FRAMING NANO

Governance in Nanoscience and Nanotechnology

FramingNano Project:

A multistakeholder dialogue platform framing the responsible development of Nanosciences & Nanotechnologies

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MAPPING STUDY ON REGULATION AND GOVERNANCE OF NANOTECHNOLOGIES

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MAPPING STUDY ON
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Executive Summary

Nanotechnologies are expected to be one of the main drivers of the technological evolution of the early part of the XXI Century. Due to the unique properties and behaviour of matter at the nanoscale and its enabling characteristics, nanotechnologies have the potential to profoundly transform all the most important industrial sectors and everyday life.

All over the world, both developed and emerging countries are devoting increasing resources to promote nanoscience and nanotechnologies in an effort aimed at gaining a leading position in the field and reaping the benefits promised.

However, the belief is also becoming widely shared that the hopes pinned on this emerging technology will fully materialise only if its development will take place responsibly.

The level of attention directed towards the health, safety and environmental (EHS) effects and ethical, legal and social issues (ELSI) deriving from nanotechnology and its applications has increased considerably in recent years. Addressing these issues properly and responsibly will be of paramount importance for the success of nanotechnology.

Most of the countries with an interest in nanotechnology and supranational organisations are placing high on the agenda their attention on how to manage the development of this technology. Governments, regulatory and standards-setting agencies/bodies have started to develop expertise and technical background to cope with the related regulatory issues.

The **European Commission** has condensed its position to promote the safe growth of nanotechnology into an Action Plan and, in the past years together with regulatory authorities and scientific committees, has started specific initiatives and published various in-depth analyses on this matter. The request to review current EU regulatory legislation to take into consideration nanotechnology is one of the instruments considered and the initiative to extend the application of REACH to nanomaterials is an example of this action.

In February 2008, the EC published a **Code of Conduct** (CoC) for responsible research in nanosciences and nanotechnologies.

The principles that guide the CoC are:

- *Meaning: research activities should be understandable by the public;*
- *Sustainability: research activities should be safe, ethical and contribute to a sustainable development;*
- *Precaution: research activities should be conducted in accordance with the precautionary principle;*
- *Inclusiveness: governance of research activities should be guided by the principle of openness, transparency and respect to all stakeholders;*
- *Excellence: research activities should meet the best scientific standards;*
- *Innovation: research activities should encourage maximum creativity and flexibility:*
- *Accountability: researchers and research organisations should remain accountable for the social, environmental and human health impact of their research.*

The CoC represents a flexible and high level instrument, applicable to existing and future applications of nanotechnologies, and providing all stakeholders with principles and guidelines for a responsible and open approach to nanoscience and nanotechnology research. All European Countries have been urged by the EC to adopt the Code for their activities in nanotechnology but, being voluntary, its effectiveness will of course depend on the level of application and on the instruments, mainly scientific, to comply with its guidelines.

France, Germany, Switzerland, The Netherlands, UK and some **Scandinavian Countries** are, in Europe, the most active in addressing the various issues related to nanoregulation.

In these countries, the commitment to understand the health and environmental implications of nanotechnology is quite strong and their governments are currently supporting a number of research activities to this end.

As a result of these initiatives, guidance documents on risk assessment and risk management of nanotechnology as well as on the implementation of current legislation (mainly based on REACH) have been published.

In the **USA**, EHS issues are now among the priorities of the National Nanotechnology Initiative (NNI) and the funding for research in this field has been stepped up considerably in the last two years. The EPA and FDA have set up specific task forces on nanotechnology, and have published reviews of their legislation in relation to nanotechnology. Most of the discussion so far has been on the applicability to nanomaterials of the EPA TSCA statute (analogous to REACH) and on FDA statutes, in particular in relation to cosmetics, food and food additives, and drugs. The Consumer Product Safety Commission (CPSC - under whose jurisdiction fall most consumer products using nanotechnology), has not so far published relevant documents on nanotechnology regulation.

Australia and Canada are also rather active on nanoregulation. Both have important programmes on EHS research and have published in-depth reviews of their regulations to assess eventual limits when dealing with nanotechnology. Even though no specific laws have been set up, the adoption of a precautionary approach principle, when dealing with nanotechnology application, is envisaged in both countries.

In **Japan, China, Korea** and **Taiwan**, which are deeply involved in nanotechnology, there are also, at different levels, important research initiatives dealing with EHS issues such as risk assessment and risk management of nanomaterials and nano-related products. They do participate in the worldwide debate on nanoregulation but no specific initiatives on the matter have been taken so far in these countries.

In the light of the lack of specific regulations for nanotechnology, various **voluntary measures**, besides the EC CoC, have been promoted to address the safety of nano-related products or activities. The EPA's Nanomaterial Stewardship Program (NSMP) in the USA and DEFRA's Voluntary Reporting Scheme (VRS) in the UK, have both started **voluntary reporting schemes** intended to collect information from industry on the manufacturing and use of nanomaterials, while other (less structured) data gathering initiatives are being running by agencies such as FDA (Food and Drug Administration, USA) and EFSA (European Food Safety Authority). The objective is to identify gaps in risk management practices and EHS research, build a firmer evidence base for regulatory/policy decisions, provide reassurance and build consumer confidence in nanotechnologies. It must be said that both the EPA and DEFRA initiatives have, so far, received only a tepid response due to the reluctance of industry to put efforts into these reporting procedures (in particular in the case of SMEs) and, above all, to disclose sensitive, and often proprietary, data.

Voluntary measures have also been introduced by private enterprises such as BASF in Germany (ResponsibleNanoCode), Buhler Partec in Switzerland (Cenarios risk management system) and DuPont/Environmental Defense (NanoRiskFramework) in the USA and by retailer organisations, such as IG-DHS in Switzerland (Code of Conduct).

Various initiatives have been established also regarding the implications of **nanotechnologies on Ethical, Legal and Social Issues** (**ELSI)**. Ethical Committees in the European Commission, USA and several EU countries have published opinions and reviews on ELSI and have underlined the different societal implications of existing and future applications of nanotechnologies. Apart from ensuring the safety of nanotechnologies, most of the attention is currently devoted to *public perception and public engagement* issues.

While in the USA and some other countries, public participation is seen, in the first instance, as an instrument to ensure public acceptance (or to avoid negative risk perception), European vision seems more focused on fostering the broader concept of "public engagement" in the development and governance of nanotechnologies.

Several other socio-economic and ethical considerations have been pointed out in relation to commercial and economic aspects (patenting, the impact of nanotechnologies in developing countries) and ethical issues associated with the development of specific applications (mainly in the medical and security sectors). The debate is somehow anticipatory insofar as many of the most advanced and intrusive applications of nanotechnology are foreseen on a medium to long term horizon, but the importance of taking into account the implication of nanotechnology on ELSI is undisputed and is considered to be an unavoidable aspect of nanoregulation. The European Commission's CoC clearly underlines the importance of various socio-ethical aspects of nanotechnologies, in particular the dialogue among stakeholders and public engagement.

From the information gathered it can be stated, as a general conclusion, that governments and regulatory authorities at present consider **existing regulatory frameworks**, such as REACH in Europe and TSCA in USA, appropriate in principle to deal with many of the nanomaterials currently in use.

Nevertheless, it is acknowledged that scientific gaps exist in relation to the characterization of manufactured nanomaterials and their effects on the environment, human health and safety, challenging their application and indicating an increased need for research in this field together with an improvement of the instruments to implement/adapt the legislation.

The level of confidence in existing regulations when dealing with nanotechnology strongly depends both on the type of product considered and the legislative framework to which it has to comply. A general distinction can be made among different class of products/materials:

- *Products subject to pre-market authorization:* pharmaceuticals or very dangerous substances are examples of such products. A safety assessment is generally requested prior to marketing, including risk benefit analysis and the development/review of testing protocols specific for the product considered. In most cases, existing provisions are considered adequate also for nanomaterials.

- *Products subject to pre-market approval:* some class of food additives and medical devices are examples of such products. Appropriateness of regulation strongly depends on the elements and gaps described above.

- *Products subject to post-marketing surveillance:* Cosmetics, sunscreens and most consumer products are example of such products. A key point here is whether information provided by or asked from the manufacturer/producer is appropriate in order to understand whether the product includes or uses nanotechnology and whether there is any kind of related risk. Only the collection of adequate information can enact adequate regulatory measures to prevent or react to risks. The need to collect this information is one of the main drivers of voluntary stewardship programmes launched worldwide.

Examples of the challenges underlined by different authorities in applying existing provisions to nanotechnologies include issues related to the scope of legislation (for example, a clear inclusion of nanomaterials in the definition of a substance or product or overlap between different regulatory systems for novel nanotechnology applications, as for medical devices) and issues related to "triggers" enacting regulation (as in threshold levels based on mass and concentration).

International cooperation is also considered fundamental to implement nanoregulation effectively and several initiatives aiming at this objective can be cited. In particular:

- The OECD WPMN (Working Party on Manufactured Nanomaterials, specifically on EHS and regulation) and WPN (Working Party on Nanotechnology) Programmes;
- The activities on preparing international standards in ISO Technical Committee TC 229 "Nanotechnologies" which has established four working groups to address four crucial issues for the governance of nanotechnology:
    - Terminology and Nomenclature;
    - Measurements and Characterisation
    - Health, Safety, and Environment;
    - Materials Specification.
- The International Dialogue Meeting series jointly organised by several countries.

Besides the above-mentioned authorities, governments and international institutions, **several organisations worldwide** also actively participate in the debate on nanoregulation and can be grouped into four categories as follows:

(a) Policy makers (such as governments, national and international authorities, regulatory agencies, standards organisations, lawyers)
(b) Industry, business and professional organizations (mainly in relation to the chemical industry);
(c) Research institutions and foundations (mainly focused on law, sustainable development and nanotechnology);
(d) Non-governmental organizations, consumer, public health, environmental, labour organisations, (from "green" associations to large transnational labour organisations, not-for- profit organisation and coalitions of CSOs focused on nanotechnology development).

Most of these organisations have published detailed reports providing information and advice about gaps in specific regulations, materials or products that give a constructive and valuable input for the development of appropriate regulatory frameworks.

There is a general agreement among these stakeholders on the **principal problems facing nanoregulation** and their priorities. In particular:

- The major source of concern regarding potential risks of nanotechnology are, at the moment, "free" manufactured nanomaterials [1]
- There is an urgent need to develop, at least for some specific nanomaterials, new approaches and methods for their risk assessment and to improve the knowledge base on their characteristics and behaviour
- There is a need for an international approach to the management of nanomaterials risks, with a particular emphasis on the development of harmonised standards and guidance, and on an effective engagement of all stakeholders.

When **the approach to regulate nanomaterials** is considered, on the contrary, there are a variety of positions. Views have evolved on the basis of the inputs arising from the development of sectors

[1] "free" manufactured nanomaterials presenting a risk of exposure to human and the environment during their entire life cycle.

and the increasing engagement of all stakeholders in the debate but differences, sometimes strong, remain between different stakeholders.

In fact, a few years ago, two mutually incompatible views (a self regulating "laisser-faire" model and the idea of a total moratorium) prevailed. Now, the discussion is broader and more articulated, with opinions and positions that however still differ, depending from the specific materials, products, use and applications considered.

The **on-going debate and attitudes** can be summarised as follows:

1) Existing regulatory situation is adequate. In the case that scientific evidence indicates the need for modification, the regulatory framework will be adapted.

2) Specific guidance and standards must be developed to support implementation of existing regulations when dealing with nanomaterials and nano-related products, but the existing regulatory situation is generally adequate.

3) Regulation should be amended (on a case by case basis) for specific nanomaterials or nanoproducts, above all when a high potential risk is identified. A precautionary approach is envisaged.

4) Existing regulatory situation is not adequate at all. Nanomaterials should be classified as new substances and they should be subject to mandatory, nano-specific regulations. Nanotechnology commercialisation has to be halted until products containing nanoparticles have been proven safe. Nanomaterials are considered as a range of materials subject to dedicated provisions.

Considering the above-mentioned categories of stakeholders, the respective positions can be summarised as follows:

- Type (a) and type (b) organisations (policy makers, industry/business) tend towards the first three options. Industry/businesses generally welcome the second approach, even though in some cases only, are they willing to disclose sensitive and (sometimes) proprietary information to authorities or to develop dedicated and often costly risk management systems. Some policy makers, such as the European Commission, tend to favour the adoption of a precautionary approach.
- Type (c) (research institutions) are generally in favour of approaches 2 and 3.
- Type (d) (Civil Society Organisations) are, in general, pushing for approach 4 and are asking for a strict precautionary approach, for all or at least some classes of nano-related products.

Finally, there two other issues on which the debate is still open:

- One is the question as to whether the burden of proof to demonstrate the safety of nano-products should rest on the regulatory authorities, or on the product manufacturers and distributors. This is a key difference between the USA legislation and REACH. The EU law (REACH) requires the **companies** to demonstrate that a chemical is safe before it enters commerce whereas, in the USA law (EPA/TSCA), the **regulators** must prove that a chemical is harmful before it can be restricted or removed from the market.

- The second is labelling of nanoproducts, in particular for consumer products. This question is widely debated among all stakeholders but the lack of knowledge regarding many nanomaterials makes it difficult to define agreed and appropriate methods. A consensus on whether and how to implement measures has not been reached yet. Standardisation bodies

are currently working on standards related to the labelling of manufactured nanomaterials, both in relation to the production phase and product itself.

In conclusion, this report points out that nanoregulation must be regarded as a dynamic affair which must adapt to the evolution of the scientific knowledge and applications and public attitude. A continuous updating must be part of the governance of nanotechnology.

At present, the general approach is to deal with nanomaterials/nanotechnologies adopting, in the first instance, existing regulatory situation, but there is also general agreement on the need to support and encourage research on EHS issues with the primary goal of developing proper standards, guidelines and risk management procedures.

The inclusion of ELSI in the framework of nanoregulation is considered crucial especially by European countries. Both research on EHS and attention to ELSI, as well as trust in regulatory bodies and between stakeholders, are fundamental in order to provide a positive answer to the position that prevails among civil society organisations, which at present tend to have a critical attitude toward nanotechnology. As may be concluded from the information gathered, public acceptance and public engagement are core aspects of the debate.

1. Foreword

Nanotechnology has the potential to penetrate and permeate all industrial sectors and spheres of human life, introducing new paradigms with transformation capabilities more disruptive than other revolutionary technologies of the recent past, such as electronics and biotechnology.

The extraordinary properties exhibited by the matter at the nanoscale are the source of a huge range of valuable new applications and benefits, but also pose the challenge of clearly understanding all the effects, beneficial or potentially harmful, associated with them.

Potential risks for the environment, human health and safety (EHS) and the implications related to the application and use, or misuse, of nano-related products (Ethical, Legal, Societal Issues - ELSI), are intrinsically intertwined with the benefits offered by nanotechnology.

Specific studies dedicated to the assessment of the risks posed by manufactured nanomaterials have highlighted they are not generally simple, with clear cut cause-and-effect connections. Risk problems of nanotechnology are instead dominated by complexity, a high degree of uncertainty and ambiguity in our knowledge about the response of humans to the use of nano-related products[2].

For these reasons, understanding, preventing and managing technological and societal implications associated with nanotechnology represent a global and trans-boundary task.

A completely new multidimensional approach to risk appraisal and management is needed. Cooperation, coordination and communication among all the stakeholders interested in nanotechnology are mandatory to promote a proactive and adaptive process capable of *framing* nanotechnology development across known and accepted boundaries.

This process should provide a clear understanding of the risks associated with this technology and also promote an extensive debate among all the players to foster the definition of a set of suitable and responsible social, political, technical actions and rules, in order to develop a sustainable **regulatory framework** for nanotechnology capable of assuring its responsible development**.**

The fact that nanotechnology is still at an early stage of its "S" development curve makes it possible to tackle the relevant questions associated with it comprehensively and globally from the beginning, so helping to avoid some of the mistakes made in the past and assuring the success/acceptance of this emerging technology.

Paraphrasing the European Commission, this means developing:

"a deliberative process involving researchers, policy makers, citizens, ethicists and CSOs to combine their skills, knowledge and understanding in an attempt to provide a societal framework for a responsible development of NS&T in the European Union, and allowing for an international dialogue notably through ad-hoc co-operative research processes."

This is the objective of the FramingNano project and in this report is condensed the situation we are starting from.

[2] White Paper on Nanotechnology Risk Governance, IRGC, June 2006

1.1. The FramingNano Project

The objective of **FramingNano** is to support the establishment of a multi-stakeholder dialogue on NS&T regulation and governance involving the scientific, institutional and industrial communities as well as the broader public. The objective is to articulate consensus and absence of consensus between the various stakeholders, sustain a European debate between them, and foster the development of a shared frame of knowledge, objectives and actions leading to constructive and practicable regulatory solutions (**Governance Plan)** for the responsible development of NS&T at European level (and beyond), which will include recommendations for future research, policy actions, and co-operative research processes over the years 2009-2013.

A joint perspective for regulation and its reflection by a stakeholder process offers a vital precondition for a responsible use and application of nanotechnology.

The involvement of *all* stakeholders will be fundamental to begin a *"co-operative research process"*[3] allowing:

- Sharing of knowledge and expertise among science and technology researchers and society researchers, to help integrate a societal perspective into the R&D process (of NS&T) and address science-society interactions as a system;
- Increasing awareness of non researchers (policy makers, civil society organization, broader public) about NS&T, *"building their capacities"* to understand, evaluate and manage NS&T.

This, as indicated by the European Commission[4]: *"aiming as much at the harmonious societal integration of new scientific and technological knowledge as to achieving the specific objective of the research itself."*

The activity is based on four pillars:

1) **Analysis** to assess existing-proposed regulatory processes of NS&T, the level of science-policy interface, the research initiatives for risk-benefit assessment (with respect to health, environment and other societal issues), identification of the relevant NS&T stakeholder organisations.

2) **Consultative process** to ascertain stakeholders' positions and needs with reference to the issues critical for them in order to gather the necessary input to frame deliberative processes and procedures (Delphi Exercise).

3) **Framing (the deliberative process)** to develop an appropriate proposal of a Governance Plan, with needs, actions, and recommendation (with reference to relevant stakeholders), necessary to pursue a responsible development of nanotechnology.

4) **Communication** and dissemination of information on NS&T governance to foster a dialogue with and stimulate the interest of stakeholders about this theme, and to prompt their engagement in the project.

[3] The emerging paradigm of 'co-operative research' indicated in the Capacities work programme has been discussed in *"From Science And Society To Science In Society: Towards A Framework For 'Co-Operative Research"* - Report of a EC Workshop Governance and Scientific Advice Unit of DG RTD, DG Research and Tech. Dev., Brussels, 11/2005 (pg 9): "*this is a new form of research process, which involves both researchers and non-researchers in close co-operative engagement....".*

[4] Fp7 Work Programme 2007, European Commission C(2007)563 of 26.02.2007)

Expected outcomes of the project are:

- A website dedicated to the responsible development of nanotechnology.
- A comprehensive analysis of existing and proposed worldwide regulatory processes on nanotechnology
- A survey identifying all of the relevant stakeholders at EU level
- An in-depth assessment, based on a two-stage Delphi Exercise, of critical issues, attitudes and needs of relevant stakeholders regarding the governance and regulation of nanotechnology
- An International Workshop to communicate the project objectives, to present the results of the analysis of the existing situation and to discuss the Delphi Exercise.
- A proposal for a Governance Plan identifying and prioritizing actions needed to ensure a responsible development of nanotechnology
- A final International event to present and discuss the proposed Governance Plan
- National Workshops in several European countries illustrating the final proposal for a Governance Plan and to deepen the understanding of NS&T governance issues at national level.

The project brings together 6 partners from 6 European countries.

1.2. Purpose of the report

The objective of this report is to provide a picture of recent developments regarding regulation and governance of NS&T in Europe and worldwide, to identify relevant NS&T stakeholder organisations and to make an assessment of this information to prepare the ground for the following phases of the FramingNano project, i.e. the consultative process among stakeholders and the definition of a Governance Plan for the responsible development of NS&T.

The report (and the FramingNano project in general) focuses on regulation and governance aimed at both risks and concerns (perception of risks), with respect to EHS and ELSI issues, that have to be understood and "framed" or "guided". Talking about risk assessment is instrumental in defining a regulatory framework. But benefits and opportunities, besides risks, will also be considered as a necessary element of the debate. In the end, governance must always take into account the trade-off between these two opposing factors. [5]

The first goal of the report is *to define the context of the debate*, as regulation and governance are terms that have been associated to a broad set of initiatives from government and other authorities, international institutions, industry, scientific and social researchers, and civil society organisations.

The topics described in this report are intended to give an overall view of the elements of the debate falling under the umbrella of the above two terms, in order to understand how these issues are currently defined and tackled by different stakeholders.

The second goal is to *shape the debate*. The analysis of the information collected permits understanding of how communication and cooperation on these themes takes place, which are the main or the most evident gaps, needs, points of agreement and disagreement, critical factors in the current knowledge and regulation framework of nanotechnology, and what is the position of the interested stakeholders.

The third goal is to *foster the debate* on regulation and governance of nanotechnology, as the report is intended to be a working document giving a comprehensive picture of the overall situation. Documents on this subject are published on a continuous basis, giving ever new inputs to the debate. With the aim of acting as a *funnel* for this information, the project plan foresees collecting and integrating it into the report throughout the project lifetime, and to use it in the development of the final Governance Plan.

[5] A detailed description of applications of nanotechnology having a relevant, beneficial impact on the environment or the human health is beyond the scope of this report. Other projects and publications, as the UNEP report "Emerging Challenges: Nanotechnology and the Enviromnent" (published in 2007), give detailed information on these issues.

1.3. Structure and methodology

Structure
The reports is organised into three main parts.

The **first part** gives an introduction to nanotechnology and its applications, and to the role of policy and regulation.

The **second part** presents, on the other hand, an analysis of what major societal actors and key-players define as areas of risks and concerns of nanotechnology. The former are the potential effects of nanotechnology on the environment, human health and safety and the latter, essentially, its ethical, legal and social implications. This will give the background for the debate on nanotechnology regulation and governance.

The initiatives and actions of the different stakeholders involved in managing and regulating nanotechnology are discussed in the **third part** of the report which structured in paragraphs referring to different topics related to nanotechnology regulation and governance:

- *Shortcoming of nanotechnology governance* gives some background elements underlining which gaps in scientific knowledge are most relevant from a regulatory point of view and introducing the main options considered by the different stakeholders to respond to these issues (to be presented in detail in the third part of the report).

- *Regulatory options* considered by policy makers (government and regulatory agencies) at European and International level and aimed at the safety of nanomaterials and nanoproducts.

- *Efforts in nanotechnology standardisation* from International and National standards bodies.

- *Voluntary or self-regulatory measures* on nanotechnology adopted by government, authorities, industry and other organisations to respond to current regulatory uncertainties.

The above paragraphs present actions and positions of the participants involved, at different levels, in regulating nanotechnology. The counterpart of the debate is represented by initiatives and positions from other stakeholders involved at different levels on these issues, as businesses, industry, scientific and social researchers, and civil society organisations. These are reported in the final paragraph.

In order to give a further insight on the themes and subjects considered, without hampering the readability of the text, some information has been included as annexes.

- In Annex 7.1 *Government strategies and action plans for nanotechnology* are reported. These are generally wide programs intended to foster the development of nanotechnology that, in some cases, include also specific actions related to EHS or ELSI issues treated in detail in the report
- In Annex 7.2 is a selection of research projects worldwide on EHS issues and ELSI
- In Annex 7.3 are given details on standards organisations dealing with nanotechnologies

Methodology
For the preparation of the report, the collation of information on existing-proposed regulatory processes of NS&T, together with information regarding risk-benefit assessment and management (official documents, guidance documents, existing legislation, reports, conference/workshop

proceedings, articles, etc.) and the definition of a first list of topics to properly classify all the documents, has been used.

In the search phase, relevant references have been identified. These key documents are produced by government and authorities on nanotechnology regulation & governance (as from European Commission, UK, Germany, Switzerland, USA) and the OECD document (last updated in April 2008) *"Current Developments/Activities On The Safety Of Manufactured Nanomaterials/ Nanotechnologies"* that has also suggested the topics to be used for the classification of the documents.

These have been briefly prioritised and selected in terms of:

- Relevance of the organisation
- Level of the initiatives (international, regional, national, local)
- Coverage of stakeholders categories (policy makers, businesses, researcher, civil society organisations)
- Coverage of topics
- Citations
- Date of publication

Since 2004 the number of initiatives referring to the above mentioned themes has seen a rapid increase and the debate has evolved based on new inputs and information. For this reason it has been decided to focus only on most recent and updated initiatives (apart from a few very relevant documents, as for example the 2004 Royal Society report on Nanotechnology). Documents used to prepare the report are mainly from 2006 onwards, with the major part of them dated 2007 or 2008. Both the websites visited and other documentation, are generally updated at October 2008.

Findings from this first assessment have allowed for the refinement of the topics used for the classification of documents and the definition of a list of relevant documents on which to base the preparation of the report.

2. INTRODUCTION

2.1. The Nature of Nanotechnologies

Richard Feynman is commonly considered to be the father of nanotechnology due to his speech in 1959 entitled "There's plenty of room at the bottom", but the term "nanotechnology" was first used in 1974 by Norio Taniguchi. The original definition of nanotechnology at the time was: "Nano-technology mainly consists of the processing of separation, consolidation, and deformation of materials by one atom or one molecule."

According to this definition nanotechnology only describes the manipulation of materials on the molecular level and it refers to structures that are typically between 1 and 100 nm (1 nm = 10^{-9} m) in size. Nanotechnology applications and products make use of characteristics which occur in the transition area between the atomic and the mesoscopic scale. This means that nanoscale particles can have different physico-chemical properties with respect to microscale or macroscale particles of the same material.

Basing on the International Standard Organisation (ISO), nanotechnology may be defined as either or both of the following:

> *(1) Understanding and control of matter and processes at the nanoscale, typically, but not exclusively, below 100 nanometres in one or more dimensions where the onset of size-dependent phenomena usually enables novel applications, where one nanometre is one thousand millionth of a metre,*
>
> *(2) Utilizing the properties of nanoscale materials that differ from the properties of individual atoms, molecules, and bulk matter, to create improved materials, devices, and systems that exploit these new properties.*

Of central relevance for the development of nanotechnology have been advances in analytical methodology for the examination of structures and surfaces on the atomic level. Optical microscopes can only display structures greater than the wavelength of the light used for the analysis. Due to the inherent characteristics of the system even today "only" resolutions of approx. 200 nanometers are possible. Only with the development of the electron and atomic force microscopes (in the 1960s and 80s, respectively) atomic structures could be displayed. This laid the foundations for the study of nanoscale structures and their use in science and technology.

With respect to the first definition, today the term nanotechnology has a broader meaning and the term nanotechnologies[6] is increasingly used. The chemical or mechanical production of nano-scaled materials is, for example, included even if there is no manipulation of single atoms. Such structures could, in fact, be part of a conventional phase or matrix or just represent an extremely thin surface coating.

Manufactured nanoparticles are a key element in nanotechnologies. They can be produced in large quanties and used in products or processes because of their particular properties. In contrast to ultra-fine particles, engineered nanoparticles are created in a targeted process and have a defined chemical composition and particle size distribution.

[6] The two terms will be used interchangeably in this report depending from the context.

Basically, nanomaterials have a higher specific surface area which has effects especially for free nanoparticles, because their entire surface is available for potential reactions. At the level of a few nanometres quantum effects can dominate, which strongly influences the optical, electrical and magnetic behaviour of these materials.

The chemical and physical properties of nano-scale materials can be fundamentally different from those of materials on the micro- or macro- scale and the novel or changed properties shown at nano- scale can be used in a targeted way and open a myriad of possibilities.

The number of products and applications using nanomaterials or nanotechnologies is rapidly increasing and this emphasizes the fact that nanotechnology is not just one technology but rather a "new way of manufacturing".

2.2. Nanotechnology Applications

2.2.1. General Approaches

In the area of nanotechnologies applications a fundamental differentiation between applications of nanomaterials in (industrial) production processes and in (consumer) products can be made. In the case of industrial processes nanoparticles can be used as means of production that will not be integrated in the final product, for instance as abrasive agents in grinding processes or inside the used hardware and equipment. An example is the use of hard cerium oxide, silicon oxide or aluminium oxide nanoparticles in the chemico-mechanical polishing of wafers. The second group comprises products that actually contain nanomaterials.

There are generally two approaches for the production of nanomaterials. One approach is summarized under the so-called "top-down" technology and refers to the production of very small structures out of material building blocks by grinding, etching or other mechanical processing. The millionfold produced, electronic microchips fall under this category. The desired conductor paths are predetermined through lithography. The distances and widths of the conductor paths currently are at less than 100 nm.

On the other hand, nanomaterials can also be manufactured according to so-called "bottom-up" technology. In this case structures are built atom by atom or molecule by molecule. There is a differentiation between chemical synthesis, "self assembly" and "positional assembly" [The Royal Society, 2004]. While in the case of "self-assembly" the single basic units (atoms, molecules) are autonomously positioned according to their natural properties, the exact position in the case of "positional assembly" is predetermined by external influences. The latter is very complex and not yet applicable on the industrial scale. Examples for **"bottom-up"** technologies are the manufacture of many raw materials by chemical synthesis, whereas the desired reaction product is available on the nano scale. The manufacture of carbon nanotubes however is based on "self assembly", because the tubes continuously grow from the gas phase through an ordered assembly of carbon. By constantly refining the **"top-down"** approaches (e.g. in information technology) and an extension of "bottom-up" applications in greater structures the two approaches increasingly converge.

In industrial production, nanoparticles in the form of raw materials (if needed in modified form) are suspended as part of production processes, integrated in composites or applied on existing, not nano-scaled materials. Often used forms of nanoparticles as an industrial raw material are oxide nanoparticles (e.g. Al_2O_3, MgO, SiO_2, TiO_2), non-oxide nanoparticles (e.g. TiC, AlN, SiC), quantum dots (e.g. CdSe, ZnS) or metallic nanoparticles (e.g. Ag, Al, Au, Fe, Cu). Additionally, carbon nanotubes, fullerenes, nano wires and nano fibres are used. Other elements with particle at the nano scale are used as catalysts in industrial processes, because the high specific surface area of nanoparticles usually increases their catalytic activity.

Not everything currently characterized as "nano" is new. Nanotechnology and nanomaterials in the broader sense have been used in the semiconductor and chemical industry on a grand scale since some time, but the rapid development of nanotechnologies observable today is linked to the improved understanding and refined analytical methods of materials and the relationship between structure and properties.

2.2.1.1. Areas of Application

As indicated above, nanotechnologies and nanomaterials are already being used in a variety of products across many sectors. Its ability to change and influence material properties at the nano-scale makes nanotechnology not only an ideal choice of technology to improve existing products or applications with additional or improved functionalities, but also to obtain totally new properties and behaviours.

Today, nanotechnologies already play a certain (minor) role in the shelves of supermarkets and, usually, nanomaterials are used to improve existing products in terms of quality or functionality.

Many applications of nanotechnologies such as, for example, those in medicine, energy generation and storage or in the food sector are, on the other hand, often still in an early concept phase, and their presence on the market is still rather far away.

