done for the whole life-cycle focusing on products most relevant to consumers. This means production, dealing with and use of nanoparticles/nanomaterials as well as the disposal of waste
- Legislation and regulation on labeling of “nanotechnology products” should be done only at the end of an assessment process and on the basis of solid knowledge.

5 Summary and outlook

Recommendations by IMPART for future legislation to be realised as immediate measures are as follows:

- The legislation policy makers should be prepared to adopt and implement several immediate measures necessary if more studies clearly show that ENP are harmful for safety and health of humans and the environment
- Foster the development of new testing methods (especially toxicological testing) in order to evaluate the safety and health risks of engineered NP
- Create new protection measures at the workplace for the people that manipulate nanomaterials. Existing threshold values – e.g. general dust limit values for the alveolar and breathable dust fraction or substance-specific limit values – must be observed

Immediate protection measures which we recommend to be adapted include the substitution options for nanomaterials and technical as well organizational protection measures.

A specific long-term regulation on nanotechnology seems technically problematic and politically improbable at the moment. It is necessary to make a consistent use of existing legislation, as long as this can be easily applied as such or suitably amended, following also the conclusions of European Communities Report: Regulatory Aspects of Nanomaterials, June 17, 2008.

For the adaptation of future legislation to the requirements of nanoscale materials we recommend to establish already now the following general long-term strategies:

- *in vivo* long term toxicity assays for inhalation, oral, skin and injection exposure with the evaluation of markers for inflammation, cell proliferation in remote organs (e.g. liver, bone marrow, kidney)
- chronic nanotoxicity assay
- extended immunotoxicity studies
- development of new technologies for effective health and safety management in workplaces
- further epidemiological and toxicological data are required to determine the properties of nanomaterials in humans
- more masurements are needed in order to establish that will be no reason for concern at workplaces
- establishment of a standard guideline for workplaces and laboratories
- identification of protection measures and development of efficient metrology infrastructure

6 References

[1] C.A. Poland, R. Duffin, I. Kinloch, A. Maynard, W.A.H. Wallace, A. Seaton, V. Stone, S. Brown, W. MacNee, K. Donaldson, *Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study,* Nature Nanotechnology **3** (2008) 423–428.

[2] A.D. Maynard, P.A. Baron, M. Foley, A.A. Shvedova, *Exposure to carbon nanotube material: aerosol release during the handling of unrefined single walled carbon nanotube material*, Journal of Toxicology and Environmental Health A **67**(1) (2004) 87–107.

[3] A. Boenke, *Nanomaterials in EU chemicals legislation: aspects for worker protection* (2006).

[4] K. Donaldson, R. Aitken, L. Tran, W. Stone, R. Duffin, G. Forrest, *Carbon Nanotubes: a review of their properties in relation to pulmonary toxicology and workplace safety,* Toxicological Sciences **92**(1) (2006) 5–22.

[5] A. Franco, F.S. Hansen, S. Olsen Irving, L. Butti, *Limits and prospects of the "incremental approach" and the European legislation on the management of risks related to nanomaterials*, Regulatory Toxicology and Pharmacology **48** (2007) 171–183.

[6] *Guidance for handling and use of nanomaterials at the workplace* (2007).

[7] P. Lin, *Nanotechnology bound: evaluating the case for more regulation*, NanoEthics: Ethics for Technologies That Converge at the Nanoscale **2** (2007) 105-122.

[8] Alivisatos AP, Gu W, Larabell C (2005) Quantum dots as cellular probes. Ann. Rev. Biomed. Eng. 7:55-76.

[9] Crane M, Handy R, Garrod J, Owen R: Ecotoxicity test methods and environmental hazard assessment for engineered nanoparticles. Ecotoxicology (2008) 17:421–437.

[10] Donaldson K, Stone V, Tran CL, Kreyling WG, Borm PJ (2004) Nanotoxicology. Occup. Environ. Med. 61:727-728.

[11] European NanOSH Conference –Nanotechnologies: A Critical Area in Occupational Safety and Health 3–5 December 2007, Marina Congress Center, Helsinki, Finland.

[12] Franco A., Hansen S.F., Olsen A.I., Butti L.: Limits and prospects of the "incremental approach" and the European legislation on the management of risks related to nanomaterials. Regulatory Toxicology and Pharmacology. 2007, 48, 171 – 183.

[13] Hood E (2004) Nanotechnology: looking as we leap. Environ. Health Perspect. 112(13), A740-A749.

[14] Hoshino A, Manabe N, Fujioka K, Suzuki K, Yasuhara M, Yamamoto K (2007) Use of fluorescent quantum dot bioconjugates for cellular imaging of immune cells, cell organelle labeling, and nanomedicine: surface modification regulates biological function, including cytotoxicity. J. Artif. Organs 10:149-157.