Basing on a commonly accepted view nanotechnologies development is divided in four stages, with well distinct timelines [19, 20]:

1) **Passive nanostructures** (as from 2000)
   dispersed and contact nanostructures, products incorporating nanostructures

2) **Active nanostructures and nanodevices** (as from 2005)
   bio-active, health effects, physico -chemical activity

3) **Systems of nanosystems** (after 2010)
   guided assembly, 3D networking and new hierarchical architectures, robotics, evolutionary systems

4) **Heterogeneous molecular nanosystems** (after 2015)
   molecular devices "by design", atomic design…

Presently, the nano-related products that exist relate to the first two stages, but those on the market are mainly based on passive nanostructures (nanomaterials). In the case of active nanostructures (nano-devices), they are still essentially at research level, though, sometimes, already at a very advanced phase of development, as in the case of medical products.

Nanoproducts referring to the last two stages are expected on the market on a medium to long term timeframe and they, are yet, partially undefined. They are linked to the improvement of the ability to manipulate matter at the nanoscale and to interact with biological systems, and open almost unlimited scenarios of applications.

This document will focus of on existing or short term applications, on which is based most of the present debate on regulation of nanotechnology

In the following paragraphs examples of application of nanotechnologies in various sectors are reported, which have been chosen for their particular relevance for nanoregulation, due to the potential impact of the corresponding nano-related products on Environment Health and Safety (EHS).

Nanomedicine

In the area of **medicine**, many hopes are directed towards nanotechnologies. Based on discussions in the European Technology Platform on Nanomedicine, the most relevant applications appear to be in the fields of diagnostic, drug delivery and tissue engineering.

Regarding, for example, drug delivery nanotechnology can facilitate attaining the essential objective, i.e. specifically transporting an active substance to a physiologically or pathologically affected organ and releasing it there. As opposed to the unspecific transport of a medical agent, possible side effects can be minimized and the optimal dose can be chosen. Drug delivery can also be limited by poor water solubility of the active substance. By using water soluble and easily dispersible nano-scaled liposomes or other nano-scaled transporters this problem can be bypassed.

For cancer diagnosis and therapy, magnetic and cytostatically activated nanoparticles are administered that accumulate in the tumour autonomously or by external manipulation. Subsequently, the specific diseased tissue is treated in a way that it is killed. Furthermore, metallic nanoparticles can be used as markers for biological screening tests or as contrast agents in MRI (magnetic resonance imaging) in the context of medical diagnosic procedures.

In diagnostics, manotechnology has also found its way into the development of medical devices, e.g. in the form of high-throughput screenings that work with biosensors on the nanoscale and with the help of which new active substances can be sought. Further applications of nanotechnology in the healthcare sector involve nano-crystalline ceramics or diamonds that can be used in implantation medicine, as they bring benefits for strength, abrasion, sliding properties and biocompatibility of implants.

Foods

In the **food** sector, so-called functional foods are currently gaining importance. Besides the supply of nutriments, functional food products fulfil additional physiological functions. There are methodologically close parallels between the nanotechnological delivery of active substances in the medical field and the administration of bioactive food additives. As in the former case, the encapsulation of food additives plays an important role with the difference that in the food industry only ingredients in food quality can be used. In the functional food area many (nanotechnological) applications are still fiction and are in a development stage. Nano-scaled micelles that transport water-insoluble nutrients, vitamins, minerals, colorants and fatty acids, however, are already used in food products. They can be easier absorbed in the bowel and are soluble / dispersible in higher concentrations in the product.

Also in the packaging field there is already a first significant application area. Silver-endowed packages and containers exhibit an anti-microbial effect and lead to an extended shelf life of packaged products. Clay particles of similar size enable gas and moisture tight foils. There are significant efforts to develop intelligent packaging devices that detect and pinpoint rotted food. However, these approaches are not market-ready at the moment and therefore not incorporated in marketed products.

Textiles

The **textile** sector represents another important application area for nanotechnology. Traditional textiles often contain fluorinated hydrocarbon in order to modify the surface properties of the fabric and to make them hydrophobic (e.g. GoreTex®). New approaches are based on the use of nanoparticles and dendrimers. If nano-scaled SiO_2 particles are integrated into the fabric, the abrasion of textiles in the washing process is decreased and the woven-in nanowires increase the fibre's strength. TiO_2 particles make UV protection possible and fluorinated dendrimers increase the water-repellent properties of the fabric (Gleiche et al., 2006). The impregnation and integration of silver particles / silver fibres results in a reduction of odour development through microbial activities and is mainly used in sportswear and socks.

Cosmetics

In the **cosmetics** field, the optimisation of the transport of hydrophobic active and nutritive substances through the skin by means of suitable carriers has priority (compare medicines and drugs). Nano-scaled particles and micelles that encapsulate the substances to be transported and release it at other parts of the body at changed environmental conditions (pH or salt content) are used. By this means, even water-insoluble substances can be absorbed by the body.

An established application field of metallic oxide nanoparticles in consumer products are sunscreens with physical UV filters on the base of ZnO and TiO_2. Due to the nano-scaled dimensions of the UV absorbing particles the creams are not white, but colourless and offer protection from incident radiation over a broad spectrum without irritating the skin as is the case with many chemical filter systems.

Composite materials

The most important application of nanomaterials in terms of volume and turnover today is probably in **composite materials**. Ceramic, metal-matrix or polymer nanocomposites are nanoparticle-reinforced materials that exhibit improved properties with relation to conductance, isolation, stability-to-weight relation, heat resistance etc.

Silicates, carbon nanotubes or carbon black are prominent examples. Carbon nanotubes (CNT) and silicates are used in composite materials as strengthening additives and result in improved stability together with a reduction of the specific weight of existing materials. In this way carbon fibre structures are strengthened in skis, tennis rackets and bicycle frames through the incorporation of SiO_2 and CNTs. Nano-scaled carbon black integrated in the rubber mass of tyres has served as a reinforcing filling agent that enables the currently available operational performances for a long time. This material is produced on the scale of several million tons per year and is (besides pyrogenic silica or those manufactured by precipitation (aerosil)) among the economically most important products on the basis of conventional nanotechnology.

Coatings

Another important field are **coatings** containing thin layers of nanoparticles that assign specific properties to surfaces. In the case of construction materials, soil-resistance, self-purification and improved water refection are in the focus. Self-cleaning glass or roof tiles decompose organic accumulations with the help of a nano-scaled TiO_2 layer which is activated by UV light. Catalytic converters of cars use nanoporous aluminium oxide mainly as carrier for the distributed noble metals. Thanks to the high surface, the efficiency factor of the catalytic converter can be increased. In order to increase the scratch resistance and preserve the brilliancy of car paints, nano-scaled ceramic particles have been used for years. Silver nanoparticles are widely used for anti-microbial coatings in air conditioning filters, fridges, vacuum cleaners or washing machines. It must be said that many commercially available cleaning and sealing agents refer to nanotechnology in their name but are, on closer examination, conventional preparations that merely leave a nanometer-thin layer upon the applied surfaces. Whether this should be called nanotechnology is a matter of definition.

2.2.2. Products Overview

To date, there is no official or conclusive database on nano-related materials or products on the market containing nanomaterials. The lack of a specific need to declare and report the use of nanomaterials in most products makes it difficult to get a comprehensive overview. However, there exist some initiatives to collect such data through the internet, continuously updating a database and providing periodic updates on the development. Such a database is The Project on Emerging Nanotechnologies' Nanotechnology Consumer Product Inventory[7] (Woodrow Wilson International Center for Scholars). As of August 2008, the list contains over 800 consumer products in eight different application areas.

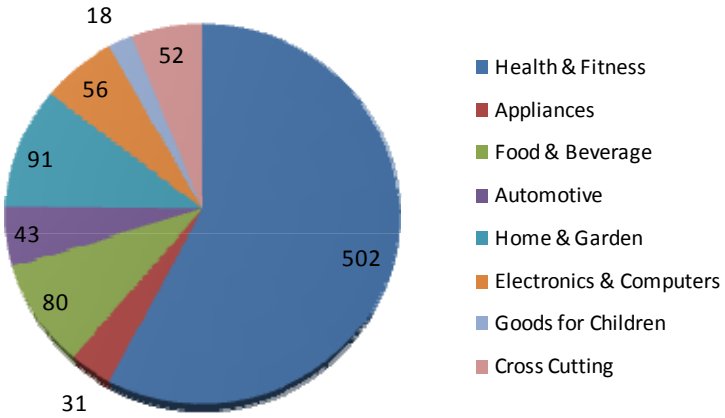
Figure 1 contains an analysis of all entries of the Woodrow Wilson database according to product categories and materials. It is evident that a major part of the products are located in the areas of health & fitness (502). These are mainly personal care products, cosmetics and clothing, but also sporting goods and sunscreens.

As indicated in the lower part of Figure 1 there is a small set of materials explicitly referenced in nanotechnology consumer products. The most common material mentioned in the product descriptions is now silver (235). Carbon, which includes fullerenes, is the second most referenced (71), followed by titanium (including titanium dioxide) (38), silica (31), zinc (including zinc oxide) (29) and gold (16). Obviously, the fraction of products containing nanosilver is exceptionally high with over 50%. This may be related to the good antibacterial properties of this material on the one hand, but also to its easy application on different textures (textiles, plastics, coatings). The use of silver in goods of daily use is not new and has already been known by the Romans who used silverware. More recently, however, nanosilver has been used ubiquitously in consumer products. In many Asian countries as well as in the USA, the use of antimicrobial articles for daily use (food packaging, toys, textiles, plastics for electronics, etc.) has risen sharply.

The inventory includes products from 21 different countries, including the United States, Canada, United Kingdom, Germany, France, Italy, Switzerland, Sweden, China, Korea, Japan, Taiwan, Malaysia, Thailand and Singapore. Companies based in the United States have the most products, with a total of 426, followed by companies in Asia (227) and Europe (108).

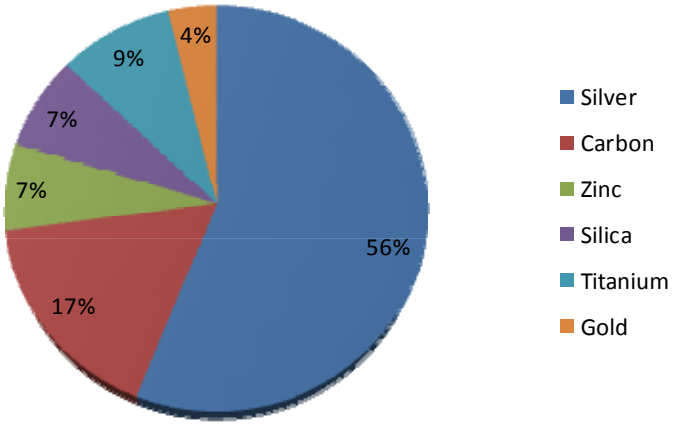
[7] http://www.nanotechproject.org/inventories/consumer/

Figure 1: Nanotechnology products sorted by application area (a) and materials (b)



a) Application Areas

Application Area	Examples
Appliances	Antibacterial air cleaners, air conditioners, refrigerators, washing machines, improved batteries etc.
Food & Beverage	Antibacterial kitchenware and food storage containers, gas-tight plastic bottles, mineral and vitamin supplements, frying oil regenerator.
Health & Fitness	Stronger golf drivers, tennis rackets and skis, antibacterial wound dressings, air purifier, socks, mineral sunscreens, remineralising toothpaste, face creams, etc.
Automotive	Sealings, car polishes, fuel borne catalyst, tires.
Home & Garden	Air sanitizer, antibacterial pet products, towels and water taps, anti-graffiti paint, sealants, etc.
Electronics & Computers	Processors, harddisks, hearing aids, memory chips, displays, antibacterial computer devices, photo paper, etc.
Goods for Children	High protection sunscreens, antibacterial plush toys and milk bottles, etc.
Cross Cutting	Mostly coated goods



b) Materials

Source: http://www.nanotechproject.org/inventories/consumer/. The database is not comprehensive and is regularly expanded. Analysis of Aug. 2008.
* Note: Some products have been counted in several application areas.

2.3. The Role of Policy and Regulation

Nanotechnologies are characterized by a high degree of innovation dynamics, which will be mirrored by the corresponding growth of the market of nano-related products. According to a survey by Lux Research, in 2007 nanotechnology was incorporated into manufactured goods representing a market of more than $50 billion. Though the forecasts about the size of the future market vary greatly, the expectations are generally high. Lux Research estimates that by 2014 this market will grow to $2.6 trillion.

Despite this expected rapid commercialization, no nano-specific regulation exists yet anywhere in the world. On the contrary, regulations and legal provisions for nanotechnology are fundamental and can serve several purposes.

From the authorities and consumers point of view they can assure the safety and protection of human health and the environment. For companies, regulations, while representing a restriction (compliance), they also can serve as a guideline that facilitates strategic decisions (legal certainty). As long as it is not known what legislative requirements have to be met, and what restrictions might be imposed, entrepreneurs are hardly interested in investing in the development of nanotechnologies. Finally, from a civil society's point of view regulations can be trust-building in the sense that they indicate a certain level of safety. Regulators must be able to provide clear threshold values with exemptions and give tolerable "risk taking" levels.

The fact that no nano-specific regulations are (yet) in place does not mean that nanomaterials are not regulated at all. For example, the European Commission (EC) has decided that the existing regulatory frameworks are, in principle, appropriate, though the need for specific adaptations must be considered. An example of this approach is the decision to apply REACH to chemical substances independently by the fact that they are in micro, macro or nano form. On February 2008 the EC has released a Code of Conduct for the responsible research in nanotechnology and the precautionary principle plays an important role in this process.

Nanomaterials can, however, display unexpected properties compared to those of the same substance on the micro or macro scale, and this raise doubts whether existing regulatory frameworks are adequate to deal with nanomaterials, or if nanomaterials need to be registered and classified as "new" or "existing" substances with all the consequences deriving from this status.

The current lack of specific regulations has led some companies to the development and implementation of a series of voluntary measures in order to establish some kind of basic trust in the public.

At the same time, also some local and national authorities have recently begun to introduce their own nano-regulations. However, by tolerating this approach, it may emerge a patchwork of individual provisions and requirements which cannot certainly last and in a later phase will need to be harmonised.

Nanospecific regulations or at least adaptations to nanotechnologies of the existing regulations are advocated from several parts. Dedicated action plans are being developed or executed to this purpose in a series of European countries.

In conclusion, the multidisciplinary and pervasive character of nanotechnology and the unique properties and behaviour at nanoscale, pose a multifaceted set of scientific, social and economical issues which, besides the discussion on regulatory options challenging the conventional regulatory/governance frame, is broadening the debate to the definition of an appropriate governance model. The development of an inclusive approach, involving all stakeholders and capable of weighing risks, socio-economical implications and ethical concerns toward benefits and advantages, is envisaged for a dynamic assessment of these technologies.

3. THE DEBATE ABOUT RISKS AND CONCERNS RELATED TO NANOTECHNOLOGIES

Basically, every new technology brings about new potential risks which must be identified. This is true also for nanotechnology whose enormous innovation potential must be checked against the possible risks for health, environment and safety (EHS) and its societal implications (ELSI).

A responsible development addressing these issues, aimed to minimise possible treats and maximise benefits for the society, is mandatory to ensure that the potential of these technologies will be fully exploited.

Due to several reasons, however, unlike previous new technologies it is not yet possible to define a uniform risk profile for nanotechnologies. In fact:

- Nanotechnologies are cross-sectional technologies that exhibit an extremely broad range of applications. They can be used in practically all industries, in diverse application areas, products and forms. Consequently, besides the physical properties, also the possible exposition paths are very diverse.
- Nanomaterials generally refer to materials not fundamentally new, but as a consequence of the specific properties at the nano scale, the current scientific database is not sufficient topredict the potential risks of these “new” substances.
- Nano-scaled substances are usually treated by legislators like conventional chemicals at the micro or macro scale. The different physico-chemical properties of the nanoscale substances are neither accounted for in declaration nor in characterisation

It became evident in the public debate about genetically modified organisms or nuclear power that a late identification of HSE risks can dampen the sustainable and successful development of a technology. In view of the great importance of nanotechnologies for the research, the economy and the society, and their expected wide-spread use, any possible risks have to be studied by comprehensive, proactive risk estimation and assessment. Based on that, measures can be taken to protect people and the environment, and to foster well-informed discussions within the society. Following this approach, the costs for a later risk and consequences assessment on EHS or possible costly liability reimbursements can be avoided (or at least reduced) as well.

In the following paragraphs, the debate about the risks and concerns potentially associated with nanotechnologies will be highlighted, segmenting the topic with reference to EHS effects, and ethical, legal and societal issues (ELSI).

The overview on EHS effects has been made basing on information from a series of comprehensive reports and review articles in the scientific literature as well as on the information in the basic report of the Swiss Action Plan on nanomaterials (published in 2007). Such overview cannot be considered conclusive. Its presence is essentially aimed to outline the complexity of problems and the issues that are at stake to properly regulate nanotechnology.

3.1. Health & Safety Effects on Humans and the Enviroment

The focus in the health and safety risk discussion is particularly on applications and products using manufactured nanoparticles that are produced for a specific purpose and have a defined chemical composition and size distribution.

When nanoparticles are added e.g. for the mechanical fortification of composite materials, they are firmly embedded in a matrix and are considered not mobile. When, on the contrary, nanoparticles are dispersed into fluid or gaseous media they are called unbound or free nanoparticles.

Specific attention in the risk discussion surrounding nanoparticles is given to products and applications for which the release of manufactured nanoparticles is expected. This pose a threat to the workers in nanotech industries because they handle nanoparticles at high concentrations and during a long time, but also the public might be at risk, from the release in the environment as consequence of accidental spills during production and transportation, wear and tear of products containing nanoparticles, the final disposal of containing products nanoparticle.

The concerns are partly based on experiences with nanoparticles that result from natural sources or combustion processes, as from diesel exhaust or soot particles in the case of wood combustion. In environmental research these nanoparticles are characterized as “ultra-fine particles”. Several epidemiologic air pollution studies have described a correlation between increased levels of combustion derived nanoparticles in ambient air and various adverse human health effects in susceptible groups [2].

Little data are, instead, available on the release, toxicity, environmental behaviour and safety of nanoparticles. In the literature it is often stressed that results for one nanoparticle cannot be generalised to other materials, because the factors for classification have not yet been defined in a uniform way. Only standardised tests for individual groups of nanoparticles and the use of recommended references would enable comparisons to be made between the different materials and studies.

However, certain general particle properties have been identified to be crucial for the toxicity of nanosized particles [reviewed in 3]:

- Reduction of particle size to the nanoscale results in a huge increase of surface area. Therefore, more molecules are present on the surface and might undergo interactions with their surroundings, depending on the chemical composition of the particle. Larger surface area might also enhance adsorption and transport of toxic substances. The concept of particle surface area as one of the most important dose metrics for the biological activity of nanoparticles has been proposed.
- Retention of particles within a physiological environment determines the cellular contact and hence causes the greater chances for damage. Retention time also determines its mobility either through clearance or migration to surrounding tissue.
- Inherent toxicity of any contaminants present in nanomaterials may exhibit more pronounced effects than the material’s intrinsic toxicity itself.

In order to avoid false positive and false negative results, knowledge about only one or two characteristics of nanoparticles is not sufficient to interpret their biological or toxicological effects. The multitude and interplay of all characteristics have to be considered [reviewed in 3].

In the next paragraphs the available scientific knowledge on the release, routes of exposure, biological activity, toxicity, environmental behaviour, and the safety of nanoparticles will be illustrated.

3.1.1. Routes of Exposure

Manmade nanoparticles may be divided in three main groups [1]:

- accidentally produced ultra-fine particles
- nanoparticles that have been manufactured for a long time (e.g. carbon black, TiO2)
- newly developed manufactured nanoparticles (e.g. nanotubes, nanospheres or nanowires).

Comprehensive toxicological data is only available on accidentally produced ultra-fine particles (e.g. in combustion engines). Less is known about nanoparticles like carbon black that have been industrially manufactured for a long time, and even less studies are available on those particles that are synthetically manufactured especially for nanotechnology, such as nanotubes, nanospheres or nanowires [1]. However, the applications of these industrially manufactured nanoparticles in food products, drug delivery systems, medical devices, consumer products and the increasing disposal of these nanoparticles in the environment imply that human exposure to nanoparticles is expected to be relevant and will increase in the (near) future. It is therefore fundamental to increase our understanding of relevant *exposure sources* in the different life-cycle stages of materials and products, of *exposure routes* (inhalative, dermal, oral, via eye..) and of the *internal exposure* mechanism in the body (absorption, distribution, metabolism, excretion) of manufactured nanoparticles

The release of nanoparticles in the environment as aerosols suggests that inhalation represents an important route for human exposure to nanoparticles. Another source of exposure for the population may be the (future) waste disposal of nanotechnology derived products. This disposal could eventually lead to increased particle concentration in soil and (drinking) water sources and in farm crops resulting in potential exposure via skin contact and ingestion. In addition, application of nanoparticles in products such as medical products, cosmetics and food also will result in exposure of the skin, eye and gastrointestinal tract. Therefore for the broad variety of nanotechnological applications different exposure routes including inhalation, oral, dermal, parenteral route and implantation will need attention in the near future.

In Figure 2, the potential lifecycle of nanoparticles in the human body is represented schematically. From a kinetic point of view, this figure gives an overview of the ADME processes (absorption, distribution, metabolism, and excretion) in the body. Figure 2 also indicates that particles can be distributed to the same organ by several routes of exposure.

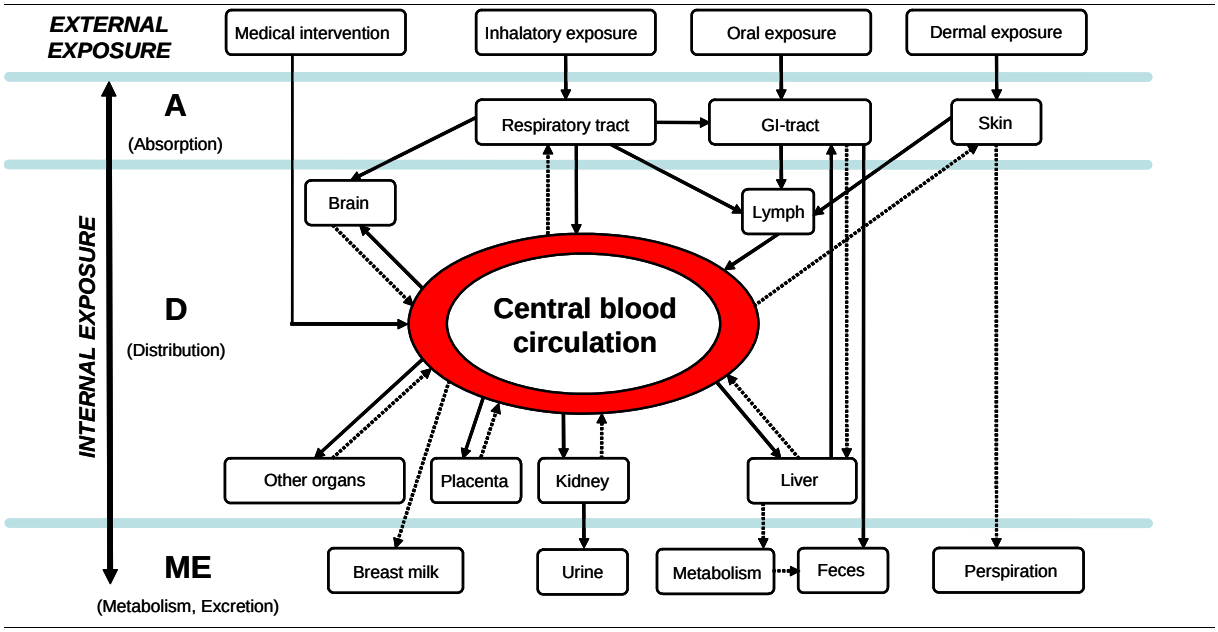


Figure 2: Overview on the hypothetic kinetic pathways of nanoparticles in the body (figure modified from reference [16].
The ADME processes (absorption, distribution, metabolism and excretion) of nanoparticles in the human body. The internal exposure is the part of the external dose that reaches the systemic circulation. The black lines represent confirmed routes for nanoparticles; the dashed lines represent hypothetical routes. The transport rates and retention times for the indicated processes are largely unknown (Other organs: e.g. spleen, heart, reproductive organs. Modified from reference [16]).

To date, the current knowledge of the kinetics of nanoparticles is too limited to allow a proper foundation of human risk assessment. To close the knowledge gaps, research should in first instance be focussed on elucidation whether and to what extent nanoparticles enter the body (e.g. various exposure scenarios). In addition, target organs should be identified [17].

In practice, extensive kinetic research will be required, including absorption, distribution and metabolism and excretion processes over time after different exposure routes. With the obtained (quantitative) nano-kinetic data, whole body Physiologically Based Kinetic (PBK) modeling will be possible. Such models provide a mechanistic approach to understand the kinetic properties of nanoparticles in the body over time. The advantage of a PBK modelling is that additional data and parameters from different sources (in vitro, in vivo studies and existing/new literature) can be incorporated. If the necessary kinetic data are available for these models, various extrapolations (cross dose, cross species and route-to-route) might allow quantitative risk assessment [18].

At the workplace, exposure to nanoparticles occurs primarily through handling nanoparticles that are produced for a specific purpose, and through working practices that generate nanoparticles as by-products. Although there is not yet an overview of the types, quantities, or forms of application of nanoparticles, as by-products they are considered to be the most widespread source of exposure in the workplace. However, not all nanomaterials are equally relevant for all routes of exposure. Light-weight materials such as carbon nanotubes are more likely to become airborne and therefore represent an increased occupational risk during production and handling, while for certain other materials, it requires considerable energy to have them airborne (e.g., quantum dots).

Inhalation uptake of nanoparticles via the **lungs** has to be considered as the most important entry port [1]. With approximately 140 m² the lung offers an enormous exposition area for inhaled nanoparticles.

The blood-air tissue barrier in the gas exchange area of the lung is only some hundred nanometres thin. It has been shown in animal experiments that particles that have passed this barrier can be transported via the blood stream in all areas of the body (lymph nodes, spleen, heart, liver, kidney, bone marrow, and even brain [2]). Even the uptake of nanoparticles by **sensory nerve endings** embedded in the airways to central nerve system (CNS) structures has been shown [reviewed in 2 and 4]. Access of nanoparticles to neural tissue via the **blood brain barrier** (BBB) is also possible [4] (see Figure 2). Of all the endothelial barriers within the body, the BBB is the tightest.

Nanoparticles also seem to have the ability to overcome the double lipid membrane that borders the cell versus the outside [reviewed in 1]. Nanoparticles with a diameter of less than 30 nm can reach the cell nucleus [1]. It is possible that smallest nanoparticles (< 2 nm) are incorporated as clusters in the channels of the DNA double helix and thus cause genotoxic effects [reviewed in 1].

Dermal uptake of nanoparticles is relevant in terms of an increasing number of cosmetic products and sunscreens containing nanoparticles. At the workplace, airborne nanoparticles can deposit on the skin. With 2 m^2, the skin offers a smaller exposition surface as compared to the lungs or the alimentary system [1].

Particles can on the one hand reach the dermis through or between epidermis cells and on the other hand penetrate into deeper skin layers through perspiratory glands, hair follicles or even through sensory nerve endings [reviewed in 1]. In healthy skin the epidermis provides excellent protection against particle penetration [1]. However, during everyday life skin may be damaged by exposure to chemicals, by scratches, hydration or dryness, sunburn, or pathological states [6]. There is an ongoing scientific debate about these effects on the quality of the barrier function of the skin.

Ingestion of nanoparticles can occur directly via food, or indirectly via mucociliary transport. It was reported that a large fraction of nanoparticles rapidly pass through the gastrointestinal tract and is eliminated via faeces [1]. However, a minor fraction may be taken up by the gastrointestinal mucosa and finally translocated to systemic organs [2].

For medical purposes, certain nanoparticles might also be **injected** directly into the body. Although the application of nanoparticles for medical use is still under development, nanoparticles offer immense potential for diagnostics and therapeutics. Toxicological safety considerations and human risk assessment will be a challenge for the future, and currently only very limited information is available on *in vivo* human use of nanoparticles loaded with drugs [2].

3.1.2. Known and Suspected Health Effects

A great number of studies already suggest that many nanoparticles are not inherently benign and actually can affect biological activities at the cellular, sub-cellular, and molecular levels [2].

In addition to the dose and the elemental composition of the nanoparticles, the tiny dimensions of nanoparticles of 100 nm or less associated with high surface area and particle numbers are believed responsible for their increased biological reaction potential [2]. Their extremely small size creates the chance for increased uptake, rapid body distribution, and toxic interaction at target sites. Additional factors such as the function of the surface, their tendency to aggregate, the form of the particles, their surface charge and the method of synthesis all play decisive roles in their distribution through the body, and their possible toxicity [1].

Effects of nanoparticles are not limited to the location of uptake, but might involve distant organs. Nanoparticles can penetrate cellular membranes and even reach cell organelles like mitochondria or the nucleus [reviewed e.g. in 1 and 5]. Today, the propensity of nanoparticles to cross cell barriers, enter cells and interact with subcellular structures is well established, as is the induction of oxidative stress as a major mechanism of nanoparticle effects [3]. Many animal studies with model nanoparticles showed that particles triggered weak to clear inflammatory reactions in the lung as well as effects on extrapulmonal organs [reviewed in 1].

In general, there is a direct relationship between the surface area, the potential to generate reactive oxygen species (ROS), and pro-inflammatory effects of nanoparticles [2]. Oxidative stress is an imbalance between the production of ROS and their degradation by antioxidants. The intracellular equilibrium may be disturbed by the presence and/or uptake of nanomaterials. The concentration of ROS may be increased by the particle itself or by the disturbance of the ROS degradation pathway. Both cause an additional production of ROS, which interacts uncontrollably with the cell membrane, DNA, and/or other cell compounds, severely damaging these cell compounds [7].

It should be noted, however, that toxicological information on nanomaterials needs to consider actual human exposure levels; any particulate material, whether nano-sized or larger, will give rise to adverse effects at high enough doses [3]. Many studies used insufficiently characterised particles, unrealistically high doses and administration settings that would probably not be present in reality. Such settings can lead to the observation of effects which are not primarily produced by the particle's intrinsic toxicity, but rather by unspecific effects such as overload of the target organs or unspecific effects which might be observed with any kind of (nano-) particle.

In addition to the dose and the elemental composition of the nanoparticles, factors such as their surface area, the function of the surface, tendency to aggregate, the form of the particles, their surface charge and the method of synthesis all play decisive roles in their distribution through the body, and their possible (genetic) toxicity [1].

The following paragraphs will give an overview on the effects that have been observed with different kinds of nanomaterials, including fullerenes, carbon nanotubes, carbon black, and metal and metal oxide nanoparticles. Other nanoparticles such as quantum dots also exist, but are still produced in small amounts only. Therefore, only the most important classes of nanoparticles are shortly discussed below.

3.1.2.1. Carbonaceous Nanoparticles

C_{60} (also: Buckminster **fullerene**) applies to molecules composed entirely of carbon that form spheres or tubes [3]. Recently a number of cosmetic products such as face creams that contain C_{60} nanoparticles have entered the market since a number of studies have shown that the C_{60} fullerene

has antioxidant properties. These studies suggested that far from being toxic, C_{60} and its derivatives could actually have a beneficial health effect [reviewed in 3].

However, other recent studies suggest that C_{60} and its derivatives actually have pro-oxidant and toxic effects and that the toxicity of fullerenes be due to lipid peroxidation of cell membranes and the resulting perturbation of membranes. Fullerenes are highly lipophilic and tend to localize to cell membranes [reviewed in 2]. It was shown that when exposed to light, fullerenes could cause cytotoxic effects, cleave DNA, affect embryonic development, and/or are distributed rapidly to many tissues in the body, where they are retained for a long time [reviewed in 2]. In other studies, the toxicity of fullerenes on various aquatic organisms has been investigated (see chapter 3.2). Fullerene toxicity strongly depends on the surface oxidation state of the molecules [5].

Besides the carbon-based fullerenes, there also exist inorganic fullerenes such as WS_2 and MoS_2. These are onion-like nanoparticles consisting of several molecular layers, with an inert surface. Since these fullerenes consist of rather exotic materials and are used for highly specific applications, their industrial production has been small until now.

Nanotubes are also members of the fullerene structural family. Similarly to the fullerenes above, besides carbon nanotubes there is also a variety of inorganic nanotubes, however, with little commercial importance yet.

Carbon nanotubes (CNTs) are extended tubes of rolled graphene sheets with a very high length-to-diameter ratio. They can be stronger than steel, harder than diamonds, flexible, lightweight, heat resistant, and of high electrical conductivity. CNTs can be divided into single-walled (SWCNT) and multi-walled carbon nanotubes (MWCNT), which may exhibit significantly different behaviour [5]. Untreated carbon nanotubes are non-water-soluble and non-biodegradable, but different degree and kind of functionalisation can significantly influence water solubility, transport behaviour [reviewed in 7] and specific toxicity [reviewed in 2, 8 and 7].

CNT toxicity has recently been increasingly investigated. Many studies show that CNTs, once taken up by organisms, may cause oxidative stress, inflammation, cell damage, adverse effects on cell performance, and, in a long-term perspective, pathological effects in the lungs [reviewed in 7]. Besides lung toxicity, which is currently mainly considered in toxicity studies, only very few skin irritation studies with CNT have been reported.

Comparison of study results and transferring the results to a real-life inhalation setting is questionable, because many studies used insufficiently characterised particles and intratracheal instillation instead of airborne inhalation as the way of particle administration. This leads to locally concentrated and high doses, different aggregation status of the particles in aqueous solution and possibly even non-material-specific effects [reviewed in 5].

SWCNT are essentially graphitic and therefore biologically extremely biopersistent [2]. Because of their unique structure, SWCNT simultaneously demonstrate features of nanoparticles and conventional fibres [2]. Recent CNT toxicity studies in rodents demonstrated toxic effects which have been compared to asbestosis [reviewed in 2, 7].

Depending on their manufacturing method, purification and functionalisation, CNT may contain significant amounts of metal catalysts as impurities emerging from production. Transition metals such as Fe are highly proficient in generating reactive oxygen species (ROS) and may cause oxidative stress [2]. Such metal contaminants have been reported to account significantly to the observed toxicity of CNTs [reviewed in 1, 2 and 5]. On the other hand, studies have shown that (regardless of the technical process of manufacturing and their types and amounts of metals) even purified CNTs are agents capable of causing inflammation, epithelioid granulomatous fibrosis, oxidative stress, and diverse toxicological and molecular changes in the animal lungs and cells [reviewed in 2 and 8].

Carbon black is a form of amorphous carbon that has a high surface area to volume ratio, and as such it is one of the first nanomaterials to find common use. Carbon black is used as a pigment and reinforcement in rubber and plastic products.

Carbon black has been recognized as a useful reference material for which toxicology and epidemiology data are available [9] and is often used to compare effects among different nanomaterials. Carbon black nanoparticles (CBNP) have been reported to cause oxidative stress in diverse cells types and cell-free systems [reviewed in 2].

3.1.2.2. Metal (Oxide) Nanoparticles

Commonly used examples of metallic and metal-oxide nanoparticles are Ag, Au, TiO_2, Al_2O_3, Fe_2O_3, SiO_2, ZnO, and CeO_2. Among the metal oxide nanomaterials, TiO_2 and SiO_2 have extensively been studied and the bulk materials of some metal oxides, such as TiO_2 and SiO_2, have been approved by national food and drug administrations as food additives. They were considered to be so-called nuisance dusts until it was observed that upon prolonged exposure in rats, inflammation and lung tumours can occur [4]. Therefore, due to drastically changed physico-chemical properties, the behaviour of nanoscale materials cannot generally be derived from their fine or bulk counterparts.

Exposure to ultrafine TiO_2 has been reported to be associated with a variety of pulmonary effects in rats, including inflammation, pulmonary damage, fibrosis, and lung tumours [reviewed in 2]. It was shown *in vivo* that such particles can be taken up by the lung, passed through the air-blood barrier, and translocated into the bloodstream [7]. However, such results have to be carefully interpreted and conclusions with regard to real-life exposure situations (such as at the workplace) may not be directly derived from these findings.

3.1.3. Physico-chemical Hazards

The specific physical and chemical properties that nanoparticles have compared with larger particles can present unexpected safety risks. The most important physico-chemical dangers are the risks of fire or explosion and of unexpectedly increased catalytic activity. Most organic, many metallic and even some non-metallic materials (if they are not already completely oxidized, such as SiO_2 or TiO_2) when finely dispersed in the air can be oxidized explosively if they come in contact with a sufficiently strong ignition source and an oxidant. For reactive metallic particles like magnesium or aluminium the maximal explosion power lies in the dimension of nanoparticles [1].

So far, these dangers have been classified as relatively low for many manufactured nanoparticles, as nanoparticles have been produced in relatively small quantities. However, this is currently changing rapidly for certain materials.

3.2. Environmental Effects

Because of the widespread and increasing use of manufactured nanoparticles in consumer products, it is expected that these nanoparticles will be released into aquatic, terrestrial, and atmospheric environments in significant quantities. The unique properties of manufactured nanoparticles, such as their high specific surface area, abundant reactive sites on the surface, as well as their mobility, could potentially lead to unexpected health or environmental hazards. Therefore, organisms, and particularly those that strongly interact with their immediate environment such as algae, plants, and fungi, are expected to be affected as a result of their exposure to manufactured nanoparticles.

It seems reasonable for both proponents and sceptics of nanotechnologies that the potentially adverse effects nanoparticles could have on humans as well as whole ecosystems need to be examined in an early phase. Evaluation of the risks that manufactured nanoparticles pose to the

environment involves a comparison of environmental concentrations with those that are toxic to organisms. Both factors are still largely unknown for many nanomaterials and ecosystems.

At present, only very few studies have been carried out on the ecotoxicity and environmental behaviour of nanoparticles. Much of the ecotoxicity data is limited to species used in regulatory testing and freshwater organisms [12].

Similarly to the situation described under section 3.1.2, a lot of studies used very high concentrations rather than environmentally relevant concentrations, and test materials that were not sufficiently characterized. However, existing data on biological effects suggest that nanoparticles can be toxic to bacteria, algae, invertebrates and fish species, as well as mammals [reviewed in 11].

3.2.1. Release into the Environment

Nanoparticles are not new and have been present on Earth since ancient times. Natural nanoparticles are generated by a wide variety of geological and biological processes, and while there is evidence that some natural nanoparticles can be toxic, organisms have also evolved in an environment containing natural nanoparticles. However, with the massive increase of burning fossil fuels, the amounts of manmade nanoparticles have increased drastically. Although a budget for nanoparticles in the different environmental compartments is currently lacking, emission inventories suggest that motor vehicles are already the primary sources of fine and ultrafine particles in the atmosphere [reviewed in 11]. With the expected further development of nanotechnologies, another substantial increase in the production and release of manufactured nanoparticles into the environment is expected. Besides direct emission into the atmosphere or photochemical formation therein, manufactured nanoparticles, as they are used in sunscreens, detergents, paints, printer inks, or tires, can also enter the environment through accidental spills during production and transportation, wear and tear, and the final disposal of the nanoparticle containing products.

There are not yet any reliable estimates of possible environmental inputs that could occur during the production, use and disposal of nanoparticles or products containing nanoparticles. This may be due to a lack of suitable methods to measure nanoparticles in the environment, but also due to difficulties to get data on production and use of nanomaterials from the industry. Although several governmental and research projects have been initiated with the aim to collect such data (see section 4.4.2), they rather have to be considered as time- and location-specific snapshots. Similarly, scarcely any data is available on by-products and breakdown products of nanomaterials.

As one of the key barriers in the pathway of nanoparticles into the environment, first studies have investigated the effectiveness of wastewater treatment plants to remove nanoparticles. Bactericidal properties of nanoparticles might come up with new effects which influence the microbial treatment steps in conventional water treatment plants.

Once nanoparticles are released into the environment, there is a requirement to understand their fate, behaviour and transport, in order to determine in which environments the particles are most likely to occur or accumulate, and hence which organisms are most likely to be exposed [3].

3.2.2. Environmental Fate and Behaviour

The physico-chemistry of manufactured nanoparticles is essential to understanding the fate and behaviour of nanoparticles in the environment, as well as their potential uptake and distribution within organisms, and the interactions with other pollutants. Stable colloidal suspensions of nanoparticles are a prerequisite for efficient interactions of nanoparticles with organisms. Manufactured nanoparticles show some complex colloid and aggregation chemistry, which is likely to be affected by particle shape, size, surface area and surface charge, as well as the adsorption

properties of the material. Abiotic factors such as pH, ionic strength, water hardness and the presence of organic matter will alter aggregation chemistry and are expected to influence toxicity [12].

Nanoparticles tend to form agglomerates, which renders them less mobile, less reactive and less well-distributed [5]. However, nanoparticle manufacturers often try to prevent agglomeration by coating, to be able to fully exploit the specific properties of the nanoscale particles. On the other hand, these properties render the particles more reactive and mobile in the environment.

Non-metallic nanoparticles (such as carbon nanotubes and fullerenes) have highly hydrophobic surfaces and are not readily dissolved in water. These particles may be solubilised by functionalisation with polar groups on their surfaces. Otherwise, the surfaces of hydrophobic carbon nanotubes are likely to interact preferentially with hydrophobic or amphiphilic compounds. As a ubiquitous component of aquatic systems, the interactions between nanoparticles and natural organic matter (NOM) may finally determine a nanoparticles' fate in aquatic systems. The formation of larger aggregates will favour the removal of nanoparticles into sediments and is likely to decrease their bioavailability. In contrast, solubilisation by natural surfactants such as lower-molecular-weight NOM compounds will increase their mobility and bioavailability. Therefore, in the presence of appropriate organic compounds, nanoparticles will have a longer residence time in aquatic systems, or enhanced mobility in soils, and may thus interact more efficiently with algae or with plant roots [reviewed in 11].

So far, there are hardly any data about biodegradation, bioaccumulation and the possibility of the accumulation of nanoparticles in the food-chain. However, investigations showed that carbon nanoparticles can be taken up by aquatic organisms [reviewed in 5]. On one hand, the storage of lipophilic nanoparticles in fatty tissues and the resulting concentration in the food-chain have to be considered, and on the other hand the accumulation of persistent nanoparticles in ecosystems and organisms if there are no pathways for their breakdown or excretion [1].

3.2.3. Effects on Organisms

Due to the relative newness of the problem, there is a remarkable lack of information on some key aspects concerning environmental effects of manufactured nanoparticles, which currently prevents a better understanding and assessment of the toxicity and ecotoxicity of manufactured nanoparticles to the key ecosystem organisms. Only recently the toxicological impact of nanoparticles on a range of organisms has started to emerge. Such studies already span the breadth of microorganisms, plants, invertebrates and vertebrates, although relatively few publications are available within each category.

The toxicity of nanoparticles to **microorganisms** has been widely studied in relation to the development of antimicrobial agents and devices for use in the environment, in industry and in medical devices [3]. Many of the applications that employ nanoparticles for antibacterial purposes use materials that are already known to possess antibacterial properties (e.g. TiO_2 and silver). The nanoparticle nature and associated larger specific surface area of the material enhance its antibacterial activity [3]. The antifungal and antimicrobial activity of manufactured nanoparticles may seriously threaten free-living nitrogen-fixing bacteria and symbiotic relationships involving fungi, bacteria, and plants (mycorrhiza, rhizobia in legumes, lichens, etc.) [reviewed in 11]. However, there is insufficient evidence to suggest that all nanoparticles have antimicrobial effects, or in fact that all nanoparticles are toxic to any organism encountered in an exposed environment [3].

Direct toxic effects of nanoparticles on organisms are mainly determined by their chemical composition and surface reactivity. Their greater surface area per mass, compared with larger-sized particles of the same chemistry, renders them more reactive biologically. This greater reactivity

might cause catalysis of redox reactions upon contact with organic molecules, and also impact on photosynthetic or respiratory processes [reviewed in 11].

As for the indirect effects of manufactured nanoparticles, they are caused mainly by the physical restraints or the release of toxic ions or the production of reactive oxygen species (ROS). ROS production is especially relevant in the case of nanoparticles with photocatalytic properties such as TiO_2 upon ultraviolet (UV) exposure [reviewed in 11]. At the same time, toxicity of manufactured nanoparticles may partly be due to the release of toxicants which they might be carrying [reviewed in 11]. Nanoparticles have also been found to act as contaminant carriers of co-existing contaminants and this interaction has altered the toxicity of specific chemicals towards D. magna.

For a series of specific materials and settings, adverse environmental effects have been reported. Zn and ZnO nanoparticles were shown to affect growth in **plants** [reviewed in 11]. In the case of alumina nanoparticles, they were shown to cause root growth inhibition in five plant species at relatively high concentrations [reviewed in 3].

Toxicity studies on **fish and invertebrates** currently only exist in fragments. Considering that invertebrates constitute 95–97% of all known animal species, there is a considerable lack of information on ecological endpoints [4]. A recent literature review indicated that there were less than 20 peer reviewed papers on environmental toxicity in invertebrates and fish available by April 2008 [14]. The most frequently tested engineered nanoparticles in invertebrate tests were fullerenes, carbon nanotubes, and TiO_2. The majority of the studies used Daphnia magna as the test organism, which may be justified by its ecological and regulatory relevance. Only a few studies have observed chronic or life-cycle related effects of nanoparticles to invertebrates, and most sub-lethal studies on vertebrates are on freshwater fish [reviewed in 12].

3.3. Ethical, Legal and Societal Issues (ELSI)

Nanoscience and nanotechnologies are broad terms encompassing different areas of science and a countless number of current and future applications. The revolutionary promises related to these technologies, if truly realised, necessarily brings with themselves relevant changes at social-economical level. This is a novel and huge field of investigation, characterised by a multifaceted set of scientific, technical, social, ethical issues which, in the last years, has sparked the interest of the scientific and social sciences communities, the economic and political world, the ordinary people.

Being the topic so large and complex no clear-cut opinions and needs have distinguished the debate in the last years. Many social and ethical issues regards potential future applications of nanotechnology, and are still in the form on questions or open points. Nevertheless the relevance of Ethical Legal and Social Issues cannot be neglected also at the present stage of development of nanotechnology and they must be taken into account in any Governance Plan for nanotechnology.

A telling document about ethics and technology has been published in January 2007 by the European Commission [3]. In the following pages are outlined some common elements emerging from the different stakeholders initiatives and positions and an interesting point is that the debate is giving input to a new approach for the appraisal of risk and concern deriving from the application of a technology.

Inclusiveness, i.e. cooperation, coordination and communication among all the actors dealing with nanotechnology and the public, is seen as fundamental to ensure a responsible development of nanotechnology and new ideas and instruments have been proposed to foster this kind of approach.

3.3.1. Defining the context

Even though no one has yet given a formal statement of what is commonly included in the Ethical, Legal and Societal Issues ("ELSI"[8]) surrounding nanotechnology, various authors have tried to make a catalogue of most relevant elements to be considered in relation with these terms.

The following (partial) list is an elaboration from different source [1,2,3,4,5,6].

- **Risk management and regulatory issues**
  Basing on the available knowledge about EHS implications and risk assessment of nanotechnology, how (and who) one should manage and regulate these risks, what is the right trade-off between benefits and risks and the correct level of precaution in using nanotechnologies.

- **Public perception and public engagement**
  How the public perceives/accepts applications and risks of nanotechnology; how to engage the public in a proactive debate on risks and benefits of nanotechnology; the role of scientific and not scientific communication; how these elements can influence the governance of nanotechnology development.

- **Commercialization and governance issues**
  Impact of nanotechnology on economy, trade, employment at regional/national or local level; rights to access to information (also in relation with the use Intellectual Property Rights); non discrimination in the access to the benefits of nanotechnology, including the questions of a nanotech divide versus the promises for a beneficial use of nanotech in the developing world.

[8] Also the term "ELSA" (Ethical, Legal and Societal Aspects) is sometime used.

- **Application specific issues (mainly in relationship with nanomedicine and security applications)**
  - *Ethical and philosophical issues related to non therapeutic human enhancement and novel applications exploring man-machine interactions;*
  - *increased personal responsibility related to novel diagnostic tools providing predictive information on diseases;*
  - *protection of personal data, privacy, limits to personal freedom, confidentiality issues raised by novel surveillance, military and medical applications of nanotechnology;*
  - *Use/misuse of novel applications in criminal or terrorist activities.*

The social, economical, political and ethical concerns pinpointed above are obviously interrelated in complex ways and their mutual importance will also evolve in time with the development of the technology. Properly addressing these concerns is instrumental to match the three pillars of responsible development: economic development, social development and environmental protection[9]. Nanotechnology, as any other technology must develop to the benefits of the society.

An interesting approach to better focus ELSI of nanotechnology has been proposed by the International Risk Governance Council (IRGC) in their governance model for nanotechnology, where the four stages envisaged for the development of nanotechnology, is provided the basis for two distinct frames of reference [7].

- *Frame One, or "passive" nanostructures (Generation 1)* [10].
- *Frame Two, or "active" and "more complex" nanostructures and nanosystems (Generations 2-4).*[11]

While the first frame mainly refers to existing or short-term applications and has essentially to do with nanomaterials, the second one is related to applications that could enter in our life only in a medium/long period.

Risk management and regulation and *public perception and engagement* are fundamental for both frames.

Commercialization and governance issues, nevertheless, are likely to become more important with a more mature technology (mass application of nanotechnology) when will be available radically new applications, and thus are more related to frame 2.

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[9] *On responsible development see, for example, the 2005 World Summit Outcome Document, World Health Organization, September 2005 - http://www.who.int/hiv/universalaccess2010/worldsummit.pdf*

[10] *"Frame1: The context of classic technology assessment looking into the impacts derived from the application of nanoparticles and other passive nanostructured materials in different areas of application (such as paint, cosmetics, food, and coatings). This frame is most suitable for issues related to the first generation of nanoproducts (passive nanostructures)." [7]*

[11] *"Frame 2: The context of social desirability of innovations looking into processes of modernization, changes in the interface between humans and machines/products and ethical issues of the boundaries of intervention into the environment and the human body. This frame addresses issues related to the future generations of nanoproducts (active nanostructures and nanosystems, and long-term implications of nanotechnology" [7]*

However, the use and access to some applications by developing countries (as, for example, nanotechnologies for clean energy or environmental remediation) is already an actual issue.

Intellectual Property Rights can, also, become increasingly important. For example, if large organisations or corporation would start to collect broad IPR portfolio on basic nanotechnology developments (as specific nanomaterials), this, according to somebody, could hinder the development of nanotechnology applications from other subjects.

Application specific issues are mainly related to the second frame. Advancement in nanomedicine are occurring very rapidly, already opening important ethical reflections, but the ability to radically change the way *"human and environmental biosystems work"* is still not much close in time.

Ethical issues raised by novel therapeutics and diagnostic systems, or sophisticated surveillance tools, are not unique of nanotechnology. For example, technologies related to pharmacogenetics and pharmacogenomics in medicine, or information technology systems (from internet, to mobile phones communication or satellite mapping/surveillance systems) are being the source of an ample debate on similar ethical issues. On one side the debate on nanotechnologies may gain inputs from these experiences, on the other side it could represent, hopefully, an opportunity to improve the ability of stakeholders and society as a whole to manage them.

3.3.2. Stakeholders involved

ELSI are gaining an increasing importance in the nanotechnology agenda of government and authorities and in the activities of several other organisations worldwide, such as universities, research institutes, civil society organisations.

Europe is from many points of view at the forefront on these themes. The need of addressing ethical and societal implications of nanotechnologies is clearly stated in the "Nanosciences and nanotechnologies: An action plan for Europe 2005- 2009". Among the future actions to be undertaken is in fact stressed: *"ensuring that ethical principles are respected and citizens' concerns and expectations taken into account"*, and *"the integration of ethical concerns, innovation research and social sciences into N&N R&D will help build confidence in decision-making related to the governance of N&N."* [12].

The European Group on Ethics in Science and New Technologies (EGE) and UNESCO have published opinions on the ethical aspects of nanomedicine and nanotechnologies [2, 8].

The EC has promoted initiatives as the "Nano Safety for Success Dialogue" events[13], and the open consultation on the "Strategy on communication outreach in nanotechnology" [9] and supported several specific projects (part of them reported in paragraph 7.2) on ELSI.

Several **EU countries** have formally requested opinions and reviews from their Ethical Committees on nanotechnology (as France [6], UK [1], Italy [10]). These and other Countries, as The Netherlands, Germany, Denmark, Sweden, Switzerland, and Austria, have funded important

[12] Also the "EU strategy on nanotechnology" adopted by the EC in 2004, already emphasises the need to respect acknowledged ethical principles: "*Ethical principles must be respected and, where appropriate, enforced through regulation. These principles are embodied in the European Charter of Fundamental Rights and other European and other international documents. Some of the basic ethical values include: the principle of respect for dignity; the principle of individual autonomy; the principle of justice and of beneficence; the principle of freedom of research; and the principle of proportionality."*

[13] http://ec.europa.eu/health/ph_risk/ev_20081002_en.htm

projects in both public engagement with nanotechnology and social science research on nanotechnology (at least partially reported in paragraph 7.2). In particular the UK is considered as one of the most active in the field, with many initiatives started since the government publication of the Outline Programme for Public Engagement on Nanotechnologies (OPPEN) in 2005 and the establishment, in the same year) of the Nanotechnology Engagement Group (NEG). A recent report from NEG [11], made a very interesting review of all UK initiatives on these themes.

Looking only at (available) data related to funding of research on the safety of nanomaterials, the European Commission has granted in the first year of the FP7 program about 28 Million € in projects dealing with these themes (on a total of about 600M€ on nanotechnology) and more than 90 projects on safety have been funded by Member States, bringing the European total funding in this area to some 80 million € (a report from the EC gives details of the more than 100 projects from the EC and Member states on these themes [12]).

In the **USA**, within the NNI, about 4-5 % of Federal funding for nanotechnology [13] are allocated on ELSI issues, mainly to the two programs on "Environmental Health and Safety issues" and "Education and Societal Dimensions", with most of the funding given to the former area.

In NNI there is a particular focus on risk perception and public acceptance of nanotechnology, considered as elements that may strongly influence the development and commercialisation of nanotechnology. To this end, the NNI program on societal dimension mainly supports initiatives on education and public communication (including outreach and engagement) and some centers within the NNI have been dedicated to these themes (as the NSF Center for Nanotechnology and Society).

Regarding other ethical issues, the President's Council on Bioethics conducted an independent study on ethical issues in relation with nanotech[14]. After this review, the NNI position is that ethical concerns in relation with nanotechnology are similar to concerns over technological advances in general and thus do not require actions and approaches different from other technologies.

One of the priority of the Science and Technology basic plan in **Japan** is "Public Confidence and Engagement" in technology. Two specific projects on these themes in relation with nanotechnology have been started by MEXT (Ministry of Education, Culture, Sports, Science and Technology) and CSTP (Coordination Program of Science and Technology) since 2006, and various workshops, conferences and dialogue events organised with stakeholders, including the public, within these initiatives. It's worth mentioning also a specific action (by the University of Tokyo and others) for the development of innovative technology assessment tools, including mechanism for public participation [14].

Most of the activities on responsible development in **China** refers to EHS study and standardization activities. However, social aspects are among the priorities of the Nanosafety Lab established by NCNST, and some open conferences on nanotechnologies have been held in China in the last years [14, 15].

In **Australia**, The Australian Office of Nanotechnology coordinates a specific "Public Awareness and Engagement Program" from 2008 to 2012, to enable an inform public debate on EHS, social, ethical and regulatory aspects of nanotechnology. [15]

The interest of social sciences on nanotech is also shown by the publication, in 2007, of a peer-reviewed journal dedicated to ELSI ("NanoEthics: Ethics for Technologies that Converge at the Nanoscale"). As is stated in its premises, the journal focus on ethical issues, and the discussion *"must be informed by, at least, the physical, biological and social sciences and the law* "[15].

[14] http://www.bioethics.gov/topics/nanotech_index.html

[15] Among the philosophical and scientific issues treated by the journal *"individual health, wellbeing and human enhancement, human integrity and autonomy, distribution of the*

In conclusion, in the debate on ELSI most of the attention is devoted to questions related to EHS implications of nanotechnology, generally considered as a priority by most of stakeholders (as reported also in other parts of this report), and *public perception and public engagement* issues.

In this context, the peculiarity of nanotechnologies make them an important case of the more general debate on the *"democratisation of governance of science" and "deliberative democracy" issues* [1, 3].

3.3.3. Public participation in the governance of nanotechnologies

A critical aspect of the management of risks and concerns of nanotechnology is the involvement of the public, intended both as specific stakeholders dealing or interested in nanotechnology and the broader public, acting as citizens and consumers. This task can be as critical to the development of nanotechnologies as the underlying technical, scientific and economic challenges, and is a key element to determine their level of acceptance within the society.

Public involvement, or participation, has a twofold purpose:

- Increase public awareness on a technology supporting the building of opinions and positions based more on facts than on speculative claims. Helping to distinguish between perceived and real risks;

- Increase the level of interface and confidence among those developing and regulating nanotechnology and the public (citizens and consumers using the technology). This is pivotal to help defining proper, acceptable, trade-offs of risks and benefits of nanotechnology.

In the words of the European Group on Ethics in Science and New Technologies (EGE): *"Public participation is of vital concern in democratic states.[…]This raises wider issues of trust and confidence building between the scientific community and the public, including the need to promote proper debate (in particular on uncertainties), and ultimately leads to issues of deliberative democracy, including questions about who draws the lines between what is allowed, acceptable, and what is not; and who overviews those who draw the lines."*

There are several factors that may shape public perceptions of nanotech risks, as information coming from the scientific community, media communication, books and narratives on or related to nanotechnology, opinions and attitudes on science and technology in general. Also background factors as the economical, political and regional contexts have obviously a very relevant role in the attitude and perspectives on a technology.

Quantitative public opinion survey on nanotechnology, both in USA and Europe, highlighted low levels of awareness for nanotechnologies and their uses [16,17]. Up to now public perception of nanotechnology seems in its formative stages, without relevant positive or negative bias within the public about it.

Results for more qualitative research studies, from focus group, seminars and workshops and other initiatives [11,16,17,18] provide some interesting elements about how and what influences public perception of nanotechnology. Attitude and opinion on nanotechnology depends not only from information and facts of technological developments, but also from social factors. In particular, people's view about who will be affected by risks and benefits of nanotechnology and the ability of regulation, regulatory authorities, and industry to manage risks and uncertainties associated with nanotechnology [3,16,17].

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costs and benefits, threats to culture and tradition and to political and economic stability. Additionally there are meta-issues including the neutrality or otherwise of technology, designing technology in a value-sensitive way, and the control of scientific research"

Building trust and confidence among all stakeholders, including the public, seems the key element of the debate on perception and acceptance of nanotechnology.

An open and transparent discussion and public involvement in policy making relating to science and technology is an acknowledged element to help achieving this objective.

In the recommendations for science policy of the NEG report, people's concerns and attitudes about nanotechnologies are synthesised as follow:

- *Social benefits of nanotechnologies: the public supports nanotechnologies that are linked to a wider social good.*
- *Uncertainty and regulation: the public is concerned about known and unknown risks associated with nanotechnologies, the ability of government and private sector to manage those risks, and about the social distribution of risks and benefits.*
- *Transparency, and public engagement: the public calls for more open decision-making about nanotechnologies, including opportunities for members of the public to input into nanotechnology policy and research.*

There are different kind of possible methods to promote interaction between institutions and the public. What is stressed by most of initiatives is that risk communication strategies should enable a two-way communication, giving the opportunity to the public to inform and shape the direction of research and development. This is what has been called early-stage public engagement or upstream public engagement [11, 19].

An open and transparent discussion should in particular make available to the public (elaboration from [19]):

- Informed opinions of scientific aspects of nanotechnology, including risks and benefits;
- clear and transparent description of the approach to regulation and funding, anticipating benefits, costs, risks and uncertainties and including information on who has the responsibility to regulate and support nanotechnology.

Fostering interaction and communication among the public and the scientific and decision-making community (including industry, academia and NGOs) is not an easy task. Several initiatives and instruments have been developed and tried in the last years, as consensus conferences, public opinion surveys, preparation of specific communication tools, citizens' jury, national debates, etc.

A description of these instruments is beyond the scope of this report, however very interesting analysis on these initiatives are available in the documentation of some projects, as the Nano-bio-raise project [16], the Nanotechnology Engagment Group [11], the report on the "Strategy for Communication Outreach in Nanotechnology"from the European Commission [9].

3.3.4. Ethical issues and socio-economical challenges

The debate on *ethical* aspects of nanotechnology has somehow evolved in the last years. The concept of "Molecular Manufacturing" of Eric Drexler (2004) and the promises of revolutionary improvements in computers, medicine, environment and arms has somehow focused the attention on radical applications of nanotechnology, as the idea of synthetic/natural self-replicating nanobiomachines. Science and social scientists, NGOs (as the ETC one in 2003, see paragraph 4.5.3.3), various media and some of the narrative on nanotechnology (as the book *Prey* from Michael Chricton) have long debated and emphasised these issues (with the predominance of the two "utopian" and "dystopian" views, as explained in detail in the 2003 and 2007 ESRC reports [1]).

This discussion has smoothed in the last years on the many different ethical and societal implications of more realistic short to medium term nanotechnology applications.

As mentioned above, the work of different Ethical Committees, and inputs from social science scholars have sustained a large debate, particularly regarding the different implication of nanomedicine development.

One of the most important ethical priorities underlined by these Committees and other sources is a proper management of the potential risks posed by nanomaterials, able to ensure safety for humans and the environment during the whole lifecycle of nanomaterials and nano-related products.