[15] Masciangioli T, Zhang WX (2003) Environmental technologies at the nanoscale. Environ. Sci. Technol. 37:102A-108A.

[16] Nowack B, Bucheli TD (2007) Occurrence, behaviour and effects of nanoparticles in the environment. Environ. Poll. 150, 5-22.

[17] OECD Environment, Health and Safety Publications Series on the Safety of Manufactured Nanomaterials No. 6 Working Party on Manufactured Nanomaterials: List of manufactured nanomaterials and list of endpoints for phase one of the OECD testing programme. Environment Directorate. Organisation for Economic Co-Operation and Development. Paris, 2008. ENV/JM/MONO(2008)13.

[18] Royal Society Report (2004) Nanoscience and Nanotechnologies: Opportunities and Uncertainties - Summary and Recommendations. The Royal Society & Royal Academy of Engineering, UK.

[19] Zhang WX (2003) Nanoscale iron particles for environmental remediation: An overview. J. Nanoparticle Res. 5(3-4): 323.

[20] Zhu YQ, Sekine T, Li YH, Wang WX, Fay MW, Edwards H, Brown PD, Fleischer N, Tenne R (2005) WS2 and MoS2 inorganic fullerenes - super shock absorbers at very high pressures. Adv. Mater. 17:1500-1503.

7 List of Directives and Regulations

- Council Directive 67/548/EEC of 27 June 1967 on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labeling of dangerous substances. OJ 196, 16. 1967, p. 1. Directive as last amended by Regulation (EC) No 807/2003 (OJ L 122, 16.5.2003, p. 8. 36).
- Council Directive 75/439/EEC of 16 June 1975 on the disposal of waste oils. OJ L 194, 25.7.1975, p. 23–25.
- Council Directive 76/769/EEC of 27 July 1976 on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations. OJ L262, 27.9.1976, p. 201. (No longer in force).
- Commission Directive 91/155/EEC of 5 March 1991 defining and laying down the detailed arrangements for the system of specific information relating to dangerous preparations in implementation of Article 10 of Directive 88/379/EEC, O.J. No L76/91) p. 35 (No longer in force).
- Council Directive 91/689/EEC of 12 December 1991 on hazardous waste. OJ L 377, 31. 12. 1991, pp. 20-27.
- Council Regulation (EEC) No 93/793 of 23 March 1993 on the evaluation and control of the risks of existing substances. OJ L84, 5. 4.1993, p. 1. Corrigendum to Council Regulation (EEC) No 93/793 of 23 March 1993 on the evaluation and control of the risks of existing substances. OJ L224, 3.9.1993, p. 34. (No longer in force).
- Council Directive 96/61/EC of 24 September 1996 concerning integrated pollution prevention and control. OJ L 257, 10.10.1996, p. 26–40.
- Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC). O.J. L131, 5.5.1998, p. 11
- Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the law, regulations and administrative provisions of the Member States relating to the classification, packaging and labeling of dangerous preparations. OJ L 200, 30.7.1999, p. 1. Directive as amended by Commission Directive 2001/60/EC (OJ L 226, 22.8.2001, p. 5).
- Directive 2000/53/EC of the European Parliament and of the Council of 18 September 2000 on end-of-life vehicles OJ L 269.
- Directive 2006/12/EC of the European Parliament and of the Council of 5 April 2006 on waste OJ L 114, 27.2.2006 pp 9-14.
- Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market; OJ L 230, 19.8.1991.
- Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market; OJ L 123, 24.4.1998.
- Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products; OJ L 262, 27.9.1976.
- Council Directive 89/391/EEC of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work. OJ L183, 29.6.1989, p. 1.
- Council Directive 89/656/EEC of 30 November 1989 on the minimum health and safety requirements for the use by workers of personal protective equipment at the workplace (third individual directive within the meaning of Article 16 (1) of Directive 89/391/EEC) OJ L 393 , 30/12/1989 pp. 18 – 28.

- Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Article 16(1) of Council Directive 89/391/EEC) (codified version) OJ L158, 30.4.2004, p. 50. Corrigendum to Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Article 16(1) of Council Directive 89/391/EEC) OJ L 158, 30.4.2004.
- Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC, O.J. L 396/1.
- Council Directive 2008/1/EC (2008) concerning integrated pollution prevention and control; OJ L 24, 29.1.2008.
- Council Directive 96/82EC on the control of major-accident hazards involving dangerous substances; OJ L 10, 14.1.1997, as amended.
- Directive 2000/60/EC of the European Parliament and of the Council establishing a framework for Community action in the field of water policy; OJ L 327, 22.12.2000.