This includes supporting of EHS research, setting of proper control and regulation tools in relation with nanotechnology at any level, from research to commercialisation, and transparency regarding decisions and procedures adopted for the safety of materials and products and in the use of nanotechnology. Regarding this latter question, different sources emphasises the role that labelling could have in help all stakeholders, in particular workers and consumers, to make informed decisions regarding handling and use of nanomaterials and nano-related products. Its important to note that some standards organisations have started activities for the development of specifications and norms for this purpose (see paragraph 4.3).

Regulatory and management options proposed for nanotechnologies are discussed in the rest of the report, in particular paragraph 4.2.

The improvement of our ability to manipulate matter at the nanoscale and to interact with biological systems opens endless scenarios on applications exploring the interaction between man and machine and affecting the intrinsic nature of the human being. While most of them are hard to predict, there are some fields of applications were improvement that could be realised thanks to nanotechnologies are already clear.

Among them, the field of tissue engineering, regenerative medicine and pharmaceuticals (drug development and delivery), where nanotechnology will open novel possibilities to cure diseases, but at the same time it will enable various kind of non-therapeutical uses, as the improvement or amplification of performances of healthy individuals for military purposes or professional sports activities. These applications opens important ethical (and political) questions related to the concepts of human identity and human dignity.[16]

In the diagnostic field, novel tools (as DNA chips, implantable biosensors, etc) promise to enable the screening of physiological and biological information of individuals, mapping of genes and genetic susceptibilities and early diagnosis of diseases.

These applications will challenge the responsibility and autonomy of individuals, and opens questions related to the information and acquisition of consent ("informed consent") from individuals on their cure and on the use of data on their organism.

The treatment and handling of "sensible" data, as biological information of individuals, is a key point of the ethical debate on nanomedicine, but common also to other potential applications of nanotechnology in the security and military sectors (as miniaturised sensors and biosensors, traceability systems, etc..).

[16] *"The overarching anthropological questions have to do with our view of ourselves and, in this context, the extent to which this view will be affected by the applications of nanotechnologies in medicine. Nano-scale implants and devices may have an impact on autonomy, integrity, self identity and freedom." (EGE, pg.50 [2])*

The use of these data from third parties, as insurance companies, employers or any other subject that can take a commercial or social advantage from them, raises several questions about the right of individuals for confidentiality and privacy and the possible misuse of these data.

The importance and the possible approaches to these issues will strongly depends on whether and how envisaged applications (and also unexpected ones) will be concretely realised in the next future.

The current uncertainties in the development of nanotechnologies makes it difficult any attempt to define solutions for these problems. For example, the development of informed consent procedures for nanomedicine are challenged by the lack of knowledge on the properties and effects of novel materials and devices.

Many of these issues overlap with other technologies, as biotechnology, genomics and information and communication technologies, and thus fruitful inputs can be gained by the discussion and activities related to them. In particular, the existing international framework on ethics and human rights is a reference also for the development and application of nanotechnologies.

The legislative instruments in place in Europe, some of which legally binding other having only a moral authority, are clearly indicated by the European Group on Ethics in Science and New Technologies (EGE). These are:

- Council of Europe Convention for the protection of human rights and fundamental freedoms
- Council of Europe: Convention on human rights and biomedicine – known as the Bioethics Convention (Oviedo)
- EU Charter of Fundamental Rights.
- Unesco Declaration on the human genome and human rights
- Unesco Declaration on bioethics and human rights

These documents give internationally acknowledged principles, values and approaches for a development of science and technology respectful of human dignity and human rights.

In the word of EGE: *"These rights are rooted in the principle of human dignity and shed light on core European values, such as integrity, autonomy, privacy, equity, fairness, pluralism and solidarity."*

These documents have been the reference point for the preparation of Code of Conduct (CoC) for responsible nanosciences and nanotechnologies research of the European commission (see paragraph 4.4.1.1)

Other legislative instruments at international and national level can be considered in relation with the ethical issues outlined above, in particular EGE underlined the role of legislation covering criteria for conducting clinical trials and the various regulatory frameworks in place for data protection in relation with information technologies [17].

If the revolutionary promises of nanotechnologies will be realised, they will have important impacts on economy, trade, employment at regional/national or local level and broader ethical and political issues will certainly arise. Nanotechnologies will be used in many different industries (electronics, biotechnology, energy, materials, etc.) and very likely their economic and social impact will be different according to the dynamics in each of these sectors [13].

[17] At European level clinical trials for medicinal products are covered by a specific "EU Directive on Clinical Trials" and data protection is covered by the "Directive on the processing of personal data and the protection of privacy in the electronic communications sector" [2].

So far, the ethical debate on the socio-economical aspects of nanotechnology has been somehow anticipatory, being mostly dedicated to figure out what could be the most critical issues of nanotechnology development and to propose possible approaches to deal with them, instead of finding solutions and answers to problems (different from other ethical debates on most pressing issues, as for example cloning, where a "yes or no" is needed)[18].

Some of the aspects that have received most of the attention, have been, from the legal side, the management of Intellectual Property and, from the social side, the implications of nanotechnologies for the developing Countries.

The former aspect is related to the danger created by patenting of basic nanotechnologies materials and processes, "building blocks" of any other more complex nanotechnology product. This would introduce a clear obstacle to the development of nanotechnology, limiting the number of subject able to research and commercialise nanotechnology. Organisations or Countries (as developing Countries) not having adequate IP portfolio on nanotech will have to foresee costs of royalties or risks of expensive patent claims before engaging in nanotechnology research or commercialisation.

The latter aspect is related to the debate on the potential beneficial impact of nanotechnology applications for developing Countries versus the risk of a nanotechnology divide.

Crucial problems afflicting Developing Countries, such as, for example, the lack of drinking water or the scarcity of energy, can get relevant help by nanotechnology applications in the energy and the environment sectors. The role of nanotechnology can be so high that the UN have included them as on of the key technologies to reach the UN Millennium Goals [20].

On the other hand, a "nano-divide" may raise due to the lack in the Developing Countries of proper scientific infrastructures and human resources, difficulties in accessing scientific data and materials, limited financial and organisational resources. International cooperation and an effort aimed to make part of the developments of nanotechnologies these Countries, is advocated to avoid/limit this danger.

Another key issue interestingly underlined by some observers is that much of the economic development in nanotechnology will depend on the ability of the education system to train scientists to develop the technologies. [13].

In order to respond to ethical and socio-economical issues related to nanotechnologies, various observers have provided (or recalled) principles and recommendations that should be followed to ensure a responsible development of nanotechnologies, including values as dignity, liberty, individual integrity and respect, quality of life, respect for privacy, justice and equity, transparency, and democracy [19].

Some key recommendations have been highlighted by different sources. These ask for:

- Safety for human health and the environment
  (intensification of research, prevention and precaution, regulation)
- Research ethics
  (ethical review of research and respect of acknowledged values and principles)
- Public participation and involvement
- Responsibility of the scientific community
  (transparency and accountability of research activities in relation to society)
- Addressing of legal implications and socio-economic challenges

[18] The President's Council on Bioethics, USA – Nanotechnology issues (transcripts) http://www.bioethics.gov/transcripts/transcripttopic.html

(sustainable development, fairness and equal distribution of benefits related to nanotech development)

In order to help the achievement of these objectives, is underlined that a sustained effort is needed to implement and integrate ethics and ethical aspects both in research activities on nanotechnology and in the careers of researchers [6].

As reported in paragraph 7.1, various Countries and economic areas (such as Europe) have established strategies dedicated to the development of nanotechnologies. Some of them take into consideration also, at different level, the various ethical, legal and social implications of nanotechnology outlined above.

In particular, the Code of Conduct on nanotechnologies of the EC collects most of the concepts and values emerged in the last years from the debate on ethics of nanotechnologies and, very likely, is currently the most important reference on the principle that should underpin research activities, the interaction among stakeholders and in general the governance of the development of nanotechnologies (see paragraph 4.4.1.1).

3.4. Research Needs

Currently, a series of large national and international programmes are on their way to investigate on the risks of manufactured nanoparticles (see paragraph 3.4). Many countries and multi-national organisations have developed strategies to coordinate and direct the risk research efforts.
There are several projects concluded or underway dealing with EHS and ELSI. A selection of them is reported in Annex 7.2.

Coordinated, proactive research into the risks of emerging technology, particularly nanotechnology, is uncharted territory. Historically, the risks are assessed after technologies are deployed, when specific risks are documented in defined settings and use patterns [19]. Nevertheless, coordination and standardisation is crucial in this early phase of risk research, since up to now, a lot of research time and money is wasted because there are no accepted and harmonised testing guidelines, experimental procedures, taxonomy and common (digital) language, simulation, validated instruments and standardised test materials in nanotoxicology. This means that results often cannot be compared or reproduced, and therefore remain unreliable or produce contradictory results.

Scientific information sharing and patent pools is also relevant for the global frame because a well balanced approach between proprietary–versus open source information systems is key for the assessment of EHS issues.

Some coordination and standardisation tasks are currently processed by international organisations like OECD or ISO, but also by coordinated research programmes such as EU's 7th framework programme.

In particular, ISO (see chapter 4.4.2) has formed a group on nanotechnology, ISO 229, which has set up four working groups focused on four topics crucial for regulate nanotechnology:

- Terminology and Nomenclature;
- Measurements and Characterisation
- Health, Safety, and Environment;
- Materials Specification.

In an effort to strategically guide risk research, Maynard et al. proposed five "Grand Challenges" to stimulate risk research, which were intended to be implemented between 2006 and 2022 [NAT]. The five grand challenges were chosen to stimulate strategic research, as well as bring focus to a range of complex multidisciplinary issues. The authors proposed the:

- development of strategic research programmes to enable the relevant risk research (within 1 year)
- development of instruments to assess exposure to manufactured nanoparticles in air and water (within 3–10 years)
- development of robust systems for evaluating the health and environmental impact of engineered nanomaterials over their entire life (within the next 5 years)
- development and validation of methods to evaluate the toxicity of manufactured nanomaterials (within 5–15 years)
- development of models for predicting the potential impact of manufactured nanomaterials on the environment and human health (within 10 years).

[19] Towards Predicting Nano-Biointeractions: An International Assessment of Nanotechnology Environment, Health and Safety Research Needs. International Council on Nanotechnology (ICON), Number 4, (May 2008).

More recently, the International Council on Nanotechnology has held two workshops to identify the research need to be able to predict nano-bio-interactions of nanoparticles within ten years[18]. Over 50 experts from 13 countries compiled a list of tasks to be done in the short, mid and long term. The following paragraphs summarise aspects which are repeatedly mentioned as being important defining future risk research activities.

3.4.1. Metrology

Until today, it remains difficult to detect and quantify nanoparticles in occupational or natural environments. Existing methods and instruments are either not sensitive enough, or they are to expensive and not mobile for routine testing. Therefore, the development of validated methods and instruments (inexpensive and mobile) for real-time measurement and characterisation of particles in different relevant systems (environment, biological media, organisms, workplace) is the key issue. The ISO Working Group on Measurements and Characterisation should set the mark on this issue (see paragraph 4.3.4).

3.4.2. Methodology

There currently exists a battery of validated toxicity and ecotoxicity tests suitable for chemicals. Nevertheless, much work is required to validate and optimize these tests for the use with nanomaterials.

Researchers agree that key elements of a future nanoparticle toxicity screening strategy should include a detailed physicochemical characterization of the nanoparticles. Parameters including size, size distribution, shape, surface area, and volume to surface ratio, chemical composition (spatially averaged and spatially resolved), purity, crystallinity, magnetic, electronic, oxidative and catalytic properties, surface structure, surface modification, solubility, agglomeration state and shape, as well as porosity have been proposed to be included in a minimum set. Precisely characterized nanoparticles should be distributed to several well recognized academic and government laboratories for 'round-robin' specified studies using same standardized operational protocols (SOPs) for in vitro and in vivo investigations. This is currently being undertaken by a consortium of researchers under the International Alliance for NanoEHS Harmonization (IANH). The objective are:

- Agreement on a common language and reporting standards;
- Establishing a minimum set of physico-chemical properties for characterisation of nanoparticles;
- Selection and characterisation of a set of representative nanoparticles as reference materials (currently done by OECD);
- Evaluation of current toxicity test methods with respect to their applicability for nanotoxicity;
- Develop high-throughput screening methods for nanoparticles;
- Development of standardised test protocols (good practice);
- Develop short-term *in vitro* tests to predict toxicity from physico-chemical characteristics;
- Establish structure-activity-relationships (SAR) to predict toxicity;
- Development of models for the prediction of the distribution of nanoparticles in the environment and their concentrations in target organs;
- Check whether *in vivo* tests can be substituted by *in vitro* tests to reduce animal testing;
- Develop system analysis methods such as life cycle assessment or materials flow analysis;
- Agreement on appropriate epidemiological methods and prospective studies of cohorts of exposed subjects;

3.4.3. (Human) Health

Toxicity studies deal with the effects of nanoparticles in living systems. Although there is an extensive database on the effects of microparticles and combustion generated nanoparticles in humans, the knowledge about health effects of manufactured nanoparticles is still in its infancy.

Many factors play a role determining the finally observable effects in the body: uptake, distribution, metabolism, clearance, and many more. However, nanoparticles present new challenges to toxicologists, because they are able to overcome barriers which bigger particles were not known to. This allows certain particles to be distributed in the whole body, reach distant target organs and cause unexpected effects. Specific research needs to better understand these risks are briefly summarised below.

- Determination of the relevant routes of exposure (pulmonal, dermal, oral, gastro-intestinal) and expected concentrations in the target tissues / organs;
- Identification of distribution, translocation, accumulation, metabolism and excretion of nanoparticles in the body (toxicokinetic profiles);
- Evaluation of the of nanoparticles on the bone marrow, spleen, liver, heart, brain, foetus, placenta, cardio-vascular system, function of immunologic homeostasis;
- Establish validated correlations between physico-chemical properties (including different coatings) of nanoparticles and their potential bio-interactions;
- Understand the mechanisms of toxicity including the ability to induce inflammation, fibrosis, and genotoxicity in all target organs;
- Development of an understanding of nanoparticle interaction with cell-signalling pathways;
- Evaluation of the capability of nanoparticles to induce toxicity via mechanisms identified for fibre toxicity, namely length, bio persistence and reactivity;
- Identification of other primary effects apart from oxidative stress (such as adverse effects on the immune system, lung disease, inflammation);
- A deeper understanding of the difference between “nano” and “bulk”, including quantum, surface and size effects, also taking into account the consequences of agglomeration and de-agglomeration of the particles;
- Effects of potential co-exposures;

3.4.4. Environment

Much work is particularly required to close the gaps regarding the current understanding of nanomaterial behaviour in the environment. Only very few environmentally relevant organisms have been investigated so far, and the behaviour of nanoparticles in natural systems is still largely unknown. Assessing the risks of nanoparticles in the environment requires an understanding of their mobility, reactivity, ecotoxicity and persistency.

- Identification of important emission sources;
- Assess potential exposure levels and pathways of uptake;
- Information on the distribution, (bio)accumulation and persistence of nanoparticles in the environment and in organisms;
- Studies on the agglomeration behaviour of nanoparticles in air, water, soil and biota;
- Further investigations on the behaviour of nanomaterials in sewage plants;
- Studies on the bioavailability of nanoparticles in environmental organisms;
- Understand the (biotic / abiotic) conversion of nanomaterials (e.g. modification of the coating) in the environment;
- Studies on possible secondary effects of nanoparticles (e.g. bioavailability of adsorbed harmful substances);
- Explore the effects of *in vivo* exposures of manufactured nanoparticles combined with, for example, metals and organics;
- Consider ecotoxicity during full life-cycle, i.e. production, use and fate;

3.4.5. Workplace Health and Safety

Although workplace health and safety also relies on many of the tasks listed under "human health", it includes some additional aspects with regard to the daily handling of nanoparticles in production and the potential long-term effects upon prolonged low-concentration exposure.

- Gather more information on the use of nanoparticles in companies and at the workplace;
- Develop basic data on the fire and explosion hazards as well as the catalytic activity of nanoparticles;
- Identify workplace expositions for different forms of use, particle types and protective measures, also considering malfunctions and accidents;
- Development of adapted dissemination and exposition models for the simulation and analysis of workplace expositions;
- Research, development, adaptation and improvement of technical and personal protection measures;
- Launch of epidemiological studies on the health of workers at workplaces with varying levels of exposition;

3.4.6. Technology Assessment (TA) and Communication

There is a high demand for scientific TA studies that independently assess the development of nanotechnologies, e.g. in the area of "nanotechnology and food", "nanotechnology in medicine (diagnosis, therapy, implants)" and "nanotechnology in the area of information and data storage". The objective of these studies must be to point at possible economic, social, legal and ethical effects at an early stage, and to give recommendations in order to allow for the potentials of technological development to be used and the risks for society and the environment to be minimized.
Future discussions will increasingly have to deal with the effects of the convergence of different areas of science accelerated by the development of nanotechnology, e.g. in the case of nano-biotechnology. Such nanotechnologies of the so-called second generation are concerned with the development of autonomous active molecular nanosystems.

- Execution of studies on risk perception and risk acceptance of manufactured nanoparticles;
- Integration of all relevant stakeholders (research, development, industry, trade, authorities, politics and consumers) in the debate on the development of nanotechnologies;
- Development and testing of integrated risk management procedures;

4. NANOTECHNOLOGIES REGULATORY APPROACHES

4.1. Shortcoming of Nanotechnology Governance

The relevance of nanotechnology has been outlined in the previous paragraph together with the debate about the issues that must be considered to foster specific actions to achieve their benefits avoiding/limiting the potential risks associated with them.

The task is complex since, due to the specific nature of nanotechnology, it is not simply a matter of updating existing regulations, but, at least in the opinion of some stakeholders, can imply an in-depth revision of them [1,2].

Another weak aspect of the regulatory frame of nanotechnologies is the lack of adequate tools for early warning, market control and, if necessary, withdrawl of nano-related procts, as well as the difficulty of enabling meanigfull "labelling" as part the market surveillance and consumers protection.

The majority of issues and challenges at stake for regulating nanotechnology have been described already. The purpose of this paragraph is to give some further element for the following paragraphs, recalling challenges and shortcoming, which regulatory options have been considered at European and International level, which authorities are involved, which groups in the society are discussing these themes and their position.

4.1.1. Regulation vs. scientific knowledge

As with any new technology, one of the challenges for regulators arises from the need of ensuring the public safety when new products and materials are introduced into the market. A necessary background to any possible regulatory or risk management option for nanotechnology is thus given by the scientific knowledge about the possible adverse effect of this technology. Regulation should be designed to address these risks, in an attempt to prevent or minimise them, while assuring the exploitation of the opportunities and the benefit of this technology.

Frameworks of scientific risk assessment and risk management are well developed. They are mainly based on three steps that help to identify and prioritise most relevant issues, understand the knowledge, or lack of knowledge, in the field, implement actions to prevent or minimise risks. [3,4,5,6]. In particular:

- Cause of hazard identification (identification of materials or processes source of concerns)
- Research to assess the risks (hazard identification, hazard characterization, assessment of human and environmental exposure)
- Identification of appropriate risk management strategies (issuing of guidance and rules, evaluation and development of regulatory options, risk communication, etc..).

In the last years, plenty of articles and reviews on nanotechnology have underlined how uncertainty in scientific knowledge challenges the application to nanomaterials and nano-related products of conventional risk assessment frameworks. One of the most authoritative document on the matter is the report "Nanoscience and Nanotechnologies: opportunities and uncertainties", published in 2004 by the Royal Society [3].

The main issues that hamper the adoption of existing regulatory frameworks for nanotechnology related products or the development of new, ad hoc, reliable ones, are the following [38]:

Diversity of materials and applications

Many of the existing materials or chemicals may be found as nanoform (with specific properties compared to their macro counterpart), and novel nanomaterials are being steadily developed (e.g. CNT, fullerenes, etc.). This means to deal with a huge number of substances, having completely different behaviours and countless applications.

Moreover, the risk associated with these diverse materials and products/devices can depend and change as a consequence of their nature, their use and, eventually, their disposal. Risks assessment, in short, must consider the entire life cycle of a product as well as the potential risks associated with accidental releases. Existing regulations, for materials as well for applications, have difficulty to cope with this diversity of materials and applications.

Lack of data characterizing nanomaterials

A thorough understanding of physical-chemical properties (such as size, shape, composition, reactivity, surface area and/or chemistry) and their influence in regulating the biological response of nanomaterials is still lacking, but, on the other hand, these data are fundamental for evaluating, modelling and predicting their ecological and toxicological behaviour, necessary for developing risk management and regulatory options.

Lack of standardization in nomenclature, metrics, and materials

The unique nature of nanotechnology challenges the establishing of standard procedures to describe, specify and measure nanotechnology – related materials and products. There is, currently, no consensus on terminology/definitions, on protocols for toxicity testing or for evaluating the environmental impact, on reference materials and standards or instruments for measurements and characterisation. The current methodologies are considered not adequate to deal with nano - products and without an international agreement on the above matters the definition and implementation of appropriate legislation will not be possible.

4.1.2. Dealing with uncertainty: different stakeholders views

Even though the whole community surrounding nanotechnology is engaged in an effort to narrow scientific gaps and help the development of a suitable framework to face the potential risks associated with it, there is still, as said above, no definitive judgment on the matter.

Nevertheless, the number of nano–products offered to the public is increasing and risk management and regulatory systems have to be implemented to deal with this uncertainty. A broad debate has taken place in the past years, and a wide spectrum of stakeholders' positions and actions has emerged.

A range of policy options for the governance of nanotechnology were highlighted during a workshop organised by the European Commission in 2004, entitled "Mapping out Nano Risks", which pointed out the most relevant positions of the on-going debate which involves regulatory bodies and policy makers, industry, researchers and the civil society. These are, to use the same wording [7]:

- *Adoption of a "laisser-faire" attitude;*
- *Decreeing a moratorium on nanotechnologies R&D and/or commercialization;*
- *Relying on voluntary measures;*
- *Launching a comprehensive, in-depth regulatory process specific to nanotechnologies*
- *Implementation of an incremental process using existing legislative structures to the maximum, revisiting them, and, when appropriate, amending them.*

As can be seen, views vary substantially, though their weight has also evolved and though there is still somebody asking for a moratorium, the tendency is for the adoption of existing regulation, if the case adapted to nanotechnology and strengthen by a precautionary approach.

4.1.3. Filling the gaps: government and policy makers actions

The idea of an incremental approach, as proposed by the EC [7], includes various actions and initiatives aiming to find proper solutions to regulate nanotechnology. Some of the governments and policy makers most involved in nanotechnology are pursuing, at least partially, this kind of approach. This implies:

- *Support of research initiatives on EHS issues*
  A major source of debate is the alleged limited funding from government for this research. Nevertheless an increase in the number of publications on these issues is reported. [8].

- *Promotion of risk assessment during all products life cycle*
  Examples are the initiatives activated since 2004 by the working groups within various EC Committees[20], OECD, ISO, BAUA (Federal Ministry of Education and Research in Germany), NIOSH (National Institute for Occupational Safety and Health) in the USA.

- *Definition and implementation of appropriate regulatory intervention*
  Since 2005 regulatory agencies and government department, in U.S.A, Germany, UK, Switzerland, Canada, Australia, from the European Commission and others countries have been active in this field.
  Till now, no regulations dedicated to nanomaterials have yet been set up [2,8,9], however, specific provisions for these materials, so far mainly regarding industrial chemicals, are taken into consideration within different regulatory systems, as in the case of REACH in Europe or EPA-TSCA statute in the USA.

- *Setting-up of a dialogue among all stakeholders*
  Initiatives by public authorities and different international bodies have been activated to disseminate information and promote a dialogue among stakeholders.

- *International coordination*
  Within recognised international bodies, working group on nanotechnology have been set up to coordinate efforts among subject involved in regulation of nanotechnology at different levels. Among them the ISO TC 229 Committee on Nanotechnology, the two OECD Working Group on nanotechnology (WPMN, WPN), the International Dialogue on Responsible Research and Development of Nanotechnology [21].

These actions are on one side trying to respond to the most urgent needs for regulating nanotechnology and, on the other side, are helping to increase the "knowledge base" on regulatory issues, sharing and collecting information among the nanotechnology players.

In this climate of uncertainty, some regulators (in particular the EC), have, as said, clearly invoked the adoption of a precautionary approach, in order to carefully evaluate and balance risks and benefits (see next paragraph). These initiatives are generally welcomed, nevertheless civil society organisations are pressing for an even larger support of EHS research, improvement or changes of regulation, strict premarket approval of nano-related products based on relevant scientific data.

[20] In particular the Scientific Committee On Emerging And Newly Identified Health Risks (SCHENIR) and the Scientific Committee on Consumer Product (SCCP)

[21] http://cordis.europa.eu/nanotechnology/src/intldialogue.htm

4.2. Existing Regulatory Frameworks Including Nanomaterials

As illustrated in the previous chapter, policy makers are challenged by nanotechnology and governments, regulatory and standards setting agencies/organizations have started to develop technical background to cope with regulatory issues related to nanotechnology.

Considering, as said above, that nano-related products are already hitting the market, and specific laws and regulations for them do not exist yet, the regulations available for conventional materials and products represent, at least in the near term, a necessary option [1,3].

The attention is essentially focused on manufactured nanoscale materials, seen along their entire life-cycle.

As illustrated in Figure 1, regulation of manufactured nanoscale materials is a multi faced affair which implies a wide range of provisions, depending on the application and the life cycle stage, made more complex by their variety and ample spectrum of applications.

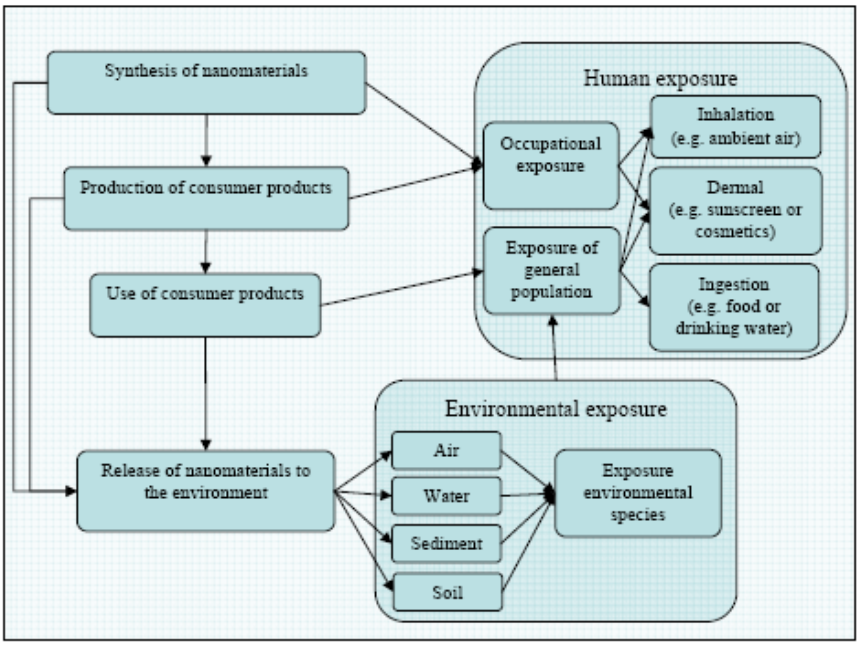

Figure 1: Potential exposure to nanomaterials during the different life cycle phases (figure from reference [10])

In this context there exist different levels of attention and the assessment of potential risks associated with nanotechnology applications has become a priority mainly in relation to [11]:

- Chemicals and materials
- Cosmetics
- Foods
- Pharmaceuticals and medical devices
- Occupational safety and environmental protection

Below are briefly illustrated initiatives and policies on nanotechnology regulation from government and regulatory agencies.
In the two cases of European Union and USA detailed information on issues and gaps arising from the application of existing legislation to nanotechnology have been reported in the document.

These two cases have been chosen considering that their activities are usually of reference at international level and also for the easier availability of specific information and reviews.

4.2.1. European Union

With the publication in 2005 of the "Action Plan for Nanotechnologies 2005-2009" [12], the EC has highlighted its commitment toward a responsible development of nanotechnology. The importance of assuring an high level of public health, safety, environmental and consumer protection, integration of the societal dimension, development of standards and norms, definition of appropriate regulatory approaches, application of "code of good conduct", and international cooperation, were clearly mentioned in the Action Plan.

Following this document several initiatives have been promoted and put in place by the EC to cope with the above issues. In 2008, the EC has opened a website collecting all data and activities related to nanotechnology governance, which included the key documents related to policies in the publication "EU Policy for Nanosciences and Nanotechnologies"[12].

In the first implementation report of the Action Plan, published in September 2007, three different actions are envisaged to respond to the current uncertainty in the area of health, safety and the environment. These are:

- *Improving the knowledge basis, via research, scientific committees, information sharing and cooperation, including at international level.*
- *Involving the public through stakeholder dialogues, voluntary initiatives etc.*
- *Examining whether current legislative frameworks offer sufficient protection, or whether modifications or new legislation is needed.*

A specific work has been carried out work by different EC Scientific Committees to review and identify gaps of risk assessment methodologies in relation with nanomaterials and nano-related products [13,14] and to review guidelines for the testing and safety issues related to the use of nanomaterials in cosmetic products [15]. Several issues regarding health and safety and regulatory challenges in the application of nanotechnology to medicine have been analysed in one report from EMEA in June 2006 [16] and one from EGE in January 2007 [17].

EC strongly endorses international collaboration on these themes. By supporting specific activities in FP7, with the presence in international bodies, such as Nanotechology Working Groups within CEN, ISO, OECD, participating in initiatives aimed to foster exchange of information such as the International Dialogue on Responsible Research and Development of Nanotechnology.

After a long preparatory work, including specific public consultation, at the beginning of 2008 the European Commission has forwarded to all Member States a recommendation for the adoption of a "Code of Conduct on for the responsible development of nanotechnologies".

It's interesting to report the opinion of the EC on the adoption of the Precautionary Principle versus the possibility of a moratorium on nanotechnology [12, pg. 20]:

> *"An open, traceable and verifiable development of nanotechnology, according to democratic principles, is indispensable. Despite some calls for a moratorium on nanotechnology research, the Commission is convinced that this would be severely counter-productive. Apart from denying society the possible benefits, it may lead to the constitution of "technological paradises", i.e. where research is carried out in zones without regulatory frameworks and is open to possible misuse. Our consequent inability to follow developments and intervene under such circumstances could lead to even worse consequences. The Precautionary Principle, as used up to now, could be applied in the event that realistic and serious risks are identified."*

To understand to which extent current legislation is applicable to nanomaterials, a review of current EU actions undertaken to this end by various European Agencies and Committee, has been

made by the EC. The findings have been published in June 2008 [11], and are summarised in the following.

4.2.1.1. European Chemicals Agency (ECHA): Chemicals

The application of REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) to nanomaterials is the source of an ample debate among stakeholders, and within the European Commission a specific activity has been dedicated to this theme [11]. At national level, reports to assess adequacy of REACH and national legislation to deal with nanomaterials were commissioned by government departments of the UK [18] and Germany [19].

REACH is entered into force in 2007 but an eleven years transitional regime is foreseen to register the huge amount of substances that will be regulated by it. During this period, specific rules for legislation implementation, also regarding nanomaterials, may be adapted and improved.

A key element is that under REACH, the burden of proof on the safety of a substance is not on the regulator (as it was in previous EC regulations) but on manufacturers, importers and producers and that REACH provisions are underpinned by the Precautionary Principle.

REACH seems to provide a powerful framework to regulate engineered nanomaterials, even though current scientific gaps raise many problems concerning its current applicability to products using nanotechnology. The way it will be put in action from ECHA and National authorities, through specific provisions and guidance and improved risk assessment methodology, will determine its effectiveness toward nanotechnology. Above all, until mass/volume threshold limits will be revised, nanomaterials are likely to fall, for most of the applications, outside the scope of REACH.

An interesting modification of REACH, pressed by concerns related to nanomaterials, regards carbon nanotubes. In REACH CNT have the same classification as carbon and graphite, and these materials were exempted by REACH registration. After a controversial debate between EC and Member States, in June 2008, the exemption for all forms of carbon and graphite was deleted by REACH. Companies selling carbon and graphite (and among them CNT) will be required to submit full health and safety data for registration under REACH[22].

Open issues and gaps in relation with nanotechnology

Different issues have been highlighted by the EC and other stakeholders about the applicability of REACH to nanomaterials [11,18,19,20,21,22,23]. In particular:

- The REACH of chemical substances, besides chemical composition, takes into accounts all physical states, crystal structures, and dimensions of particles. Therefore it can be applied also to nanomaterials. However, the threshold limits in terms of mass/volume metrics, could not be adequate for nanomaterials (as clearly expressed by SCHENIR Committee Opinions [13], [14]). The 1tonn/year registration limit is likely to exclude most of existing nana-related products and materials.

- Approval procedures and requirements depend from substance registration. For nanomaterials classified as "new substances" (for example fullerene) a registration is needed, and thus the strict "no data, no market rule" of REACH apply. When nonmaterial refers to an existing substances already registered (for example Silver) and a new use is envisaged, a registration update is needed as required by REACH[23]. Thus REACH should be

[22] http://chemicalwatch.com/788

[23] *"When an existing chemical substance, already placed on the market as bulk substance, is introduced on the market in a nanomaterial form (nanoform), the registration dossier will have to be updated to include specific properties of the nanoform of that substance. The additional information, including different classification and labelling of the nanoform and additional risk management measures, will need to be included in the registration dossier.*

able to regulate also this kind of substance. In both cases current risk assessment procedure could not be appropriate (as clearly expressed by SCHENIR Committee Opinions [13], [14]).

- Basing on current scientific uncertainties on nanomaterials, ECHA may decide to include some of them (on a case-by case basis) in the list of substances subject to authorisation (substances "of high concern"). In this case a very strict chemical safety assessment could be required and specific restriction imposed. This procedure could be critical, considering that methodologies for chemical safety assessment may not be appropriate for assessing risks associated with nano-substances.

- Uncertainties in determining the risk of a nanomaterials may lead to the application of the Precautionary Principle, but depending on how it is applied from ECHA, provisions for specific nanomaterials could vary very much [20].

4.2.1.2. European Medicines Agency (EMEA): Medical products and Medical devices

(Medicinal products and medical devices fall under different regulations, but some issues related to nanotechnology are common)

Specific initiatives by EMEA and some EC Committee have been set up to deepen the understanding of regulatory issues in relation to nanotechnology-related medical products and medical devices. In particular:

- The EMEA Committee for Medicinal Products for Human Use (CMPH) has published a reflection paper on nanotechnology-based medicinal products for human use [16],

- EMEA has established a specific "nano-group" within the Innovation Task Force (ITF) [24]. Its mission is the coordination EMEA scientific and regulatory competencies and to provide a forum for early dialogue with applicants regarding emerging technologies (including nanotechnologies)

- The ethical aspects of nanomedicine have been discussed by the "European Group on Ethics in Science and New Technologies (EGE)". A document on the matter has been published on January 2007[17].

- The Medical Devices Experts Group has set up a working group on "New and Emerging Technologies in Medical Devices (N&ET Working Group), with nanotechnology as a priority. It has issued a specific report on nanotechnology in the medical sector on July 2007 [24].

In general, these documents consider the methodologies used to evaluate toxicity in the present authorization procedures of **medicinal products** adequate also for nanotechnology. There is a similar opinion also for the extensive post marketing surveillance foreseen by the current legislation.

Various medicinal products containing nanoparticles have been authorized by EMEA. The Agency reported that in these cases detailed and clearly understood manufacturing processes and techniques were used, with no need of any unconventional testing procedure [23].

The risk management measures and operational conditions will have to be communicated to the supply chain." [11, pg 4]

[24] http://www.emea.europa.eu/htms/human/raguidelines/itf.htm

Up to know, no specific rules have been put in place for risks related with the use of nanomaterials or nanotechnology in medicine (i.e. nanomedicine). However, in the view of the EMEA-ITF[25]:

"Specific guidance on quality, toxicology, clinical development and monitoring aspects may be developed in the future, once sufficient scientific experience has been gained for specifically identified sub-technologies within the field of nanomedicines".

For medical devices manufactures are obliged to carry out an assessment of the risks as defined in the Medical Devices Directive [11]. Risk assessment must be based on "the generally acknowledged state of the art", in this way the Directives:

"Ensure that the manufacturer must take into account not only risks of established technology, but also those associated with any new and emerging technologies, such as nanotechnology".

In the view of the EC, the Medical Devices Directive *"allows, in principle, risks associated with nanomaterials to be covered"*, even though the development of specific guidance or standards is envisaged.

Open issues and gaps in relation with nanotechnology

- According to the opinion of CHMP and N&ET Working Group, novel nanomedical products, combining biological, biomedical, and pharmaceutical devices, diagnostic and therapeutics functions, challenge the current criteria of classification between medicinal product and medical devices and, probably, also among the different categories of medical devices.

- In particular, the N&ET Working Group proposed a tentative classification rule (with a 3/5 year review) for free nanoparticles in medical devices, based on the principle that *"All devices incorporating or consisting of particles, components or devices at the nanoscale are in Class III unless they are encapsulated or bound in such a manner that they cannot be released to the patient's organs, tissues, cells or molecules".*

- The N&ET Working Group recommended the development of new standards regarding the biological evaluation of nanoparticles used in medical devices, development of dedicated guidelines on potential novel risks from nanomaterials, in particular for free nanoparticles, improvement of post-marketing surveillance systems, collection of information, also through Voluntary Reporting Scheme.

4.2.1.3. European Food Safety Authority (EFSA): Food and Feed products

Following a specific request from the EC, the agency has set up in November 2007 an expert working group, involving people from national food safety authorities, to prepare a first scientific opinion on the potential risks related to the application of nanotechnology in food and feed safety and the environment. A draft of this report has been published and is currently (November 2008) open for consultation [26].

The opinion objectives are to highlight the need for specific risk assessment approaches for nanotechnology, and to help clarifying issues related to authorisation procedures of products containing nanomaterials, presence of nanoparticles as contaminants in food and feed, changes in nutritional value or bioavailability due to the application of nanotechnologies in food production.

Within this activity, EFSA has launched a specific call to "third parties" (closed in March 2008) for Scientific Data on Applications of Nanotechnology and Nanomaterials used in Foods and Feeds.

[25] http://www.emea.europa.eu/htms/human/mes/emergingtechnologies.htm

[26] http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902132298.htm

Open issues and gaps in relation with nanotechnology
- Regarding foods and feeds law in general, it is opinion of the EC and EFSA that the risk assessment procedures need to be adapted to take into account specific risk arising from the use of nanotechnologies.

- In case of products included in their bulk form in lists of authorised substances, the critical point is to recognise whether substances produced in "nano" form, need to undergo a novel risk assessment and authorisation procedure or not.

Concerns have been raised in particular regarding the authorisation of additives realised by encapsulation or nanosizing of existing food additives to increase bioavailability [11,25]

4.2.1.4. Other EU Agencies/ Directives

Apart from the regulations described above, the European Commission examined also various other legislations considered relevant for the effects on health, safety and environment of nanomaterials. In particular:

- Health and safety of workers,
- Product requirements for health and safety of workers, consumers and protection of the environment:
    - Groups of products: plant protection products, biocides, new approach legislation, cosmetics, aerosol dispensers, medicinal products and cars;
    - Food legislation: general food law, novel food, food contact materials, food additives, food supplements, feed legislation;
- General Product Safety Directive on consumer products not covered by specific regulation
- Environment: Directives on Integrated Pollution Prevention and Control (IPPC), major accidents (Seveso II Directive), water, waste, air quality, soil protection and environmental liability.

Even though these directives do not explicit mention nanomaterials and nanotechnologies, they define a legislative framework that applies also in case of presence of nanomaterials, and thus they are considered to cover in principle the potential health, safety and environmental risks potentially associated with nanomaterials. They include, at least in their scope, nanomaterials and nano-related products.

In the view of the EC, the question is more on improving the implementation of current legislation, than on the legislation itself.

In light of the currents knowledge gaps on characterisation of nanomaterials, their hazards, exposure levels the EC and EU regulatory agencies intend to review the different test and risk assessment methods that serve as a basis for implementing legislation, administrative decisions and manufacturer's and employer's obligations.

In particular, more research on nanomaterials is recommended in the following areas:

- Development of reliable measurement methods, reference materials and materials characterisation;
- Review and development of test methods and reference materials referring to human health, safety and the environment;
- Development of data of exposure throughout the life-cycle of nanomaterials,
- Review of existing risk assessment methods;
- Risk management for workers' protection purposes;

- Foster existing networking and establish new infrastructures to examine health, safety and environmental aspects of nanomaterials.

There is a general agreement at international level on these areas. The work undergone by standardisation bodies (as ISO TC 229) in the field of nanotechnology, the programme within the OECD WPMN and strategic plans on EHS issues of different authorities, as in USA, UK, Germany, Switzerland, are all focused on these topics.

Meanwhile, in the EC opinion, authorities and agencies in charge of implementing legislation should continue to carefully monitor the market, and use Community market intervention mechanisms in case risks are identified for products already on the market.

As for labelling of products, the Commission does not exclude the possibility "that a need would be identified for specific labelling requirements" for nanomaterials. Until then nanomaterials must comply with the existing EU law on the labelling of products, warnings and other information for consumers on the properties of products.

Currently the Committee on Nanotechnology of the British Standard Institute (BSI/NT/1) has issued Publicly Available Specification and ISO TC 229 is planning to develop standards regarding labelling of nanomaterials (see paragraph 4.3.3).

4.2.2. France

In 2005, the French Ministry of Industry made a survey on nanomaterials with respect to a sustainable development perspective. To deal with the issues related to materials, processes and occupational safety of nanomaterials a dedicated group has been established within the French association, called ECRIN[27].

Subject from both research institution and industries participates in ECRIN, to exchange data and information related to research, development and manufacturing in the nanotechnology fields.

Other French Ministries, in charge of i.e. health, labour, pollution and prevention of risks, require stakeholders to examine the health and environmental risks that nanomaterials and nanotechnologies may pose on a short-, medium – and long-term basis [32].

Recommendations have been issued by the Comité De La Prévention Et De La Précaution (CPP) and the French Agency for Environmental and Occupational Health Safety (AFSSET) regarding the need for anticipatory and precautionary measures to be taken in the workplace, for instance, and to comply with the new European regulation REACH.

Two reports were published by these agencies:

- " Nanotechnologies, Nanoparticules: Quels Dangers, Quels Risques ? " - Ministère De L'écologie Et Du Développement Durable, Comité De La Prévention Et De La Précaution, May 2006
- "Nanomaterials : Effects on the Environment and Human Health" - French Agency for Environmental and Occupational Health Safety (AFSSET), July 2006.

In the AFFSET report, the Agency recommends:

- Increase of research activities on EHS issues
- Improve standardisation and regulation
- Coordination and harmonisation of studies on EHS and regulation of nanomaterials at international level.

[27] http://www.ecrin.asso.fr/nanomateriaux

- Take into account the specificity of nanomaterials in REACH regulations
- Develop tools enabling the definition of manufacturers' responsibilities and independent reflection on the timeliness of procedures ensuring traceability of manufactured nanomaterials.
- Study the consequences of trade secrets on the assessment o environmental and health risks of manufactured nanomaterials.
- Create a publicly accessible international register of nanomaterials, already or soon to be marketed, and of products likely to contain them

Two ongoing EC funded projects are coordinated in France: NANOSAFE 2 by CEA (Atomic Energy Commission) which is designed to develop technological solutions to the problems of nanomaterials safety, and NANO-STRAND by LNE (National Metrology and Testing Laboratory) to roadmap the European standardisation needs and pre-normative research items for nanotechnologies.

France participates into the ISO/TC 229, Nanotechnologies, and CENT/TC 352, Nanotechnologies. A technical committee, AFNOR TX X457, Nanotechnologies, mirroring the above committee has been also set up. France is involved into the OECD initiatives on nanotechnologies.

The Agencies currently collecting information on implication of nanomaterials and nanorelated products are AFFSET, regarding risks of workers, the French Food Safety Agency (AFSSA), monitoring food and drinking water, the French Health Products Safety Agency (AFSSAPS), monitoring drugs, medical devices and cosmetics [9].

4.2.3. Germany

The importance of a responsible development of nanotechnology is explicitly mentioned in the German Action Plan (discussed in paragraph 4.1), and includes specific actions as:

- Evaluation of the effects on health and environmental
- Adoption of a precautionary strategy on regulatory issues
- Establishment of a dialogue with stakeholders

The BMBF (Federal Ministry of Education and Research) lead since 2006 the Nanocare cluster project on health aspects of synthetic nanomaterials, to increase the knowledge on risk characterization and risk management of nanomaterials. This project has been included in the German research strategy on "Health and environmental risks of nanomaterials", initiated and coordinated by BAuA (Federal Institute for Occupational Safety and Health), UBA (Federal Environment Agency), BfR (Federal Institute for Risk Assessment) and finalised in a report published in December 2007 [30].

In this report the following strategic aims are indicated:

- Risk-oriented approach
- Comprehensive risk characterizations and risk assessments
- Integration into the statutory and sub-statutory regulatory framework
- Research that is application-oriented and relevant from the regulatory viewpoint
- Assessment of the novelty of nanomaterials
- International cooperation and coordination
- Sustainability and the precautionary principle
- More efficient structures for a targeted promotion of research

The strategy defines also a specific set of priorities on research on EHS issues, mainly regarding characterization of nanomaterials and their toxicological and ecotoxicological behaviour and risk management.

At international level German Federal Authorities participate in the work performed by OECD - WPMN and the German standard organisation (DIN) participated in the work of ISO on nanotechnology.

The Federal Institute for Occupational Safety and Health and the German Chemical Industry Association (VCI), made in 2006 a survey in the chemical industry on occupational health and safety in the handling and use of nanomaterials. This has been the starting point for the publication in 2007 of the document "Guidance for Handling and Use of Nanomaterials at the Workplace" [31].

A dialogue among stakeholders has been fostered by the German Government through various activities. The most recent is the "Nano-Dialog 2006 – 2008" an initiative coordinated by the Federal Environment Ministry (BMU), through a specific NanoCommission, aiming to provide a platform to discuss among different stakeholders (policy makers, researcher, industry, CSOs) advantages and disadvantages of nanomaterials for sustainable development. Three working groups have been established:

- Opportunities for the environment and health;
- Risks and safety research;
- Guidance document for responsible handing of nanomaterials.

Various events to present results of the platform are foreseen in 2008[28].

Considering nanotechnology regulation, the Federal Environmental Agency (UBA) has released in 2007 an expert report [19] which analysed the current EU and German regulatory framework in relation with nanotechnology. Gaps in regulation that exist at European and national level in connection with "nanotechnologies" were identified and possible regulatory approaches indicated. The analysis of the different regulatory areas (chemicals, worker safety, products, environmental protection) has made clear that, with regard to the specific properties of nanomaterials, gaps exist at many points in the sectoral legislation. The findings are essentially similar to those of other reviews on the matter (report of EC and UK) and mainly refer to knowledge gaps that hinder the application of existing regulations.

As stated above, the German strategy underlines the importance of improving the knowledge base on EHS issues, and uses a precautionary approach on nanoregulation. The inclusion of nanomaterials into the existing regulatory framework is envisaged, without developing specific legislation but improving, if needed, existing ones.

The responsibility to implement the research strategy, also from a regulatory point of view, mainly lies with Federal Ministry of Education and Research (BMBF), Federal Ministry for Labour and Social Affairs (BMAS), the Federal Environment Ministry (BMU) and the Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) and the corresponding institutions at European level

4.2.4. Italy

The activity in nanotechnologies is in Italy quite intense, and it refers to both public research institutions and private enterprises.

A specific national initiative dedicated to this sector doesn't yet exist, nevertheless various initiatives and projects are supported by the Italian Government (within the National Research Program, the university funding program PRIN and other instruments) to promote the development of nanoscience and nanotechnologies.

[28] http://www.bmu.de/english/nanotechnology/nanodialog/doc/40549.php

A certain (small) amount of the funding is devoted also to research projects to investigate EHS issues associated with nanotechnologies.

The activity involves research centres and, at institutional level, the Ministry of Health, governmental agencies such as ISPESL (National Institute of Occupational Prevention and Safety), ISS (National Institute of Health), INAIL (Italian Workers' Compensation Authority[29]). The Bioethic Committee of the *"Presidenza del Consiglio dei Ministri"* has established a specific Commission to deepen question related to ELSI (a report was published in June 2006 [56])

In particular, ISPESL has established in November 2008 a Working Group dedicated to Safety of Nanomaterials at the Workplace (WG "Nanomaterials"), with the following priorities:

- Strengthen coordination and collaboration on Occupational Health and Safety research on nanomaterials;
- Develop a multidisciplinary approach to risk assessment through the support of collaborative research activities;
- Identify appropriate tools to foster communication and knowledge sharing about safety of nanotechnologies.

Italy participates to OECD WPMN with delegates from ISS and INAIL. In the context of the national standardization body (UNI) it has been activated a commission dedicated to Nanotechnology (Technical Commission U22-Nanotechnologies), which is structured in four working groups mirroring the ISO TC229 working groups:

- Terminology
- Instrumental measurement and characterization
- Health and safety aspects
- Nanotechnological products and processes.

Specific research studies concerning risk assessment of nanomaterials are underway at several Italian universities [27] and research centres. Some of these activities refer to FP6 and FP7 European Projects.

Among the initiative activated in the last years there can be cited (see annex 7.2 for more details):
- ECSIN *(European Center for the Sustainable Impact of Nanotechnology)*
- CIGA *(Centre for Environmental Law Decisions and Corporate Ethical Certification)* at University of Padova [30];
- NanoOSH Italia , ISPESL
- the FP6 projects ParticleRisks, Dipna, CellNanotox, Canape and Nanodialogue

The Italian Chemical Industry Association (Federchimica) has launched in 2006 the initiative PNIC (*"Programma Nanotecnologie nell'Industria Chimica"*- Nanotechnology Program in the Chemical Industry) to promote nanotechnologies within their members. Fostering research on EHS issues and supporting the implementation of nanomaterials into REACH are among the activities prompt by the PNIC initiative.

AIRI/Nanotec IT (Italian Center for Nanotechnologies) act as a focal point of organisations dealing with nanotechnologies in Italy, with most of industry, academia and research institutions active in nanotechnologies being among its members. The Centre participates to UNI-TC Nanotechnologies and ISPESL-WG on Nanomaterials, coordinates the FP7 project FramingNano and is a partner (dealing also with nanoregulation) of the FP7 project ObservatoryNano [31].

[29] Not just a compensation authority but a global protection system for all workers http://www.inail.it/

[30] http://www.ciga.unipd.it/about_us_en.htm

[31] http://www.observatorynano.eu

It has formally endorsed a pledge to the Italian Government, signed from representative of some of the largest industries and research institutions in Italy, for the establishment of a National Nanotechnology Initiative which would favour the responsible development of nanotechnologies.

4.2.5. The Netherlands

One of the main issues in the Dutch "Cabinet's View" is the subject of managing the risks of nanotechnologies ("Cabinet's View Nanotechnologies: From small to great", 2006 [52]). In this document, it is described that the Dutch government wants to move towards a situation in which humans and the environment have only a negligible risk caused by nanoparticles and especially free, synthetic nanoparticles. Based on current knowledge, the government assumes that restriction of application of nanoparticles is not relevant, as well as the interference in the process of development of new nanotechnology applications. Therefore, government activities are focused on generation and sharing of knowledge and on application of existing legislation. Because uncertainties with respect to the potential risks of nanotechnology will remain large in the near future, the government wants to cope with these risks in a wise and precautious way. Therefore an approach in line with the report "Coping rationally with risks" [54], which was published in 2004 at the request of the Dutch State Secretary of the Environment, is chosen to achieve this. This approach is characterised by transparent political decision making, clear responsibilities of government, industry and civilians and the involvement of the public in the process decision making [52].

The Netherlands participates within the subgroup of nanotechnology under the REACH competent authorities. This is a first step to include nanoparticles within the implementation of REACH. According to the Dutch Action Plan Nanotechnology, the government also considers it important, in the short term, to develop knowledge about the risks of nanoparticles. For this purpose, several pilot studies are initiated, in cooperation with other countries. One of the spin-offs of the Dutch Cabinets view is a Strategic Research Agenda, which will be filled in in detail later this year. Furthermore, the government not only wants to develop knowledge, but also stimulates sharing knowledge of already developed information in companies and institutions about risks. For this purpose the government directed the "Stakeholder group Nanotechnology Risks" with the business and social organizations [53].

As mentioned in annex 7.1.5, the Knowledge and Information point Risk of Nanotechnology (KIR nano), is established at the RIVM to observe and monitor the risks of nanotechnology, gather scientific literature on this topic and give advice to the government. Recently, a first report has been published that describes a global overview of risks in the total field of nanotechnology [55]. Also the creation of expert panels on different topics (food and consumer products, workers, and environment) of is one of the primary actions of this Knowledge and Information point.

For the longer term the government focuses on the development of standards, tools and methods for risk assessment. It wants to generate global agreements on terminology and standardization. These aspects are handled in the OECD and by the International Organization for Standardization (ISO). The Netherlands are a member of different working groups that work on these topics [53].

4.2.6. Switzerland

In spring 2006, the Federal Office for the Environment (FOEN) and the Swiss Federal Office of Public Health (SFOPH) started a project to develop an action plan on "Risk Assessment and Risk Management for Synthetic Nanomaterials 2006–2009". The action plan will indicate the work required in order to deal safely with nanoparticles. The Swiss action plan follows on from the EU action plan of June 2005, but concentrates on the situation in Switzerland. In addition to representatives from the FOEN and the FOPH, the panel of experts also includes representatives from the State Secretariat for Education and Research (SBF), the State Secretariat for Economic

Affairs (seco), the Swiss Federal Laboratory for Materials Testing and Research (EMPA), the Centre for Technology Assessment (TA-SWISS), Suva, Swissmedic as well as the ETH-Council.

In the context of the action plan, the principals for the assessment of the need for action were worked out in a basic report in collaboration with a professional committee of experts. This report outlines the current state of our knowledge about the potential risks of manufactured nanoparticles, identifies gaps in our knowledge and topics where there is a need for research to be carried out, and provides the basis for formulating recommendations for action to protect the environment and the health of consumers and employees.

Overall it was concluded that there is not yet sufficient basic information of scientific or methodological nature for a conclusive risk assessment of nanoparticles to be carried out, and for them to be regulated. However, in Switzerland, at the level of laws, the basic legislative prerequisites to regulate manufactured nanoparticles are in place, but it will be necessary to adapt ordinances, norms and guidelines. For instance, instead of using threshold values for mass, new parameters such as surface area / volume will have to be considered. The Swiss regulations employ various tools such as authorisation, self-supervision, positive and negative lists, the obligation to provide information and limits for emissions.

Manufactured nanoparticles used in biocides, pesticides, drugs, etc. are subject to the appropriate legislative regulations. For any new approval, extensive safety investigations must be carried out on animals and on human beings, during which the kinetics also have to be shown. However, for other areas the question basically arises of whether the framework is adequate for a procedure of self-supervision to ensure a level of protection of humans and of the environment comparable with that obtainable through an authorisation procedure. In certain areas, lists of prohibitions or restrictions on use provide the possibility of banning certain dangerous nanoparticles.

Several concrete actions in the area of research (national research programme), communication and risk assessment have therefore been proposed to and adapted by the Federal Council in April 2008. Currently, the implementation of work proposed in the action plan is carried out.

The new European legislation on chemicals (REACH) came into force on 1 June 2007. REACH introduces more stringent conditions for the handling of chemical substances. Currently, it is being discussed whether certain elements of REACH should be implemented into Swiss legislation. This would induce revision of the existing chemicals and environmental legislation (ChemG, USG). As of October 2008, there is no official governmental mandate to undertake the adaptation yet, but various stakeholders including governmental institutions are discussing and working on this topic.

4.2.7. United Kingdom

The publication of the 2004 report of the Royal Society/Royal Academy of Engineering, raised a range of questions from many UK (and not UK) stakeholders including the UK Government about the safe development of nanotechnology.

Following this report (see paragraph 4.5.2.6 for a synthesis of conclusions), in order to ensure an understanding of potential risks to human health and the environment and promote a responsible development of nanotechnology, the Government set up two groups two coordinate policy and research across Government Departments, Agencies and Research Councils: the Nanotechnology Issues Dialogue Group (NIDG) and the Nanotechnology Research Coordination Group (NRCG). These two bodies now report into a Group of Government Ministers who meets regularly to review progress and policy on nanotechnologies.

The NRCG has developed and oversees the implementation of a cross-Government research programme on the potential risks to human health and the environment from free engineered nanomaterials. It also includes oversight of the programme on public dialogue and social research

issues and considers the outputs of stakeholder dialogue and the public to enhance and inform research decisions.

External review of the Government's objectives is carried out also by the independent Council for Science and Technology (CST) which reports directly to the above said Ministers. In March 2007 CST published a review of government's progress on nanotechnology policies and research [33].

Taking into consideration the recommendations made by the CST, NRGC published in December 2007 a second report on UK strategy, activities and achievements regarding EHS research, updating the research programme and discussing the work completed and that in progress[26].

NRGC activities are organised in 5 task forces, reflecting the issues considered of highest priority in relation with EHS research. These are:

1. Metrology, characterisation and standards (reference materials);
2. Exposure issues – occupational and environmental;
3. Human health hazard and risk assessment;
4. Environmental hazard and risk assessment;
5. Social and economic dimensions of nanotechnologies.

The UK has been playing a leading role in international fora, as the ISO, CEN and OECD activities on nanotechnology. The British Standard Institutes has published a number of UK standards that will represent relevant inputs for the development of European and International standards.

Running in parallel with the research on EHS issues it has been made an assessment on how nanomaterials would fit into existing regulatory regimes. The UK has looked at the various regulatory reviews commissioned to governments and agencies, as HSE (February 2006), DEFRA (March 2006), the Food Standards Agency (FSA) (March 2006) and the Medicines and Healthcare Products Regulatory Agency (MHRA) (September 2006) [27].

The results from these reports were drawn together in one report, "An Overview of the Framework of Current Regulations affecting Development and Marketing of Nanomaterials", published in December 2007 by Cardiff University [18] (it includes also an overview of EU legislation relevant from a national perspective).
This report is an in-depth analysis of the potential gaps in the regulation of the development, manufacture, supply, use and end of life of free engineered nanoparticles across all current and future foreseeable applications of nanomaterials.

The principal result is that the source of most of the regulatory gaps identified is the lack of information on the impact of nanomaterials on human health and the environment and not the regulation itself. In its conclusion, the reports underline the role that standards can play to improve and adapt existing regulatory frameworks to deal with nanotechnology:

> *"An integrated approach is needed, especially since current regulation was never designed with nanotechnology in mind and is inevitably piecemeal, being contained in various statutory provisions spread over different areas of regulatory activity. Nonetheless in the interim the existing framework can be adapted generally by ensuring that where appropriate the regulation extends to nanomaterials. In this context the work of international standard setting bodies is crucial in resolving issues of definition and taxonomy, allowing effective standard setting in relation to nanoparticles and opening up the prospects of a uniform global response to the marketing and circulation of nanomaterials."*

Eventually, the **government position** on research and regulatory issues related to nanomaterials has been condensed in the "Statement by the UK Government about Nanotechnologies", published in February 2008 [28]. The document underlines the following:

- Free manufactured nanoparticles and nanotubes, rather than fixed to or within a material NP, are the major source of concerns related to health and environmental safety.

- Results of various regulatory reviews shows that existing regulatory framework is broadly adequate, although there is the potential for engineered nanoscale materials to fall outside regulatory control in certain specific circumstances.

- An increased understanding of potential risks and thus of the adequacy of the risk assessment models within existing legislation is needed to understand whether these are real regulatory gaps or not.

- As with any other product, risks should be managed according to the current state of knowledge, and a precautionary approach taken if there is reason to believe that there might be harm, even if the extent of that harm has not yet been identified.

- The need for new or amended legislation for free engineered nanoscale materials will be considered on the base of the results of the substantial amount of research activities on EHS going on at national and international level (and sponsored also by the UK Government).

- At present protection is provided by current legislation, offering well established instruments to ensure safety and prompt actions in case products is a risk for health, safety or the environment.

- Non-legislative controls, as guidance and advice tools are considered fundamental to respond to potential nanotechnology risks. Among them the development of standards and guidelines (as the ones developed within the British Standard Institutes), voluntary Reporting Schemes (as the one conducted by DEFRA), code of conducts (as the ones from EC or the Royal Society) and other information exchange initiatives.

- Specific labelling of nanoproducts is considered valuable, basing on indication given by the BSI good practice document "Guidance on the labelling of manufactured nanoparticles and products containing manufactured nanoparticles" [29].

4.2.8. Other EU Countries

In the other major European countries, there is not a specific activity of regulatory agencies or government in relation with nanotechnology. Nevertheless, most of EU Countries are following closely the development of REACH and other regulation on this matter [9]. Some of these countries, such as Denmark, Finland, and Norway are developing Action Plans to promote nanotechnology. In these action plans EHS issues are taken into account, but, as said above, are not considering specific initiatives on nanoregulation (see annex 7.1).

4.2.9. United States of America

The commitment toward progress in research to protect public health and the environment within the NNI is underlined in the report published in February 2008 "NNI-Strategy for nanotechnology related environmental, health and safety research" [34], aiming to define clear roles among the various NNI agencies, coordinate and focus efforts on the five priority EHS research areas considered (instrumentation, metrology and analytical methods, nanomaterials and human health, nanomaterials and the environment, human exposure assessment, risk management methods). This work should give input to improve product use, regulation, conduct of research, and societal response on nanotechnology.

Within the NNI organization chart, the Nanotechnology Environmental and Health Implications (NEHI) Working Group (established in 2005), provides a forum for agencies to coordinate their individual activities related to understanding potential risks of nanotechnology.

The NNI amendment Act of 2008, approved in June 2008 by the U.S. House of Representatives, requires an increased effort and coordination of all NNI Agencies to allocate the level of resources and management attention necessary to ensure that the ethical, legal, environmental, and other appropriate societal concerns related to nanotechnology, including human health concerns, are addressed[32].

From the research side, government agencies in the National Nanotechnology Initiative, as in particular EPA, FDA, NIOSH, NIH, NIST, NSF, US Army EDRC, USGS, and many university research centres, namely those responding to the National Science Foundation (NSF), are doing research on EHS issues. An update of their nanotechnology related EHS research activities and highlights is reported in [34,35].

The development of nanotechnology standards is also considered a priority within the NNI, and various Federal Agencies are engaged in national and international standard development activities and, particularly as far as it regards NIST (US National Institute of Standards and Testing), in the development of reference materials, test methods and other standards to provide support for the development of safe nanotechnology-based products.

With reference to regulation, the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), within the Department of Health and Human Services, the Consumer Product Safety Commission (CPSC), and the Occupational Safety and Health Administration (OSHA), within the Department of Labour, are actively exploring EHS implications, risks and possible needs for regulations. These agencies have a regulatory authority in their fields of operation and ought to regulate also nano-related materials, products and processes.

Below a brief overview of the activities concerning nanoregulation undertaken by the Federal Agencies is reported.

4.2.9.1. Environmental Protection Agency (EPA)

The Environmental protection Agency created in 2004 a specific working group (within the EPAs Science Policy Council) to examine nanotechnology from an environmental perspective, that brought to the publication of the EPA nanotechnology white paper [5], also based on comment from an open consultation on the draft version of the document.

The document provides an extensive review of risks and benefits for health ecological and environmental applications and implications of nanotechnology, and a discussion on the role of EPA in this field, including the definition of risk research needs and priorities and possible regulatory options regarding nanotechnology. The Agency collect data, also through own research activities, regarding hazard assessment, risk assessment, and risk management relevant to the EPA mission and regulatory responsibilities.

To this aim, the EPAs Office of Research and Development (ORD) has published on June 2008 a Nanomaterial Research Strategy[37], in order to address the science needs of the Agency in this field (in particular in relation with gaps and needs identified in the EPA white paper).

Recently (2007), EPA has launched also a Nanoscale Materials Stewardship Program (NMSP), to gather information by manufacturers on nanoproducts they are making and about any associated health or environmental risks and risk management practices.

[32] http://www.opencongress.org/bill/110-h5940/text

From a regulatory point of view, EPA statutory authority is implemented through a wide range of statutes or programs, depending on the specific media of application or release considered.

Many "programs" can be related to the life cycle of nano-related products, as reported for example in Figure 2 [1].

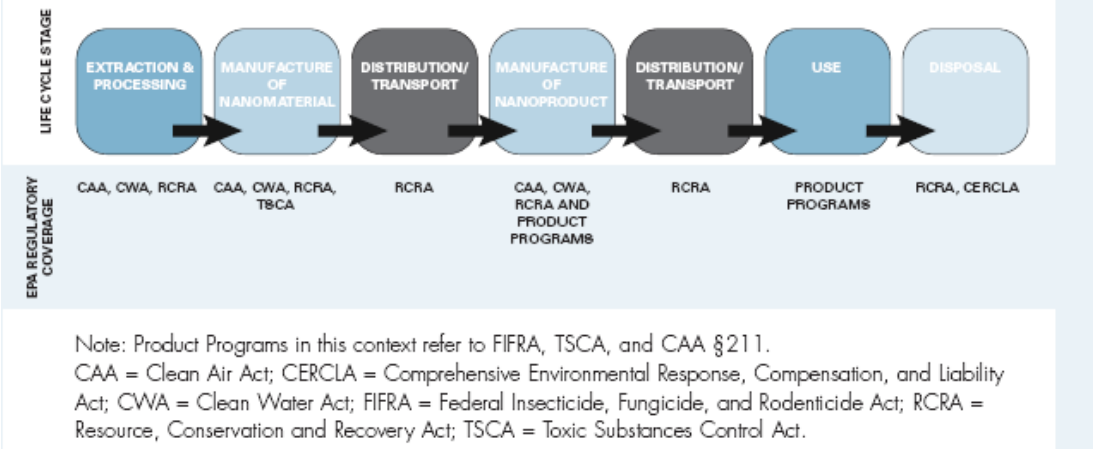

Figure 2 Nano Life Cycle and corresponding EPA regulatory coverage (figure from reference [1])

Some of these programs are considered more relevant, at least in a first stage, to evaluate and manage risks associated with nanomaterials and nanoproducts. Among them [5]:

- Toxic Substances Control Act (TSCA) - Chemicals,
- Federal Insecticide, Fungicide and rodenticide Act (FIFRA) - Pesticide
- Clean Air Act (CAA), Clean Water Act (CWA), Safe Drinking Water Act (SDWA) – Environment
- Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) – Environment
- Toxics Release Inventory Program - Environment

While some programs are focused on the end products of economic activities (emission and discharge into the environment) other (called product programs), as TSCA and FIFRA and part of the CAA, are dedicated to engineered or manufactured products.

The latter are the most interesting because provide EPA with the authority and obligation to regulate chemicals before and during their use, giving the possibility to review and control nanomaterials and nanoproducts before they enter into commerce.

So far, most of the attention has been devoted to the **Toxic Substances Control Act (TSCA)**, considered by EPA (and also other observers) as one of the most suitable programs to address the potential risks posed by nanomaterials and nanoproducts.

EPA consider TSCA definition of substances broader enough to include nanomaterials, and thus to regulate nanomaterials under TSCA.

A key element is that in this definition, only the "molecular identity", and not other properties relevant for nanomaterials, as size, are included. This makes difficult to distinguish between a nanomaterial and the "macro" form of the same material.

Another element of these provisions is that TSCA is based on a burden of proof from the Agency to enact regulation. EPA have to show that a chemical pose a risk before applying provisions to obtain more information, require testing, limit or prohibit the use of a substance. Considering the limited information available, this approach weakens the effectiveness of TSCA in regulating nanomaterials.

These two elements represent a substantial difference with the European REACH regulation on chemicals.

Regarding TSCA approval procedures, nanomaterials classified as new substances are subjected, as any other new chemical, to a pre-manufacture review process (pre-manufacturing notification – PMN-), to identify and assess risks of the substance considered. Instead, nanomaterials classified as "existing substances" (because their macro form is included in TSCA Inventory of existing substances) are not subjected to a pre-market review, unless a "significant new use rules (SNUR)" is issued by EPA. Despite the many nanomaterials in commerce, no information is publicly available about EPA application of SNUR procedure to nanomaterials classified as "existing substances" [8].

The EPA stewardship program (NMSP) should help the collation of more information on current commercial use of nanomaterials and give to EPA a relevant base to improve regulation of nanomaterial through TSCA statute (see paragraph 4.4.2.2).

As in the case of REACH, until mass/volume threshold limits will be revised, nanomaterials are likely to fall, for most of the applications, outside the scope of TSCA.

Another relevant EPA "products" program is **FIFRA** (Federal Insecticide, Fungicide, and Rodenticide Act). Pesticide products containing nanomaterials are subjected to strict review and registration requirements under this statute, and thus must produce an assessment of the potential effect of a product on human health and the environment before being marketed.

An interesting and well-known case is that of Samsung Silver Wash washing machine, which releases nanosilver ions into each wash load in order to kill bacteria and other microbes. In 2007, EPA revised its previous decision of considering the silver machine just a device, requiring the Silver washing machine to register under the act as a pesticide. This controversial EPA decision has been specific to this case, and does not regard other anti-microbial products using nanosilver or nanomaterials in general.

Other statutes, like **CAA (Clean Air Act), CWA (Clean Water Act) or RCRA** (Resource Conservation and Recovery Act), are "end of pipe" provisions. They prevent and/or control discharges or emission of toxins into water and air during or after production. Generally, they establish standards and threshold values, and give permission or restrictions based on these standards. These environmental statutes are considered by EPA applicable to nanomaterials.

There are very few publicly available information of the application of these statutes to nanomaterials, most cited is the registration of fuel additives (containing nanomaterials) under CAA [5] (an example is nano-cerium oxide particles added to diesel fuel to decrease toxic diesel emissions and increase fuel efficiency [38]) even though no specific restrictions to nanomaterials have been so far applied [8].

Some critical points have been highlighted by different observers about the applicability of TSCA and other statutes to nanomaterials [1,2,39,40,41,42]:

- TSCA, as many other statutes, is based on mass/volume measurements, and this very likely would exclude most of nanomaterials on the market.

- Technical challenges associated in characterising nanomaterials and distinguishing them from conventional-size materials, and the strict definition of EPA of nanomaterials (based only on chemical identities), may create substantial confusion about TSCA applicability to nanomaterials.

- Even when nanomaterials are clearly identified, and thus subjected to approval procedures (as PMN for new substances or SNURs for new use of existing substances), data gathered

could be inadequate to permit a reasonable evaluation of health and environmental effects of these substances.

- Lack of data on production and use of nanomaterials, level of exposure are critical gaps also in identifying chemicals that present specific health or environmental risks, and thus enacting regulation of these substances through TSCA specific provisions for dangerous substances.

- The question whether all products using antimicrobial and antibacterial properties on nanosilver should be regulated as pesticide under FIFRA statute or not is debated among EPA and various stakeholders. In a specific petition has been asked to EPA to consider nanosilver products as new pesticide (different from bulk silver), requiring specifying registration, toxicity data requirements, testing and risk assessments.

- Regarding environmental statutes, uncertainty in defining a nanomaterial "hazardous" and in collecting/interpreting data on quantities, use, exposure level and life cycle of nanomaterials and nano-products makes critical enacting and applying these regulations for nano products.

4.2.9.2. Food and Drug Administration (FDA)

The FDA has broad regulatory authority over a range of products were nanomaterials will have an increasing role. In August 2006 the agency established the internal "FDA Nanotechnology Task Force", to help assess nanotechnology regulation with respect to FDAs regulatory authorities.

A Nanotechnology Interest Group (NTIG) is also active among different FDA Centers and Offices to share information and coordinate activities on nanotechnology.

The FDA Task Force released in July 2007 a report with a review and analysis of science and policy issues related to FDA activities and authority [42]. The task force keeps also updated a website dedicated to nanotechnology. FDA conducts research internally and in collaboration with other centres also on nanotechnology.

The Agency is currently collecting views from stakeholders on information and data needed to ensure safety and effectiveness, and how to improve regulatory procedures of FDA-regulated nano-products. The last initiative has been the second " FDA Nanotechnology Public Meeting" held in September 2008 (USA). Up to 2007, FDA approved 24 nano-based drugs, and 26 nanodrugs were undergoing clinical trials [1].

The ability of FDA provisions to regulate nanomaterials varies depending of the different approval procedures foreseen for different type of products[33] [42].

In case of **products subjected to pre-market approval** (*pharmaceuticals, high-risk medical devices, food additives, colours, and biological products),* existing requirements are expected to be adequate to regulate also most of nanotechnology products, even though FDA recognize that characterisation and testing data may not be adequate for nanoscale materials having novel biological response. A case by case approach is in these cases suggested. In FDA words "*as new toxicological risks that derive from the new materials and/or new conformations of existing materials are identified, new tests will be required*".

A particular case is that of medical devices having multiple uses, resulting from the combination of drugs, biological products, and or/devices (e.g. theranostic devices), where different regulations, as pharmaceuticals, medical devices and biological ones, may be of concern.

[33] http://www.fda.gov/nanotechnology/regulation.html

FDA decided to assign them to the category of "combination products", but current requirements could need to be assessed to ensure they are treated through the most appropriate regulatory pathway.

Based on specific indications from the agency, manufacturers may make modifications of products already on the market (and subjected to premarket approval), without the need of a novel approval procedure (**products subject to premarket "acceptance"**). Relevant examples regarding nanotechnology are sunscreens.

Sunscreens fall under the FDA category of drugs, and thus are subjected to a strict pre-market approval procedure. So far, FDA has considered engineered nanoparticle ingredients used in sunscreen has just a reduction in size and not a new drug ingredient, permitting sunscreens manufacturers to market these products based on the safety assessment of bulk material sunscreen (pre-market acceptance procedure). This issue has been the basis of a specific petition from Civil Society Organizations (see ICTA-NanoAction position hereafter).

The same problem arise also for other products that can be modified and improved adding a nanomaterial (or reducing to the nanoscale an ingredient of the product), as for drugs, food additives, or medical devices. FDA generally recognises the need to require specific information to manufactures on the effects on product safety and effectiveness of the use of nanoscale materials in their products and the agency is currently developing guidance on these issues [8].

FDA authority is more limited in case of products subjected to **Post Market Surveillance** (as *foods, cosmetics, radiation emitting electronic products, and materials such as food additives and food packaging*). Even though manufacturers generally are not required to submit data to FDA prior to marketing, they are still responsible for ensuring their products are safe. In these cases it would be important to identify data that can substantiate the safety of products containing nanomaterials.

In particular, products already on the market and considered safe (as in the case of food ingredients classified as GRAS - "generally recognized as safe"), modified by means of use of nanoscale materials, may not be recognised as substantially different from the original ones and thus not subject to any specific risk assessment procedure.

This issue is of particular relevance for products such as cosmetics, food additives and dietary ingredients, because both of their direct contact with the human body (high exposure potential) and the lack of exhaustive information on their effect on human health [1,42]. Moreover, in these products nanotechnology is increasingly used.

Some points have been clearly highlighted by different observers about FDA regulation of nanotechnology [1,42,43]:

- For most of products under FDA provisions, current reporting and notification mechanisms do not contains specific information to assess safety of nanomaterials (for example may not ask data on particle size).

- Criteria for determining which nanomaterials are "new" for regulatory purposes (and thus subjected to a safety review) or not, in particular for products subject to pre-market acceptance (as sunscreen) or products modified using nanomaterials (as "GRAS" food additive).

- Classification of medical devices having multiple properties functions (as theranostic devices).

- Limited agencies authority over high risk/high exposure products, like cosmetics, food additives, dietary supplements (no pre-market approval is foreseen, and responsibility on

FDA to prove that a nano-related product is safe; limited power of the agencies to retrieve specific information on product composition and health and safety data before and after marketing).

As for other regulatory frameworks, issues related to the appropriateness of current exposure triggers (expressed in mass/volume metrics), adequacy of toxicological data and testing protocols and of analytical methodologies and toxicity test have been also underlined by different observers.

4.2.9.3. Other USA Federal regulatory agencies

Apart EPA and FDA, two other agencies, the U.S. Consumer Product Safety Commission (CPSC) and the Occupational Safety & Health Administration (OSHA) are considered those most concerned in relation with nanotechnology regulation [36].

The U.S. Consumer Product Safety Commission (CPSC) jurisdiction includes over 15,000 types of consumer products used in or around the home, except certain items excluded by statute, such as, for example, motor vehicles, tobacco, food, drugs, cosmetics, most medical devices, and pesticides. A preliminary analysis from PEN [46], indicates that approximately half of nanotechnology consumer products currently on the market would fall under CPSC jurisdiction.

Under CPSC laws, no pre-market registration or approval of products is foreseen. Responsibility is on the manufactures to ensure that their products are safe and comply with agency standards. Agency authority is mainly expressed through post-marketing procedures, as monitoring of product-related injuries and recalling of dangerous products.

As declared in their 2005 "CPSC Nanomaterial Statement" [47], the Agency considers that the potential safety and health risks of nanomaterials can be assessed under existing CPSC statutes, regulations and guidelines, even though they recognize that *"the introduction of consumer products containing nanomaterials into the marketplace may require unique exposure and risk assessment strategies"*.

The **Occupational Safety & Health Administration (OSHA)** role is to promote the safety and health of US.A. workers, setting and enforcing standards at the workplace. OSHA has not started any specific action regarding nanotechnology. However, the **National Institute for Occupational Safety and Health (NIOSH)**, which sources OSHA with scientific advice and recommendations on occupational safety, has a relevant commitment on nanotechnology and nanomaterials.

NIOSH is not a regulatory agency, but the Federal agency responsible for conducting research and making recommendations to prevent work-related injury, illness, and death. NIOSH communicates recommended standards to regulatory agencies, in particular OSHA.

NIOSH established the NIOSH Nanotechnology Research Centre (NTRC) in 2004 to accelerate progress in nanotechnology research across the Institute.

NIOSH, recognise current scientific gaps in risk assessment and risk management of nanomaterials and nanotechnology. In 2008 has published a *"Strategic Plan for NIOSH Nanotechnology Research and Guidance – Filling the Knowledge Gaps"* [48] were different critical research areas are identified and addressed through the definition of specific actions.

An extensive research activity is carried out by the Institute on these themes. At international level, NIOSH is actively engaged with nanotechnology activities of the Organization for Economic Co-operation and Development (OECD), the World Health Organization (WHO), the International Organization for Standardization (ISO), and the International Council on Nanotechnology (ICON).

NIOSH website, report, guidelines [49,50,51] [34] provides one of the most updated sources of information on occupational health and safety issues in relation with nanotechnology.

4.2.9.4. U.S.A. local and state initiatives

Initiatives aimed to nanoregulation have been activated in the last years in USA also at state and local level to address the potential risks related to engineered nanomaterials. In absence of absolute evidence on the implications of these materials and of a clear Federal regulatory framework, these institutions are trying to develop instrument to monitor, and regulate the use of nanomaterials from local manufacturers and production plants, in order to prevent any potential negative implication for health safety or environment locally.

The only initiative that already brought to specific regulations is that from the City of Berkeley (California) which adopted in 2006 a "manufactured nanoscale material disclosure ordinance". This law requires that facilities producing or handling engineered nanomaterials provide specific safety reports on the use of these materials. In particular, the ordinance asks to include in the report information for the nanomaterial used, its physicochemical properties, toxicological and ecological data, and occupational and environmental protection information.

The regulation also specifies that these disclosure requirements will carry no minimum threshold and will apply to "*all manufactured nanoparticles, defined as a particle with one axis less than 100 nanometers in length*." [35]

Similar initiatives have been recently started or are in discussion in Wisconsin, the city of Cambridge (Massachusetts), in Minnesota, New Jersey. [40].

4.2.10. Australia

Initiatives toward a responsible development of nanotechnology are among the priorities of the Australian National Nanotechnology Strategy (as described in annex 7.1.11).
Government views regarding nano regulation are clearly expressed in the position paper "Australian Government Approach to the Responsible Management of Nanotechnology" [36].

Regulatory arrangement in place are considered robust enough to address EHS issues associated with nano materials and products, as well as related manufacturers' and suppliers' liability obligations.
Relevant Australian Government agencies are gathering information from all available scientific sources and they participate in various international inititatives on this theme, including OECD WPMN programme and ISO TC 229 on standardisation.

In the Government view, *"there has so far been no demonstrated need for a specific regulatory system for engineered nanomaterials"*, and Australia is committed in monitoring developments of nanotechnology to ensure that the regulatory frameworks will be kept in line with these changes.

In particular Australian Government and regulatory authorities will continue to:

- Use an evidence based approach to making decisions about nanotechnology.
- Use existing regulatory frameworks to deliver an efficient and effective response to the health, safety, and environmental impacts of nanotechnology.

[34] available from http://www.cdc.gov/niosh/topics/nanotech/

[35] http://www.ci.berkeley.ca.us/uploadedFiles/Planning_(new_site_map_walk-through)/Level_3_-_General/Manuffactured%20Nanoscale%20Materials.pdf

[36] http://www.innovation.gov.au/Section/Innovation/Documents/ObjectivesPaperFINAL.pdf

- Ensure that regulatory schemes are reviewed to assess their ongoing ability to deal with the impact of nanotechnology, and regulatory or procedural changes implemented as necessary.
- Apply a precautionary approach consistent with Australia's international obligations, including the Rio declaration.
- Ensure information about the health, safety and environmental impacts of nanotechnology is based on scientific evidence.

A review of the Austrialian regulatory framework in relation with nanotechnologies has been carried out by The Monash University [44]. The report concluded that there is no immediate need for relevant changes in legislation, but identifies some regulatory issues which may need to be addressed . These are [44]:

1) *'New' or 'Existing' substances or Products?*
   The most significant potential gap concerns the uncertainty as to whether new nanoforms of conventional products will be considered as 'different' to traditional products.
2) *Weight or volume*
   Many regulatory triggers currently exist on the basis of a threshold weight or volume. For nanomaterials such thresholds may not be meaningful.
3) *Knowledge of presence or implications of presence of nanomaterials*
   In some instances appropriate regulation requires particular knowledge of either the presence of nanomaterials and/or the risks posed by nanomaterials.
4) *Risk assessment protocols or conventional techniques*
   Australia's current regulatory regimes often rely on risk assessment protocols as a means of ensuring human or environmental safety of products or applications. However it is uncertain whether the current risk assessment methodologies being employed by various regulatory agencies are suitable for goods that contain nanomaterials.
5) *Research and Development exemptions*
   There are some gaps relevant to research and development, which although not unique to nanomaterials may apply when there are regulatory exemptions for R&D purposes that are based on weight thresholds.
6) *International documents*
   Many of Austrlian regulatory frameworks refer to international documents or documents sourced outside regulators. If these documents themselves do not adequately address health, safety and environment concerns raised by nanomaterials, this may lead to a further potential regulatory gap.

Interestingly, these points are not much different from gaps identified in other regulatory frameworks, as in U.S.A or EU.

4.2.11. China

Main activities regarding EHS issues in China refer to the China Nanosafety Lab within the National Center for Nanoscience and Technology (NCNST). The "drafting of regulatory frameworks for research and industrial activities on nanotechnology" is also among the priorities of the Centre.
Moreover, currently about 30 research organizations in China have started activities related to toxicological and environmental effects of nanomaterials/nanoparticles (other details in annex 7.1.12).

As far as regard regulation, in 2006 the State Food and Drug Administration of China (SFDA) made an amendment of the medical devices regulation.

Products using biological materials engineered at the nanoscale were previously (since 2004) classified as Class II medical devices. Considering the peculiar behaviour of nanomaterials, in 2006 the agency decided to re-classify these types of products as Class III devices (subject to more

detailed registration requirement). The amendment was not applied to already registered products (about 10 of such products were on the market) [9].

China participates at the activities of OECD WPMN and has been one of the first countries to start an activity on nanotechnology standardisation. Standardization Administration of China (SAC) has established the Committee on Nanotechnology in 2005, and up to now has published more than 15 standards on this theme, mainly regarding measurement, characterization and terminology of nanomaterials.
China is currently the convenor of the Working Group 4 on "material specification" within ISO TC 229.

4.2.12. Japan

Within the topic of "public confidence and engagement" in the Japan Science and Technology Basic Plan, initiatives from various institutions has been launched regarding EHS issues and nanotechnology.

The Ministry of Economy, Trade and Industry (METI) is conducting a 5 year project on toxicity test protocols and risk assessment methodologies for manufactured nanomaterials "Evaluation of the Potential Risks of Manufactured Nanomaterials based on Toxicity Tests with Precise Characterization", with a specific priority on fullerene and carbon nanotubes.

The National Institute of Occupational Safety and Health Japan (JNIOSH) has started a three-year project on exposure to manufactured nanomaterials at the workplace.

The National Institute of Advanced Industrial Science and Technology (AIST), the National Institute of Health Science (NIHS), the National Institute for Environmental Studies (NIES), the National Institute of Materials Science (NIMS) are also involved in research programmes on EHS issues.
Regarding regulation, METI is considering to include EHS issues in the framework of chemical management in METI's Policy Council on Chemical Issues.

In the current regulatory system, the Chemical Substance Control Law obliges manufacturers to notify the government about nanomaterials if they are new chemicals subject to the law, and some notifications concerning fullerene derivatives have been submitted under the small quantities exemption of the new chemical notification. [9]

However, no specific regulatory measures regarding nanomaterials are currently foreseen in Japanese legislation.

Japan participate in the work of OECD WPMN and ISO TC 229 (in particular is the convenor of the Working Group on Measurement and Characterization

4.2.13. Organisation for Economic Co-operation and Development (OECD)

OECD is playing a pivotal role in the process of standardising and coordinating national activities with nanotechnologies. Under the Committee on Scientific and Technological Policy (CSTP) a *Working Party on Nanotechnology* was established in March 2007. The objective of this Working Party is to promote international co-operation that facilitates research, development, and responsible commercialisation of nanotechnology in member countries and in non-member economies. The Working Party has initiated six projects to achieve its objectives:

- **Indicators and Statistics**, aiming at providing an overview of nanotechnology trends based on available comparable indicators and statistics, while identifying policy makers' needs for further indicators, and establishing a framework for the development and collection of new indicators and statistics.

- **Impacts on Companies and Business Environments**, which complements the statistical work with a large set of company case studies across different application areas and countries. It analyses the impacts and business environment of nanotechnology to identify possible new challenges for the business community.
- **International Research Collaboration**, designed to facilitate research collaboration in the field by mapping available research infrastructures and S&T agreements globally.
- **Outreach and Public Engagement**, aiming at promoting the exchange of experience in outreach and public engagement through questionnaires, possible country case studies and a set of workshops.
- **Policy Dialogue**, aiming at facilitating a policy dialogue and help develop an overall synthesis of the WPN work. It relies on a questionnaire and other material to highlight policy responses and challenges across countries, combining this with workshops dedicated to specific policy themes.
- **Global challenges: water**, which focuses on the contribution of nanotechnology to the purification of water and the barriers that will need to be addressed. The purification of water is a key global challenge, especially for developing countries.

A work programme called *Manufactured Nanomaterials: Work Programme 2006-2008 [17]*[37] has been established. The main aim of the programme is to promote international co-operation in human health and environmental safety related aspects of manufactured nanomaterials, in order to assist in the safe development of manufactured nanomaterials, while avoiding non-tariff barriers to trade.

The Programme of Work is structured in three work areas: i) Identification, Characterisation, Definitions, Terminology and Standards; ii) Testing Methods and Risk Assessment; and iii) Information Sharing, Co-operation and Dissemination. Six specific projects (organised by Steering Group) have been defined:

- **SG1:** Development of an OECD Database on Human Health and Environmental Safety
- (EHS) Research.
- **SG2:** EHS Research Strategies on Manufactured Nanomaterials.
- **SG3:** Safety Testing of a Representative Set of Manufactured Nanomaterials.
- **SG4:** Manufactured Nanomaterials and Test Guidelines.
- **SG5:** Co-operation on Voluntary Schemes and Regulatory Programmes.
- **SG6:** Co-operation on Risk Assessments.

A new Programme of Work is under discussion for 2009-2012. This will be considered by OECD's Chemicals Committee in November 2008.

The work of the *Working Party on Nanotechnology* complements other activities underway in OECD. The OECD *Working Party on Manufactured Nanomaterials* was established in September 2006 and is looking at international co-operation in health and environmental safety related aspects of manufactured nanomaterials. In essence, by working together, member countries will better understand the potential challenges and opportunities related to nanotechnology so that they can support the responsible development of this technology.

Recently, in November 2007, the OECD's *Working Party on Manufactured Nanomaterials* launched a "sponsorship programme"[38] where countries will share the testing of a representative set of manufactured nanomaterials (MNs). In launching this programme the Working Party agreed a priority list of MNs for testing (based on materials which are in or close to commerce) as well as a list of endpoints for which they should be tested.

[37] http://www.olis.oecd.org/olis/2008doc.nsf/LinkTo/NT00000B76/$FILE/JT03240538.PDF

[38] http://www.olis.oecd.org/olis/2008doc.nsf/LinkTo/NT000034C6/$FILE/JT03248749.PDF

Furthermore, the OECD organises regular *Tour de Table* meetings[39] to update member and non-member countries about the following developments and activities on the safety of manufactured nanomaterials:

- any national regulatory developments on human health and environmental safety including recommendations or discussions related to adapting existing regulatory systems or the drafting of laws / regulations / guidance materials;
- developments related to voluntary or stewardship schemes;
- information on any risk assessment decisions;
- information on any developments related to good practice documents;
- research programmes or strategies designed to address human health and / or environmental safety aspects of nanomaterials;
- information on any public / stakeholder consultation.

The objectives of the OECD member state meetings lie in facilitating the implementation of a series of goals by listing recent and planned national activities in

[39] http://www.olis.oecd.org/olis/2008doc.nsf/LinkTo/NT00000E8A/$FILE/JT03243507.PDF

4.3. Standardisation

4.3.1. Definition and scope of standardisation

Following the definition of ISO/IEC a standards is "*a document, established by consensus and approved by a recognized body, that provides, for common and repeated use, rules, guidelines or characteristics for activities or their results, aimed at the achievement of the optimum degree of order in a given context*".

The process of preparing a standards involve the active engagement of interested parties (public authorities, research and industry organizations, professional organization, employee's union. etc), and are adopted by a recognised standardization organization.

Standards are public and are applied voluntary, i.e. standardization organization can not enforce their implementation.

They can be implemented in regulatory frameworks by public authorities, referring or incorporating the content of a standard or a technical specification in the regulation.

The developments of international standards are the result of a relevant preparatory work, and different development phases are foreseen before an international standard is officially released. During these phases intermediate documents, as for example Publicly Available Specification (PAS) or Technical Specification (TS), or supporting documents as Technical Reports (TR) can be published.

4.3.2. Standards and nanotechnologies

Standards are ubiquitous, they apply on any kind of process, product or application, throughout their whole lifecycle. They are related to a wide range of aspect of a technology, giving common tools and methods for measuring, describing and testing, and also providing instruments for management and reporting of products and processes (as for example standards for quality, or environmental management). They are voluntary and their definition is the result of the interaction and agreement of different stakeholders.

Considering the unique characteristic and issues related to nanotechnology, standards can represent a powerful instrument to develop a common and shared "knowledge base" on various aspects of nanotechnology, and favour nanotechnology development, from research to manufacturing, trade and commercialization.

The development of these standards is also pivotal for the definition of appropriate regulatory frameworks in the field of occupational, consumer, and environmental health and safety.
These regimes will provide certainty and confidence for workers, consumers, manufacturers and users alike.

Most of the economies that are investing significantly in nanotechnology development are well aware of the importance of standardization. As an example, already in 2005 the Action Plan of the EC on nanotech stated "The Commission will […] *develop with Member States, international organisations, European agencies, industry and other stakeholders, terminology, guidelines, models and standards for risk assessment throughout the whole life-cycle of N&N products* ".

Since 2004 various national standard bodies have established Technical Committee dedicated to Nanotechnology, as China (SAC/TC279), UK (BSI –NT/1), U.S.A. (ANSI-NSP) and others.

In June 2005 ISO has formally established the ISO TC 229 on nanotechnology and in June 2006 IEC has established the IEC TC 113 on nanotechnology.

A list of standards organisations dealing with nanotechnologies is reported in Annex 7.3.

Standards are generally developed with the maturity of a technology, based on common practises well established at production and market level. The case of nanotechnology seems different, most of standards will be anticipatory as nanotechnology is still an early stage of development [1]

There is a general consensus on standardization needs and priorities related to nanotechnology. As also reflected in the Working Group established within ISO TC 229, the focus of nanotechnology standardization is on [2]:

- terminology and nomenclature *(providing a common framework for commercial, scientific, and legal purposes);*
- Metrology *(developing methods, equipment and systems to measure basic characteristics of nano products).*
- Materials *(characterization of physical/chemical properties of nano materials and their applications);*
- safety and risk assessment *(methods to prove nanomaterials toxicity and ecotoxicity, protocols for life cycle assessment of nanoscale materials, devices and products; occupational health safety);*

Standardization activities from national bodies fall under the umbrella of the Nanotechnology Technical Committees of ISO and IEC. Other subjects involved or interested in the development of standards on the thematic areas indicated above are:

- Other ISO and IEC Technical Committees
- SDOs and other private standard organizations
- International bodies (as OECD)
- Institutes doing research on metrology, industry, other stakeholders

Standard on nanotechnology are being developed by ISO TC 229, IEC TC 113, national standard bodies, in particular BSI –NT/1, SAC/TC279, ANSI-NSP but also by SDOs as ASTM E56 and IEEE.
Some other ISO Committees and SDOs have published standards relevant, even though not specific, for nanoscale technology and management, as for example ISO TC 194 (Biological evaluation of medical devices), ISO TC 209 (clean rooms and associated controlled environments), ASTM E42 (Surface Analysis).

The Working Party on Manufactured Nanomaterials of the OECD's Chemical Committee elaborate and implements a programme of work aiming to promote collaboration on health and environmental safety aspects of nanomaterials, that promise to give various inputs on nanotechnology standardization (ISO TC 229 is actively participating in this Working Group).

Figure 4.3 gives an impressive overview of the number of organisations potentially involved in nanotechnology standardization, in relation with different sectors of application of nanotechnology. The organisations reported in the inner circle of the figure have already established liaisons with ISO TC 229, while potential liaisons are indicated in the outer circle (the figure is updated at May 2007).

ISO TC 229 is being establishing liaisons with these organisations in order to coordinate and harmonize activities; in particular two of the Working Groups of ISO TC 229 are jointly held with IEC TC 113.

An international workshop on measurement and characterization for nanotechnologies was organised in February 2008 by IEC, OECD and NIST (US National Institute of Standards and Testing), aiming to establish a forum among organizations with an interest in nanotechnologies standardization.

Among the outcomes of the workshop, the intention to establish a "Nanotechnology Liaison Coordination Group" among these organisations and to develop international databases dedicated to standards on nanotechnology. A detailed list of standards related to or relevant for nanomaterials and nano-related products is included in the report of the workshop [40].

Some standardization issues, as terminology or measurement standards, could be (at least partially) common to different applications of nanotechnology, considering that there are similar nanostructures and measuring needs [2].

Other standards will be instead specific to the material, product and life cycle stage considered (e.g. standards developed for biomedical, electronic products, standards for manufacturing compared to standard for the disposal of a product).

In 2006 ISO TC 229 undertook a survey of standardization needs of members, identifying over 100 high priority topics. The information collected has been used to prepare a standardization road map on which the activity of the different ISO TC 229 working group is based.

Documents currently discussed within standards organisations dealing with nanotech are mainly focused on:

- Terminology and definition for nanomaterials and Nan manufacturing
- Measurement and characterization of nanomaterials, in particular carbon nanotubes
- Development of protocols for toxicity testing of nanomaterials
- Safe handling and disposal of manufactured nanomaterials during manufacturing and occupational health issues

Product specific standards are being developed in the electronic field, where there is a long lasting experience in working at the micro/nano scale, and in some other sectors, as the medical field.

[40] http://www.iso.org/nanotech-workshop

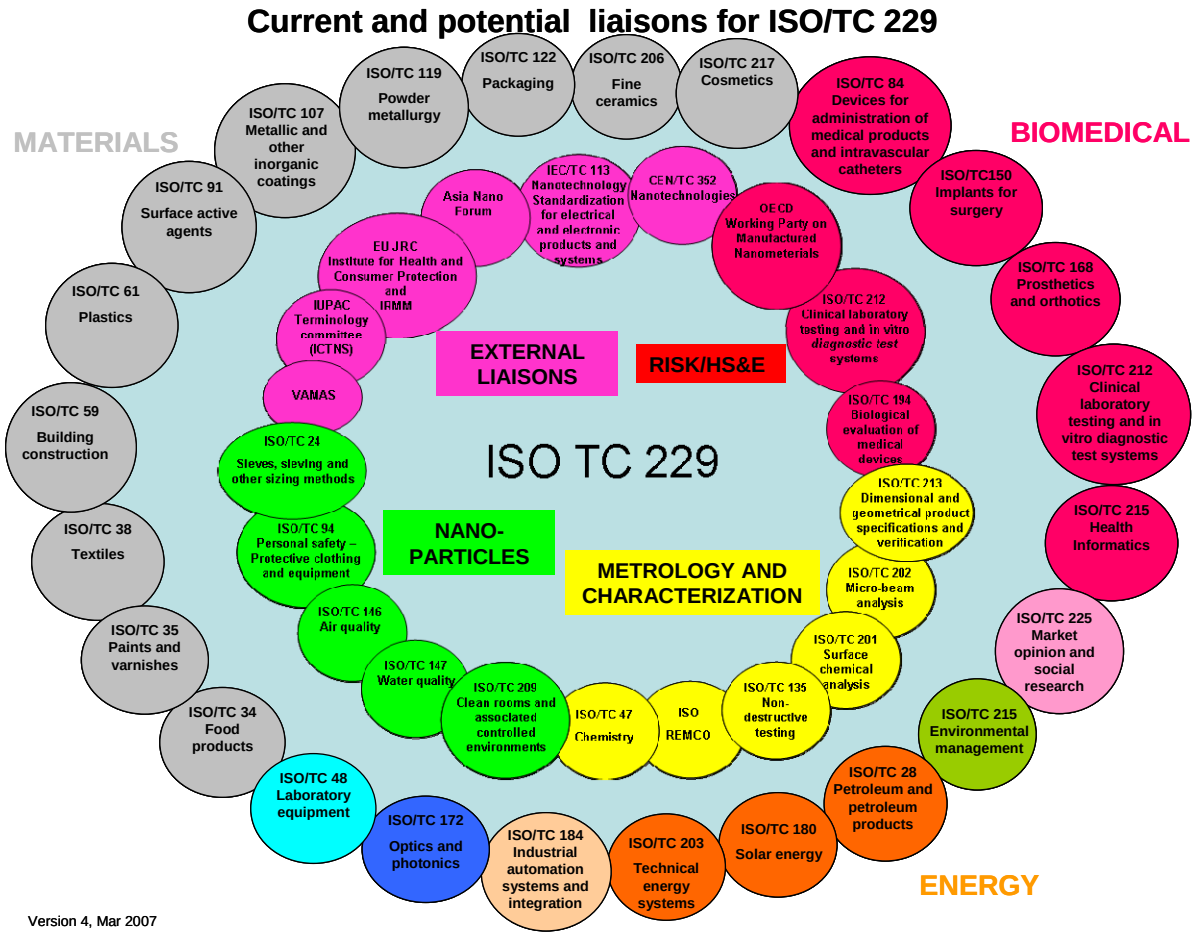

Figure 4.3 Organisations and Committees potentially involved in nanotechnology standardization/ Current and potential liaisons for ISO/TC 229 (figure from [3], updated at May 2007]

4.3.3. Terminology

The development of a universally valid and internationally accepted nomenclature is a fundamental aspect of the development of nanotechnology. This is necessary to avoid the confusing set of definitions and terms used by individuals and organisations involved at different level in nanotechnology and provide a common platform to share, compare, exchange information and products among all stakeholders, and also enabling the development of clear and unambiguous tools to manage and regulate nanomaterials and nano-related products.

A major challenge is how the definitions and terminology developed will be integrated into existing standards and how they will be interpreted, in particular in commercial security, health and environmental fields [2].

In the word of the Convenor of ISO/TC 229 Working Group on terminology:
"such a structured terminology must have the potential for being comprehensive and coherent for nanotechnology terms across the entire field of nanotechnology and must be translatable into existing definitions and terminology across the entire field of standards".

The ISO TC 229 Committee is currently basing on the following draft definition of nanotechnology (ISO/TC 229 Business Plan [1])

> *(1) Understanding and control of matter and processes at the nanoscale, typically, but not exclusively, below 100 nanometres in one or more dimensions where the onset of size-dependent phenomena usually enables novel applications, where one nanometre is one thousand millionth of a metre,*
>
> *(2) Utilizing the properties of nanoscale materials that differ from the properties of individual atoms, molecules, and bulk matter, to create improved materials, devices, and systems that exploit these new properties.*

Standards documents on terminology have been prepared so far by ISO TC 229 and IEC TC 113, but also by other standard national Committees in particular CEN TC 352 (with ISO TC 229), BSI NT/1, SAC/TC279, ASTM E56. In the table below are reported standards and documents under development on this theme within the ISO TC 229 Committee. A joint Working Group (JWG1) has been established by ISO TC 229 and IEC TC 113 on issues related to terminology and definitions.
The activities of JWG1 comprise the preparation of basic definitions and terminology for [8]:

- nanotechnology
- nanoprocesses
- nanoproduction
- nanomeasurements
- nanomaterials
- devices and applications

The first international standard on nanotechnology published by ISO TC 229 is on terminology, the document is the ISO/TS 27687:2008 (Nanotechnologies -- Terminology and definitions for nano-objects -- Nanoparticle, nanofibre and nanoplate), that lists *"unambiguous terms and definitions related to particles in the field of nanotechnologies"* [5].

Among the work planned in the future, CEN TC 352 is currently discussing a New Work Item Proposal for the development of a guide to labelling of manufactured nanomaterials and products containing manufactured nanoparticles.

The question of labelling is the source of an ample debate among stakeholders, and is one of the key points in the positions of many civil society organisations on nanotechnology regulation.

Labelling and materials specifications are important tools for several purpose, for example to clearly identify materials at production and marketing level, to help defining regulatory requirements, to inform consumers of the presence of nanomaterials in final products. Labelling should facilitate traceability and the monitoring of health and environmental impacts of nanomaterials and help informed decision along the entire life cycle of a material or product.

The engagement of standardisation bodies to develop a common approach to labelling is thus an important step toward openness and transparency in the development and commercialisation of nanotechnology.

A Publicly Available Specification on this issue has been already published in 2007 by BSI NT/1.

ISO/AWI TS 11751	Terminology and definitions for carbon nanomaterials
ISO/NP TS 12144	Nanotechnologies – Core terms -- Terminology and definitions
ISO/NP TS 12808	Nanotechnology - Terminology for the bio-nano interface
ISO/NP TS 12843	Nanotechnologies - Terminology for medical, health and personal care applications
ISO/NP TS 12921	Nanotechnologies - Terminology and definitions for nanostructured materials
ISO/NP 13013	Nanotechnologies -- Terminology for nanoscale measurement and instrumentation
ISO/TS 27687:2008	Nanotechnologies -- Terminology and definitions for nano-objects -- Nanoparticle, nanofibre and nanoplate
ISO/AWI TR 11360	Nanotechnologies – Outline of nanomaterials classification (Nano tree)

Table 4.1 ISO TC 229 standard documents under development relevant to JWG1 activities

4.3.4. Metrology, materials characterization and specification

The accurate measurement of the characteristics of nanoscale materials, devices and systems is a fundamental step for research, production and regulation of nanotechnologies.

The novel properties that some nanomaterials exhibit when at least one of their dimension is at the nanoscale open new technological requirements for their measurement and characterization.
Besides measurement of traditional quantities (as length, mass, etc..) other factors influence their behaviour and need to be evaluated, as for example volume, surface structure and composition, adsorption, porosity, force, etc. and principle of measurement of these parameters at the macroscopic level may be no more valid at the nanoscale (as for example weighing with accuracy a nanoparticle below 10nm) [2].

Given this background, the main priorities regarding metrology and materials characterization for nanotechnology are the development and standardization of appropriate measurement techniques, instruments and calibration procedures and of certified references materials.
This must be done ensuring accuracy and reproducibility and full traceability basing on International System of Units (SI).

This work is fundamental also for the development of standards for health and environmental safety of nanomaterials (activity within the ISO TC 229 WG3). Appropriate metrology tools are for example instrumental for the development of characterization methods for the assessment of toxicity and ecotoxicity of nanomaterials, and for measuring exposure to nanomaterials.

To this end, OECD WPMN has recently published a *"list of manufactured nanomaterials and list of endpoints for phase one of the OECD testing programme"[9],* giving a priority list of materials (based on materials that are or will reach soon the market) and factors to consider for the assessment of human health and environmental safety. Among these factors, various physical-chemical properties, toxicological properties, information on environmental fate, information on composition, morphology, etc.

Standards documents on measurement and characterization have been prepared so far by ISO TC 229 and IEC TC 113, but also by other standard national Committees, in particular SAC/TC279, IEEE, ASTM E56. In the table below are reported standards and documents under development on this theme within the ISO TC 229 Committee.

A joint Working Group (JWG2) has been established by ISO TC 229 and IEC TC 113 on issues related to measurement and characterization. Priority themes identified regards the development of standards for [8]:

- Carbon nanomaterials
- Engineered nanoparticles
- Coatings/nanostructured materials
- Basic metrology (parameter as length, depth, force, traceability, definition of measurand, uncertainty)

Also other activities on standardization are important regarding measurement and characterization at the nanoscale. Among these, standards developed by other ISO-TC Committees, as the ones from TC 209 (Cleanrooms and associated controlled environments), TC 146 (air quality), TC 201 and ASTM E42 (surface analysis), ISO/TC 24 (particle detection/sizing), ISO/TC 202 (micro beam analysis) and in general standards developed for the semiconductor industry (as for example from SDOs as IEEE).

A detailed list of these standards is included in the report from the international workshop on measurement and characterization for nanotechnologies organised by IEC, OECD and NIST [6].

It's worth noting that in this workshop the establishment of databases on characterisation tools and methods for nanotechnology is envisaged, even though without giving an exact time planning.

Regarding material specification (addressing specifications for nanomaterials in terms of possible applications) recently a dedicated Working Group has been established within ISO TC 229 (WG4). The WG is convened by China and part of the work done so far (reported in the table below) is based on previous documents produced on material specification by SAC/TC279.

In particular SAC has published since 2004 four standards on materials specifications [10], regarding nano-nickel power (GB/T19588-2004), nano-zinc oxide (GB/T19589-2004), nano-calcium carbonate (GB/T19590-2004), nano-titanium dioxide (GB/T19591-2004).

The two working items on nano-calcium carbonate and nano-titanium dioxide aim to specify characteristic and measurement methods of these nanomaterials in relation with their use in industrial applications.

The third item (ISO/NP TS 12805) is developed with BSI NT/1 (that has already published PAS on these arguments) and will provide guidance on the preparation of comprehensive technical specifications for manufactured nanomaterials.

ISO/AWI TS 10797	Nanotubes -- Use of transmission electron microscopy (TEM) in walled carbon nanotubes (SWCNTs)
1ISO/AWI TS 10798	Nanotubes -- Scanning electron microscopy (SEM) and energy dispersive X-ray analysis (EDXA) in the characterization of single walled carbon nanotubes (SWCNTs)
4ISO/NP TS 10812	Nanotechnologies -- Use of Raman spectroscopy in the characterization of single-walled carbon nanotubes (SWCNTs)
5ISO/NP TS 10867	Nanotubes -- Use of NIR-Photoluminescence (NIR-PL) Spectroscopy in the characterization of single-walled carbon nanotubes (SWCNTs)
6ISO/NP TS 10868	Nanotubes - Use of UV-Vis-NIR absorption spectroscopy in the characterization of single-walled carbon nanotubes (SWCNTs)

7ISO/AWI TS 10929	Measurement methods for the characterization of multi-walled carbon nanotubes (MWCNTs)
8ISO/AWI TS 11251	Nanotechnologies -- Use of evolved gas analysis-gas chromatograph mass spectrometry (EGA-GCMS) in the characterization of single-walled carbon nanotubes (SWCNTs)
9ISO/AWI TS 11308	Nanotechnologies -- Use of thermo gravimetric analysis (TGA) in the purity evaluation of single-walled carbon nanotubes (SWCNT)
12ISO/AWI TR 11808	Nanotechnologies -- Guidance on nanoparticle measurement methods and their limitations
13ISO/AWI TR 11811	Nanotechnologies -- Guidance on methods for nanotribology measurements
14ISO/NP TS 11888	Determination of mesoscopic shape factors of multiwalled carbon nanotubes (MWCNTs)
17ISO/NP 12025	Nanomaterials -- General framework for determining nanoparticle content in nanomaterials by generation of aerosols

Table 4.2 ISO TC 229 standard documents under development relevant to JWG2 activities

ISO/NP 11931	Nanotechnologies -- Nano-calcium carbonate
ISO/NP 11937	Nanotechnologies -- Nano-titanium dioxide
ISO/NP TS 12805	Nanomaterials - Guidance on specifying nanomaterials

Table 4.3 ISO TC 229 standard documents under development relevant to WG4 activities

4.3.5. Risk management

The main role of standards regarding health, safety and the environment is, paraphrasing the Business Plan of ISO TC 229 [1], to *"improve occupational safety, and consumer and environmental protection, promoting good practice in the production, use and disposal of nano-materials, nanotechnology products and nanotechnology-enabled systems and products"*.

A range of research needs related to implications of nanomaterials for human health and environmental safety are reported in paragraph 3.4. Standards can play an important role in responding to these needs, helping to define validated methods and tools to deal with nanomaterials.
The first three standardization priorities defined in the roadmap of the ISO TC 229 working group 3 (WG3) mirror some of these needs. These regard the development of:

- Standard methods for controlling occupational exposures to nanomaterials
- Standard methods for determining relative toxicity/hazard potential of nanomaterials
- Standard methods for toxicological screening of nanomaterials

The definition of such standards implies the development of different aspects of nanomaterials standardization, as is shown in Figure 4.4, were a schematic picture of the WG3 roadmap and the relation with other standardisation activities (mainly from WG2) is reported.

In particular the development of appropriate terminology and metrology tools are fundamental achievements for all these three priorities. Adeguate workplace monitoring methods and tools are needed for controlling exposure at the workplace (first priority), physico-chemical characterization

of nanomaterials, toxicity and inhalation testing are fundamental to develop the second priority, development of in vitro and in vivo toxicity testing are fundamental for the third priority.

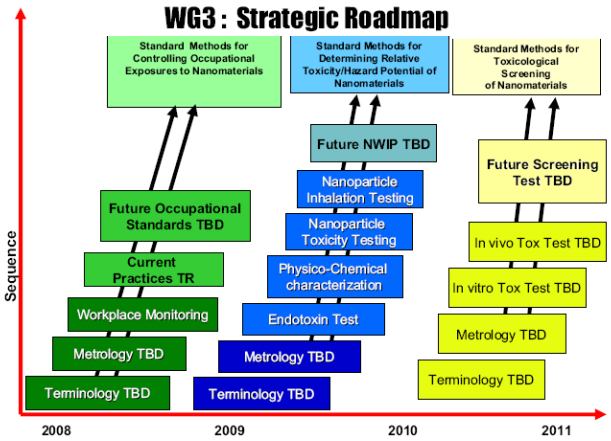

Figure 4.4 Schematic picture of the relation among activities of WG2 and WG3 (figure from [7])

These priorities are reflected in the standards documents discussed within WG3 of ISO TC 229, reported in the list below.
Standards documents on measurement and characterization have been prepared so far by ISO TC 229 and IEC TC 113, but also by other standard national Committees. In particular CEN TC 352 (with ISO TC 229), BSI NT/1, have prepared standard documents on issues related to risk characterization and risk management of nanomaterials.

The activity of OECD WPMN is of particular relevance regarding these issues, and a liaison has been established between OECD WPMN and ISO TC 229, mainly regarding the activities of WG3.

A Technical Report has been already published by ISO TC 229 on WG3 activities. The document is *"ISO/TR 12885–Nanotechnologies--Health and safety practices in occupational settings relevant to nanotechnologies"*. It focuses on the occupational manufacture and use of engineered nanomaterials and the content is broadly applicable across a range of nanomaterials and applications.

Also standards developed by other ISO-TC Committees are relevant regarding the theme of JWG3, as is shown in Figure 4.4. For example, the ones from TC 146 (Air quality), TC 94 (Personal safety – protective equipment), or other product specific activities as TC 194 (Biological evaluation of medical devices), TC 34 (food and food products), TC 217 (Cosmetics) [5].

ISO/CD 10801	Nanotechnologies -- Generation of nanoparticles for inhalation toxicity testing
ISO/CD 10808	Nanotechnologies -- Monitoring nanoparticles in inhalation exposure chambers for inhalation toxicity testing
ISO/TR 12885	Nanotechnologies -- Health and safety practices in occupational settings relevant to nanotechnologies
ISO/NP TS 12901	Nanotechnologies -- Guidance on safe handling and disposal of manufactured nanomaterials
ISO/CD 29701	Nanotechnologies -- Endotoxin test on nanomaterial samples for in vitro systems

Table 4.4 ISO TC 229 standard documents under development relevant to JWG3 activities

4.4. Voluntary Measures

The current attitude of regulatory authorities, at least partially agreed also by other stakeholders, is, as said already, not to build completely new regulations for nanotechnologies, but instead to carefully look at existing provisions and, when necessary, adapting them in view of nanotechnologies. The improvement of instruments to implement legislations is seen as a priority and a "case by case" approach is envisaged whether an high level of uncertainties for the safety of specific materials and products exist.

Lacking specific guidelines or provisions, some authorities and stakeholders envisage, in the mean time, the adoption of a precautionary approach and increased self-responsibility of producers regarding nanotechnologies.

In this context, voluntary safety standards represent the first option to protect human health and the environment while using the time to clarify the needs and develop the required scientific and methodological database.

Today, there are several voluntary measures which are being taken internationally, such as stewardship programmes, risk management systems and code of conducts. Some of them are more specific than others – but all of them should be looked at in the light of the precautionary principle and the industry's self-reliance.

The Code of Conduct of the EC and also the Responsible Nano Code from The Royal Society have an even broader objective, being designed for different kind stakeholders, industry, university, policy makers, civil society organisations. Their aim is to be an high level tool to guide strategic decisions on governance, regulation and control of nanotechnologies.

Their inclusive character make them a promising tool for building of new models of interaction among stakeholders on the governance of technology development.

It is important to note that within the work of OECD-WPMN, the Steering Group N.5 is dedicated to the "Co-operation on Voluntary Schemes and Regulatory Programmes" (see paragraph 4.2.13), with the aim to analyse and provide inputs to the national information gathering programmes and regulatory initiatives regarding nanomaterials and nanotechnologies. Voluntary measures are of different types and following the most know of them are reported.

4.4.1. Codes of conduct

4.4.1.1. European Commission Code of Conduct

On February 7th 2008 the Commission recommended to adopt, on voluntary basis, a Code of Conduct (CoC) for responsible nanosciences and nanotechnologies research. The Recommendation was accompanied by an annex giving definitions, general principles, guidelines on concrete measures to be taken.

The preparation of the CoC has been announced in the first report on the implementation of the EC Action Plan in Mid 2007, and a first draft has been prepared based on the consultation of experts from Member States, of the Forum of National Ethics Councils and of the European Group on Ethics (EGE).

The draft and the paper "Towards a code of conduct for responsible nanosciences and nanotechnologies research" [16] have been the basis for a consultation of stakeholders held from July to September 2007 that gave inputs to the final version of the document.

The starting point of the principles to be set out in the Code of Conduct have been the legal guarantees resulting from the international legislative framework on ethics and human rights (reported in paragraph 3.3.4).

Aim of the CoC is to provide all stakeholders involved or interested in Nanosciences and nanotechnologies a set of general principles and guidelines favouring a responsible and open approach to N&N research. The CoC is *complementary* to existing regulations.

The CoC covers all N&N research activities, at European level, and is targeted to *"Member States, employers, research funders, researchers and more generally all individuals and civil society organisations engaged, involved or interested in nanosciences and nanotechnologies (N&N) research".*

Members stated are invited to follow general principles and guidelines outlined in the CoC and encourage the voluntary adoption of the CoC by all kind of national stakeholders.

The Code should be also an instrument of dialogue among all stakeholders on nanotechnology development, in particular for Europe and Member States in relation with third countries and international organisation.

The seven principle of the CoC are (synthesis):

- Meaning: research activities should be understandable by the public and they should respect fundamental rights and conducted in the intereset of individuals and society;
- Sustainability: research activities should be safe, ethical and contribute to a sustainable development;
- Precaution: research activities should be conducted in accordance with the precautionary principle;
- Inclusiveness: governance of research activities should be guided by the principle of openness to all stakeholders, transparency and respect for the legitimate right of access to information. It should allow the participation in decision-making processes of all stakeholders involved in or concerned by N&N research activities
- Excellence: research activities should meet the best scientific standards;
- Innovation: research activities should encourage maximum creativity and flexibility:
- Accountability: researchers and research organisations should remain accountable for the social, environmental and human health impact of their research.

The document gives also detailed indications and guidelines on actions to be taken to achieve good governance of N&N respect to the principles outlined above.

The actions regards (synthesis from European Commission presentation at the 2008 Swiss Nanoregulation Conference [1]):

- Good governance of the N&N research
    - Stakeholders awareness
    - Favouring an inclusive approach
    - Addressing key scientific priorities (standards, risk assessment, priority to protection and positive impacts, balanced assessment)
    - Prohibition, restrictions or limitations regarding ethical and safety aspects
- Due respect of precaution
    - Protection of people (best practises on safety and labelling, monitoring ELSI)
    - Reduction of uncertainty (research on EHS and ELSI)
- Wide dissemination and monitoring
    - Awareness of all relevant legislation
    - Monitoring at national level and synergies

Considering the long and detailed preparatory work that brought to the definition of the CoC, the wide scope of the initiative and the fact that it has been adopted by one of the economy most investing in nanotechnologies worldwide, the CoC can be very likely considered the most advanced existing model of regulation and governance of nanotechnologies.

[http://ec.europa.eu/nanotechnology/pdf/eu_nano_policy_2004-08.pdf]

4.4.1.2. Responsible NanoCode

The Royal Society, Insight Investment, the Nanotechnology Industries Association and the UK Nanotechnology Knowledge Transfer Network (an initiative sponsored by the UK Government) are the founding organisations of the Responsible NanoCode.

Since 2007, the founding partners have established a specific working group, composed of about 15 organisations from industry and business, academia and science and civil society, for the preparation of the Code of Conduct. The preparatory work included the consultation of several other experts and stakeholders, a series of events and workshops and almost a year of study and comments.

The first version of the Code and an accompanying series of Examples of Good Practice have been released in May 2008, the official launch of the Code has been in October 2008.

The specific behaviour of engineered nanomaterials, the potential unquantified risks and the pervasive character of nanotechnologies are the main reasons that prompt the development of a CoC specific for nanotechnologies.

The objective of the imitative is to develop a voluntary, principles-based Code of Conduct that may be adopted by organisations, both public and private, involved in the research, production, retail and disposal of products using nanotechnologies.
The Code is intended as an high-level tool, targeted to decision-makers of a different kind of organisations, giving strategic guidance on the governance of nanotechnology.

In the premises of the document is underlined that purpose of the Code is not to *"supersedes or replaces the development of future legislation and regulation for nanotechnologies"* but instead to *"provide guidance on best practice for organisations during the transitional period in which the appropriate national and international regulatory frameworks are being evaluated and, if necessary, developed, and to complement any existing regulation."*

Therein, the participating organisations are encouraged to consider the economic and societal effects of their activities in the field of nanotechnology. Besides commercial and scientific/technical questions, broader social and ethical issues shall also be treated.

The Seven Principles of the Code are:

1) *Board Accountability: "Each Organisation should ensure that responsibility for guiding and managing its involvement with nanotechnologies resides with the Board or governing body"*
2) *Stakeholder Involvement: "Each Organisation should proactively engage with its stakeholders and be responsive to their views in its development or use of products using nanotechnologies"*
3) *Worker Health and Safety: "Each Organisation should identify and minimise sources of risk for workers handling products using nanotechnologies, at all stages in the production process or in industrial use, to ensure high standards of occupational health and safety"*
4) *Public Health, Safety and Environmental Risks: "Each Organisation should carry out thorough risk assessments and minimise any potential public health, safety and environmental risks relating to its products using nanotechnologies"*

5) *Social and Ethical Implications and Impacts: "Each Organisation should consider and respond to any social and ethical implications and impacts in the development or sale of products using nanotechnologies"*
6) *Responsible Sales and Marketing: "Each Organisation should adopt responsible practice in the sales and marketing of products using nanotechnologies"*
7) *Engagement with Suppliers: "Each Organisation should engage with suppliers and/or business partners to encourage and stimulate their adoption of the Code and so assure its own ability to fulfil its Code commitments"*

The document provides also examples of Good Practice in the application of the Code. These will be further developed in the next phases of the imitative in a detailed benchmarking framework that will be used to evaluate the level of application of the Code within companies and other organisations.
[http://www.responsiblenanocode.org/]

4.4.1.3. BASF

The Germany based multinational company BASF is working on nanotecnologies since several years and defines itself a leading company in the field of chemical nanotechnology.

BASF R&D activities regards the production and formulation of nanoparticles and the development of nanostructured surfaces and material for several applications, with nano-related products already on the market in sectors as cosmetics, textile, constructions and plastics and several on-going research activities on nanotechnology.

Regarding nanotechnology regulation, BASF view is to *"establish risk-appropriate, solid standards and to support relevant legislation"*. It considers REACH provision the suitable regulatory instruments to regulate nanomaterials, basing on REACH statements that all substances are covered by this provision regardless of their physical state and that on registration, all applications, including those in the nanoscale range, must be included and relevant data submitted.

However, considering that some years will be needed before full application of REACH will be realised, in the transitional period BASF *"trust in the industry's sense of self-responsibility"* and for this purpose has developed a Code of Conduct dedicated to Nanotechnologies.

The Code of Conduct is meant has a guidance for all the company's employees worldwide and a commitment of the company towards customers, business partners and society.

BASF CoC highlights aspects of occupational and consumer safety, environment protection, transparent information and dialogue. The principles and commitments of BASF CoC are (synthesis):

- Careful identification and evaluation of any potential risks related to the use of nanotechnologies to take the appropriate measures to safeguard humans and the environment.
- Early identification of source of risks in occupational settings and elimination of these risks using the appropriate measures.
- Involvement in the development of a scientifically based database for the assessment of potential risks as well as in the improving and refining of product-based testing and assessment methods.
- Transparency in safety procedures along the whole supply chain
- Markets products only if safety guaranteed on the basis of all available scientific information and technology
- Economic considerations do not take priority over safety and health issues and environmental protection
- Commitment to transparency and engagement in public debate
- Immediate disclosure of new findings to authorities and the public

The company has developed a website dedicated to nanotechnology products, including information on the safety procedures adopted at the workplace and information on risk assessment of the nanomaterials used by the company.

A clear distinction is made between nanostructured materials, and materials that contain nanoparticles. From BASF website: *"Nanostructured materials have nanoscale surfaces, cavities or structures. These nanostructures present no risk. Examples include nanoporous foams, nanostructured construction materials or nanopore systems organized in the form of cubes."*.

Regarding dialogue and sharing of information with stakeholders, BASF is involved in organizations such as the German chemical industry association (VCI), the European Chemical Industry Council (Cefic), and the American Chemical Council (ACC) and participate in OECD and ISO working parties on nanotechnologies.

[http://www.basf.com/group/corporate/en/content/sustainability/dialogue/in-dialogue-with-politics/nanotechnology/index]

4.4.1.4. IG DHS

In Switzerland, the retailer's organisation (IG-DHS[41]), in collaboration with the Innovation Society, has developed a code of conduct dealing with the handling of nanomaterials in consumer products, in particular regarding food and packaging products.

The signing retail companies commit to the precautionary principle and the highest possible transparency for consumers. In the light of a lack of specific legal regulations the retailers require their suppliers to disclose information on nanomaterials. Moreover, the code contains specific requirements for the risk management of manufacturers and suppliers.

The two pages CoC defines both obligations for IG DHS members and requirement for manufacturers and suppliers. The former regards (in relation with nanotechnology):

- personal responsibility (product safety as a top priority)
- Procurement of information (request of information to manufacturers and suppliers)
- Information for consumers (open information, ensuring products characterised as nanotechnological actually do contain applications of nanotechnology)

The CoC requires manufacturers and suppliers to consider nanotechnology in their products risk management procedures and to disclose relevant information on nano-related products to the production and distribution chain. In particular IG DHS requires manufacturers and suppliers the following minimum set of information:

- *Benefit or added value of the "nano-product" compared to the conventional product*
- *Evidence of the nanospecific effects and/or modes of action*
- *Technical specifications (physical-chemical data, e.g. size, structure, etc.)*
- *Risk potential for humans, animals and the environment (toxicology, ecotoxicology, degradability, disposal, etc.)*

[http://www.innovationsgesellschaft.ch/media/archive2/publikationen/Factsheet_CoC_engl.pdf]

[41] Among the members of IG DHS the most important actors in the Swiss retailing, such as Coop, Denner, Manor, Migros and Charles Vogele.

4.4.2. Nanoscale Materials Stewardship Programs

In some countries authorities aim at collecting information from the industry on the manufacturing and use of nanomaterials on a voluntary basis. Such information would complement fundamental research and allow for data in the areas of applications.

4.4.2.1. DEFRA, UK

The UK Department for Environment, Food and Rural Affairs (DEFRA), with other UK Government departments and agencies, launched in September 2006 the UK's Voluntary Reporting Scheme (VRS). The VRS concluded in September 2008.

The reporting scheme aims to build an evidence base on health, environmental and safety issues related to nanomaterials in order both to give inputs to the research programme on EHS issues supported by the UK Government and to develop, in a short time, appropriate controls and regulatory instruments for nanomaterials.
The objectives of the UK's VRS can be summarised as following [1]:

- Identify organisation working with nanomaterials
- Build an inventory of nanomaterials manufactured, imported and used in the UK
- Collect information on nanomaterials, their properties and hazards
- Identify gaps in EHS research
- Provide reassurance and build consumer confidence

The reporting scheme has been designed for companies or organisations involved in manufacturing, using, importing or managing wastes consisting of engineered nanoscale materials and it is focused on engineered nanoscale materials that are free at any stage of a product's life-cycle, in detail materials that [4]:

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

Information can be submitted through a data submission form (available on DEFRA website), but additional data can be also added. Requested information regards: identity of the nanomaterial, use, benefits and exposure pathways, physico-chemical properties, toxicology, ecotoxicology information, risk management practices.

At August 2008 DEFRA received submissions from 11 organisations, 9 from industry and 2 from academia [6].

In view of DEFRA, the reasons for low participation to the scheme have been the too wide objectives, limited resource (above all regarding participation of SMEs), problems related to confidentiality of data, lack of incentives and lack of information on the applicability of the scheme[42].

The VRS evalutation phase is currently on-going, however the UK government has already expressed its commitment to continue and improve the scheme. Various options are considered to encourage further participation, including making it mandatory or introducing early registration for REACH regulation for UK companies dealing with nanomaterials.

Inputs from the work of WPMN Steering Group 5 (Reporting Schemes and Regulatory Programmes) will be also used to this end.

[42] http://www.defra.gov.uk/environment/nanotech/pdf/nrcg-meeting16-081006.pdf

[http://www.defra.gov.uk/ENVIRONMENT/nanotech/policy/index.htm]

4.4.2.2. EPA, USA

The US Environmental Protection Agency (EPA) launched on January 2008 the Nanoscale Materials Stewardship Program (NMSP) as part of its oversight of nanomaterials under the Toxic Substances Control Act (TSCA), the provision dedicated to regulation and control of chemical substances in the USA [2].
The program has been the result of a long preparatory work, started from an initial public meeting on June 2005 and including consultation of experts, request and integration of public comments and the preparation of various supporting documents. Among them the NSMP concept paper, and the NSMP inventory paper (or "TSCA Inventory Status of Nanoscale Substances") that defines the substances that can be included in the program [43].
The program objective are clearly reported in the NSMP concept paper:

- *Assemble existing data and information from manufacturers and processors of existing chemical nanoscale materials;*
- *Identify and encourage use of risk management practices in developing and commercializing nanoscale materials;*
- *Encourage the development of test data needed to provide a firmer scientific foundation for future work and regulatory/policy decisions.*
- *Encourage responsible development.*

The collection of information on type, use, quantities and available risk assessment data on nanomaterials would help to better understand and prioritise research and regulatory activities on their safety.

The program has been designed for participants who already manufacture, process, use, or import (for commercial purposes) nanomaterials and for researchers who develop or study engineered nanomaterials.

Organisations can participate to the basic program or the in depth program. In the former case EPA asks the submission of information and data on nanomaterials, through an optional data submission form (available on EPA website) or any other reporting format. Requested information regards nanomaterials physical and chemical properties, hazard, exposure, use and risk management practises or plans.

The latter program follows the basic reporting phase and is intended to identify interested stakeholders willing to collaborate with EPA for the development of in-depth risk assessment data on specific set of nanomaterials (mainly identified in the first phase).
The deadline for the basic program was July 2008, while the full NSMP will end after two years (January 2010).

At September 2008, EPA received submissions under the basic program from 22 organisations, covering more than 93 nanoscale materials, with additional commitments to participate from 10 other organisations to participate. Three submission have been received under the in-depth program. The type of organisations that participated have been large companies, small or start-up companies and trade associations.

Even though there has been collected information on a large range of nanomaterials, the participation to the program has been far below EPA early expectations (the initial target was 240

[43] *"Nanoscale materials that are either new or existing chemical substances (as determined by the status of the substance on the TSCA Chemical Substances Inventory) can be included in the program. See TSCA Inventory Status of Nanoscale Substances – General Approach (2008)"* - http://www.epa.gov/oppt/nano/nmsp-inventorypaper2008.pdf

submissions from about 180 companies), above all regarding SMEs participation. The reasons for the poor result are likely the same put forward by DEFRA.

EPA will publish an interim report on NSMP after one year from the start of the program and a detailed report with program evaluation and indication of further initiatives in two years [1].
[http://www.epa.gov/oppt/nano/stewardship.htm]

4.4.3. Risk management systems

4.4.3.1. Cenarios

CENARIOS® (Certifiable Nanospecific Risk Management and Monitoring System) enables the potential risks and opportunities involved in nanotechnology and their possible impacts on people to be identified, analysed and assessed rapidly and comprehensively.

CENARIOS is designed to complement existing risk management systems and was developed in 2006 by TÜV SÜD (Munich) and the Innovation Society (St.Gallen) to cater to the particular requirements of nanotechnology risk assessment.

The system integrates the latest scientific and technological developments into risk management, thus enabling objective risk assessment to be performed in a rapidly developing market characterised by a high level of uncertainty. An up–to-date evaluation will be applied and combined with a foresight element, monitoring strategic and relevant risk areas (toxicity, regulation, consumer attitude, etc). It sets the basis for strategic decision making processes under conditions of high uncertainty.

It covers four individually combinable modules:

- **Risk Assessment / Risk Evaluation.** All available data are reviewed to assess products and production processes for health, environmental and occupational safety risks, and findings are documented in a comprehensive product and process risk portfolio.
- **360° Risk Monitoring System.** To provide a comprehensive outlook of strategically relevant developments in a highly dynamic environment, the risk monitoring applies a prospective analysis to future relevant risk fields, thus ensuring timely recognition and integration of relevant trends into risk management. Assessment covers risk trends in the fields of health and safety (toxicology, occupational safety), environmental protection, but also trends in society, regulation (e.g. tightening of legal regulations, impending liability risks etc.) and observations in technology and the respective market segments.
- **Issues Management & Communication.** In the case of a crisis, risk communication plays a key role. This module includes tools for crisis prevention and measures for professional crisis management (documentation and, if necessary, training).
- **Certification**. CENARIOS® is certified and audited regularly in an independent quality standard process in which a TÜV SÜD certificate is awarded. The annual recertification ensures that continuous improvement of the risk management takes place and enhances communicability of the efforts.

By covering the state of the art of science and technology and by including societal, regulatory and market related risks, CENARIOS is especially suitable to take control of complex technology risks under conditions of high uncertainty and highly dynamic markets.

[http://www.innovationsgesellschaft.ch/index.php?page=88]

4.4.3.2. Nano Risk Framework

The NANO Risk Framework has been created by a multidisciplinary team from DuPont and Environmental Defence. The activity started in Mid 2005, the final project report was published in June 2007 and the framework is now currently adopted by DuPont for its research and production activities in nanotechnologies.

DuPont view on nanotechnoloy regulation in relation with the development of the framework is clearly stated in the website dedicated to the project *"a comprehensive, consistent, and appropriate regulatory policy for nanomaterial development is needed. To the extent that the Framework helps in the development of such a policy – as one piece of input in an open process – DuPont (and Environmental Defence) support that goal".*

The framework objective is to realise a practical risk assessment guidance for identifying, managing, and reducing potential EHS risks of engineered nanomaterials across all stages of a product's lifecycle, enabling the development of data profiles of nanomaterials properties, inherent hazards, and exposure potential. It focus on engineered nanoscale materials, both as single materials or ingredient in a product.

The NANO Risk Framework puts a strong focus on toxicity and also requires the user to perform such tests; it is therefore suitable in first place for large companies.

A primary goal of the initiative is to diffuse and share this procedure to a wide range of stakeholders, any kind of company actively working with nanomaterials and nanoproducts but also other stakeholders as government agencies, interest groups and civil society organisations.
Sharing of information, transparency and accountability of risk management procedures are considered in the framework as key elements to build confidence among stakeholders on nanotechnology.

A website with relevant information, tools and methods of the framework is available, including case history of framework's application on some nanomaterials (titanium dioxide, Carbon nanotube, nano-sized zero-valence iron).

The procedure is based on six steps (synthesis from Dupont presentation at Nanogovernance 2008 Conference [9]):

- Describe Material and expected application
  (especially note differences between the material and its macro counterpart)
- Profile Lifecycle(s)
  (Consider the material's full lifecycle, develop physical-chemical properties, hazard and exposure profiles)
- Evaluate Lifecycle risks
  Review and evaluate hazard and exposure risks, identify knowledge gaps
- Assess Risk Management
  determine needed level of protection, adequacy of current practises, best practises, monitoring, compliance and reporting tools
- Decide, Document, and Act
  review information collected, plan and decide whether and how to proceed (considering business, legal and stakeholder issues), document chosen procedures
- Review and Adapt
  monitor decisions on a regular basis

An output worksheet is provided with the framework, as a template to organise and share information and procedures.
[http://www.nanoriskframework.com]

4.5. Stakeholders Initiatives and Positions

Some organisations from the research and business community, or representing in different ways the civil society, have in the last years expressed their views and positions regarding the regulation of nanotechnology.

The recent initiatives of governmental agencies has also prompted these organisations to further comment and discuss these issue, providing specific inputs to their work. Hereafter is a brief overview about the position of these organisations.[44]

4.5.1. Industry, business, professional and research organisations

4.5.1.1. American Bar Association (ABA)

ABA is the largest voluntary professional association in the world; its mission is to be the national representative of the legal profession, serving the public and the profession by promoting justice, professional excellence and respect for the law.

ABA-SEER (Section of Environment, Energy, and Resources) established in 2006 the "Nanotechnology Project", to give a comprehensive review of the core federal environmental statutes and assess their suitability regarding EHS risks of nanotechnology. Up to know, it has published seven white papers on EPA statutes most relevant for nanotechnology (CAA, CERCLA, CWA, EMS, FIFRA, RCRA, TSCA) and is preparing other 4 white papers on FDA and other agencies statutes (FPQA -Food Quality Protection Act, FFDCA-The Federal Food, Drug, and Cosmetic Act, NEPA -The National Environmental Policy Act, ESA-The Endangered Species Act). Their reports give sound, objective analysis about the ability of different US statutes to regulate nanotechnology from a legal point of view. They underlined the difficulties in implementing legislations based on current knowledge gaps on nanomaterials (as limits in risk assessment methods and use of mass concentrations as trigger for legislation).
[http://www.abanet.org/environ/nanotech]

4.5.1.2. American Chemistry Council (ACC)

ACC represents companies engaged in the business of chemistry. It formed in 2005 a Nanotechnology Panel, that consists of companies engaged in the manufacture, distribution, and/or use of chemicals and have a business interest in the products of nanotechnology.

A panel on nanotechnology is developing recommendations for EPA and the chemical industry regarding environmental, health, and safety issues and regulatory guidelines for nanomaterials, in particular it's supporting the EPA-NMSP.

Their position paper on nanotechnology states that to deal with nanomaterials it is necessary to:

[44] The list is not intended to be exhaustive of all organisations dealing with governance and regulatory issues related to nanotechnologies. Those reported here are the result of the search performed for the purpose of this report. Moreover, among the organisations identified, only those for which positions papers and opinions on these issues are publicly available and relevant to the objective of this chapter have been reported. Also authors (and their organisations) of articles and reviews on regulation and governance of nanotechnology are generally not reported in this list. However, some of these articles have been used to prepare this report and thus are included in the report bibliography.

increase funds for EHS research, promote international regulatory coordination and "convergence", assess existing regulatory framework for chemical manufacturing and use and promote responsible laws, regulations, guidance and standard. ACC members should adhere to product stewardship principles of the ACC's Responsible Care Management Systems, applying also to nanotechnology. [http://www.americanchemistry.com/s_responsiblecare/sec.asp?CID=1298&DID=4841],

4.5.1.3. European Chemicals Industry Council (CEFIC)

CEFIC, based in Brussels, is the organization representing the European chemical industry. CEFIC represents, directly or indirectly, about 29,000 large, medium and small chemical companies which employ about 1.3 million people and account for nearly a third of world chemical production.

CEFIC has established a working group dedicated to nanomaterials, and on November 2006 issued a position paper on nanotechnology and is actively participating in the ISO, CEN, OECD Working groups for nanotechnology. In June 2008 CEFIC organised a stakeholder engagement workshop dedicated to nanomaterials. Key elements of CEFIC position on nanomaterials are:

- Current risk assessment methods in principle provide a suitable framework for the assessment of nanomaterials, but new approaches and methods may need to be developed.
- Upcoming REACH legislation offers a sufficient framework for the evaluation of new and existing nanomaterials. Whether scientific evidence would indicate the need for modifications of current legislation, the EU chemical Industry will constructively cooperate with all stakeholders toward its improvement.
- Support of the review of existing guidelines to determine if they are adequate for nanomaterials.
- Call for an international approach for the management of nanomaterials risks, led by OECD
- Commitment to a proactive engagement with stakeholders to address EHS and ELSI issues.

[http://www.cefic.be]

4.5.1.4. Society for Chemical Engineering and Biotechnology (DECHEMA)

DECHEMA is a not for profit scientific and technical organisation based in Germany, with over 5000 private and institutional members. Its aim is to promote research and technical advances in the areas of chemical engineering, biotechnology and environmental protection.

DECHEMA and VCI have established as early as 2003 the joint working group "Responsible Production and Use of Nanomaterials" which consists of high-level European academic and industrial experts and is regularly joined by representatives from German authorities. The group shares scientific findings and best practices on safety aspects of the production and use of nanomaterials.
[http://www.dechema.de]

4.5.1.5. German Chemical Industry Association (VCI)

VCI represents the politico-economic interests of 1,600 German chemical companies and German subsidiaries of foreign enterprises, representing over 90% of the entire German chemical industry. The German Chemical Industry is committed to a responsible production and use of nanomaterials.

To support member companies, and customer companies in the value chain, to address the health, safety and environmental aspects of nanomaterials throughout their entire life cycle. VCI, on March 2008, has published in March 2008 the document "Responsible Production and Use of Nanomaterials" that provides guidance for a good product stewardship of nanomaterials (including information on Product Safety and Regulatory Compliance, in particular regarding REACH, guidances on safety data sheets for nanomaterials, a roadmap for safety research and standardisation.
[http://www.vci.de]

4.5.2. Academia, Research organisations, "Think Thanks"

4.5.2.1. Environmental Law Institute (ELI)

The Environmental Law Institute is an independent, non-profit research and educational organization.

In 2007, the Institute has published a report (with PEN – Project on Emerging Technologies) on end-of-life regulation of nanotechnology, analysing specific EPA statutes such as CERCLA and RCRCA. Since 2005 the Institute calls for an effective governance plan for nanotechnologies, which should provide interim measures, focus on data development, inform and involve stakeholders and public in general, and overall adopt a lifecycle approach, considering multi-statute regulation, for managing risks posed by nanomaterials.

This approach includes regulatory and voluntary programs under existing environmental statutes, corporate stewardship, tort liability, state legislation, disclosure, liability insurance, and international measures.
[http://www.eli.org/Program_Areas/nanotech.cfm]

4.5.2.2. Centre for Business Relationships Accountability Sustainability and Society (ESRC-BRASS)

The Economic and Social Research Council (ESRC) is an independent organisation, established by Royal Charter and partially funded by the UK Government, that funds research and training in social and economic issues. The ESRC Centre for Business Relationships, Accountability, Sustainability and Society (ESRC-BRASS) published two authoritative reports on nanotechnology governance and regulation:

- "Overview of the Framework of Current Regulation affecting the Development and Marketing of Nanomaterials (2006)
- "Nanotechnology: From The Science To The Social: The social, ethical and economic aspects of the debate" (2007)

Key recommendations on regulation (from the first report) includes adapting current regulation, develop an integrated approach among different regulations, develop and improve international standards and guidance. Moreover, at the light of the general lack of information about the risks associated with nanotechnology, the reports underlines the need to examine specific properties of free, engineered nanomaterials and assess their associated risks prior to place these materials on the market.
[http://www.brass.cf.ac.uk/projects/Resource_and_Technology_Management/resource-and-technology-management-for-sustainability--Nanotechnologies--Current-areas-of-research.html]

4.5.2.3. International Council on Nanotechnology (ICON)

ICON is an international, multi-stakeholder organization whose mission is to assess, communicate, and reduce the environmental and health risks of nanotechnology while maximizing its societal benefit. Through the engagement and consultation of relevant stakeholders worldwide, ICON provides updated assessments of EHS research needs, risk management best practises and development of standard related to nanotechnology. Since 2006 ICON has been hosting the development of an internet site on occupational practices for the safe handling of nanomaterials (utilizing a software platform "GoodWiki: Good Occupational Practices for the Nanotechnology Industry"[45]), a database om EHS research, called The Virtual Journal of Nanotechnology

[45] http://icon.rice.edu/projects.cfm?doc_id=12207

Environment, Health and Safety[46], and has published various relevant reports on nanotechnology and occupational safety.
[http://icon.rice.edu/]

4.5.2.4. International Risk Governance Council (IRGC)

IRGC, an independent foundation, is a public-private partnership that supports governments, businesses, and other organizations worldwide. IRGC aims to help improve the anticipation and governance of global, systemic risks.

With respect to the development of nanotechnology and nanoscale products, IRGC is developing frameworks for adequate risk governance approaches at the national and international levels, and has conducted a surveys on the role of governments, non-governmental organizations, industry, and research organizations in nanotechnology risk governance. In 2007 published the IRGC white paper on nanotechnology governance.
[http://www.irgc.org/Nanotechnology.html]

4.5.2.5. Project on Emerging Nanotechnologies (PEN)

The Project on Emerging Nanotechnologies is a partnership between the Woodrow Wilson International Center for Scholars and the Pew Charitable Trusts, of USA. The Project aim is that of helping to ensure that as nanotechnologies advance, possible risks are minimized, public and consumer engagement remains strong, and the potential benefits of these new technologies are realized.

The project has published a relevant number of reports and publications dedicated to governance, policies and regulatory issues related to nanotechnology. It has provided in the past years detailed analysis on the development of nanotechnology, in particular highlighting gaps and needs in terms EHS research, regulatory authorities (mainly in USA), governance. It has become one of the most cited source of information about these themes worldwide. Different testimony from the Project to the U .S. congress about governance & regulation issues are available on the project website.

In one of its latest reports "Nanotechnology Oversight: An Agenda for the Next Administration", published in July 2008 the project defines a roadmap for the US administration, which indicates immediate and longer term steps necessary to face the current shortcomings in nanotechnology governance.

Most of the existing products using nanotechnology are considered under-regulated and the project underlines that both current funding (and activity) for EHS research and Agencies engagement in improving and adapting current legislation to nanotechnology, are largely inadequate.
It asks both for short term actions using existing legislative options, and for a longer term, in depth revision of the regulatory system specific for nanotechnology.
[http://www.nanotechproject.org/]

4.5.2.6. Royal Society and Royal Academy of Engineering

In June 2003 the UK Government commissioned the Royal Society and the Royal Academy of Engineering to carry out an independent study of likely developments and whether nanotechnology raises or is likely to raise new ethical, health and safety or social issues which are not covered by current regulation.

The aims of the Royal Society and Royal Academy of Engineering study were to:

1. define what it is meant by nanoscience and nanotechnology;
2. summarise the current state of scientific knowledge about nanotechnology;

[46] http://icon.rice.edu/virtualjournal.cfm

3. identify the specific applications of the new technologies, in particular where nanotechnology is already in use;
4. carry out a forward look to see how the technology might be used in future, where possible estimating the likely time scales in which the most far-reaching applications of the technology might become reality;
5. identify what environmental, health and safety, ethical or societal implications or uncertainties may arise from the use of the technology, both current and future;
6. identify areas where regulation needs to be considered.

The *final report*[47] was published in July 2004 and assesses how this emerging field should be regulated as it develops. The report lists a series of recommendations, which (among many others) include that…

- all relevant regulatory bodies consider whether existing regulations are appropriate to protect humans and the environment from the hazards outlined in this report and publish their review and details of how they will address any regulatory gaps.
- regulatory bodies and their respective advisory committees include future applications of nanotechnologies in their horizon scanning programmes to ensure any regulatory gaps are identified at an appropriate stage.
- the ingredients lists of consumer products should identify the fact that manufactured nanoparticulate material has been added.
- the consideration of ethical and social implications of advanced technologies (such as nanotechnologies) should form part of the formal training of all research students and staff working in these areas […].
- the Government initiates adequately funded public dialogue around the development of nanotechnologies.
- the Chief Scientific Advisor should establish a group that brings together representatives of a wide range of stakeholders to look at new and emerging technologies and identify at the earliest possible stage areas where potential health, safety, environmental, social, ethical and regulatory issues may arise and advise on how these might be addressed.

In February 2005, the Government responded[48] to the report and agreed in most points, however no new funding for the essential research required to underpin this regulation has been announced. The Government has made an important commitment to a public dialogue on nanotechnologies which will inform both the direction of research and development and progress on regulation.

In 2008, the process resulted in a statement by the UK Government about nanotechnologies[49], which indicates a series of tasks and duties and discusses specific issues such as regulatory reviews, labelling, stakeholder engagement and many others (a synthesis is reported in paragraph 4.2.3). [http://www.nanotec.org.uk]

4.5.3. Non-governmental, consumer, public health, environmental, and labour organisations

4.5.3.1. Alliance of Social and Ecological Consumer Organisations (ASECO)

The Alliance of Social and Ecological Consumer Organisations is an association of consumer organisations, with member coming from 12 European Countries.

[47] http://www.nanotec.org.uk/report/Nano%20report%202004%20fin.pdf

[48] http://www.berr.gov.uk/files/file14873.pdf

[49] http://www.dius.gov.uk/policy/documents/statement-nanotechnologies.pdf

In 2006 ASECO published a position paper on nanotechnology, basing on consumers' rights principles declared in the United Nation Guidelines for Consumer Protection and on the United Nation Millenium Goals.

Among the elements underlined in the articulated ASECO paper:

- Encourage research on EHS and risk assessment, in particular regarding occupational exposure
- Favour international consensus on regulation, above all regarding standards for nanotechnologies
- Revise and adapt the EU regulatory frame, also considering the establishment of a dedicated authority for nanotechnologies
- Agree with consumers and social (local) communities research and regulation of nanotechnologies
- Apply the precautionary approach in approving marketing of consumer nano related products
- Urgently adopt appropriate labelling provisions for nano-related products
- Promote beneficial applications of nanotech, in particular in the medicine and environment sectors

[http://aseconet.org/index.php?option=com_content&task=view&id=18&Itemid=28]

4.5.3.2. Environmental Defence (ED)

Environmental Defence is an U.S.A. not for profit organization which links "*science, economics and law to create innovative, equitable and cost-effective solutions to society's most urgent environmental problems.*"

Among ED activities regarding nanotechnology, there can be cited the development of Nano Risk Framework with DuPont, the engagement in developing international standards through the collaboration with OECD, ASMT, ANSI, ISO, various inputs and proposal to EPA, National Nanotechnology Initiative (NNI) and other governmental agencies, the updating of ED Nano Blog on nanoregulation.

The organisation considers nanomaterials under-regulated, in particular in the case of EPA statutes, (claiming for specific revisions of TSCA statutes regarding nanomaterials). Above all, ED asks policy makers to use existing capabilities and authorities to deal with potential risks of nanomaterials before they are incorporated into products for commercial production.
[http://www.edf.org/article.cfm?ContentID=5135]

4.5.3.3. ETC Group

The ETC Group is an international civil society organization based in Canada, dedicated to the conservation and sustainable advancement of cultural and ecological diversity and human rights. To this end, ETC group supports socially responsible developments of technologies useful to the poor and marginalized and it addresses international governance issues and corporate power.

The group has been probably the first CSOs publicly asking for a moratorium of nanotechnology (in 2003), until a "transparent global process" for evaluating nanotechnology's various implications has been established, in conjunction with calling for the development of a legally binding, international body for the evaluation of emerging technologies (the proposal is detailed in the "NanoGeoPolitics…" report)

In April 2007 ETC signed, with other CSOs, a petition to reject the DuPont-Environmental Defence Nano Regulatory Framework. ETC joined NanoAction since its establishment and they agree with the position express by this group on nanoregulation.

ETC has published reports on various nanotechnology applications with clear recommendation regarding the need for a specific nano policy, among them:

- The Big Down- Atomtech: Technologies Converging at the Nanoscale, January 2003.
- Down on the Farm: The Impact of Nano-Scale Technologies on Food and Agriculture, November 2004.
- NanoGeoPolitics ETC Group Surveys the Political Landscape, August 2005.
- Nanotech Rx – Medical Applications of Nano-scale Technologies: What Impact on Marginalized Communities?, September 2006.

[http://www.etcgroup.org/en/issues/nanotechnology.html]

4.5.3.4. European Trade Union Confederation (ETUC)

The European Trade Union Confederation represents 82 National Trade Union confederations from 36 European countries, as well as 12 European industry federations, with a total of 60 million members. ETUC is one of the European social partners and is recognised by the European Union, by the Council of Europe and by EFTA as the only representative cross-sectoral trade union organisation at European level.

In June 2008 ETUC has published a resolution on "nanotechnologies and nanomaterials" with which, while recognising both potential benefits and risks of nanotechnology, calls for clear and specific actions regarding nanoregulation, in particular:

- Substantial increase of support and funding for research on EHS issues.
- Urgent development of standardised terminology for nanomaterials.
- Obligation to manufactures to determine whether insoluble or biopersistent nanomaterials can be released from them at all stages of their life cycle and to ensure safety of products along the whole life cycle.
- Full compliance (regarding nanomaterials) with REACH's "no data, no market" principle, in particular through the amendment of 1tonn/year threshold for nanomaterials to include all nanomaterials in registration, and the requirement of a Chemical Safety Report for all substances for which a use at nanometer scale has been identified.
- Amendment of Chemical Agents Directive 98/24/EC on health and safety at work with specific provisions able to ensure safety of worker using nanomaterials. Inclusion of information on nanomaterials in safety data sheets.
- Labelling of all consumer products with manufactured nanoparticles which could be released under reasonable and foreseeable conditions of use or disposal of the product.

ETUC welcomes Industry Voluntary Initiatives and Responsible Codes of Practices, but it will endorse such initiatives only if workers' representatives are involved, if sanctions are foreseen in case of non-compliance, if companies participating disclose hazard and risks information and commit themselves to be fully accountable for liabilities incurred from their products.
[http://www.etuc.org/IMG/pdf_ETUC_resolution_on_nano_-_EN_-_25_June_08.pdf]

4.5.3.5. International Centre for Technology Assessment (CTA) - NanoAction

The International Centre for Technology Assessment is a not for profit, bi-partisan organization, based in USA. committed to provide the public with full assessment and analysis of technological impacts on the society. With reference to nanotechnology the Centre has been in the last years particularly active:

- In May 2006, with other CSOs organisations, CTA issued a legal petition asking the FDA to address the EHS risks of nanomaterials in consumer products, particularly nanocosmetics and nano-sunscreens. The petition calls for comprehensive nanomaterial-specific

regulations, classification of nanomaterials as new substances, mandatory nanomaterial product and ingredient labelling, nano-specific toxicity testing. In particular, the petition clearly asks to classify sunscreens including nanomaterials (currently regulated by FDA in the category of "human drugs") as new drugs, forcing manufacturers to submit dedicated applications for these products.

- In May 2008, with other CSOs organisations, the Centre issued another a legal petition to EPA demanding the Agency to use its pesticide regulatory authority to regulate numerous consumer products now using nano-sized versions of silver. It asked, in particular, to classify nano-silver as a new substance and regulate nano-silver products as new pesticides, requiring for these products strict pre-market approval. Current products would have to be removed until and unless they receive EPA approval.
- With the promotion of NanoAction, a broad coalition of civil society, public interest, environmental and labour organizations, CTA collects opinions and positions on nanotechnology developments

NanoAction coalition is composed of about 40 civil society organisations worldwide, among them some of the organisations that in the last years have been most active in the debate on nanotechnology governance and regulation (as ETC, Friends of the Earth, Greenpeace).

In July 2007, NanoAction published a position paper "Principles for the Oversight of Nanotechnologies and Nanomaterials", that gives a clear picture of the opinion of a relevant number of CSOs around the world on this technology.

Overarching objective of the initiative is *" seeks to halt the commercialization of nanotechnology until products containing nanoparticles have been proven safe. NanoAction also seeks to force Federal regulatory agencies to adopt an accurate and standardized definition of nanotechnology and to regulate emerging nanotechnologies as they would with other materials whose safety has not been determined."*

The declaration outlines eight fundamental principles for an effective oversight and assessment of nanotechnology:

1) **Precautionary Foundation**: Product manufacturers and distributors must bear the burden of proof to demonstrate the safety of their products: if no independent health and safety data are available, then no market approval.
2) **Mandatory Nano-specific Regulations**: Nanomaterials should be classified as new substances and subject to nano-specific oversight. Voluntary initiatives are not sufficient.
3) **Health and Safety of the Public and Workers**: The prevention of exposure to nanomaterials that have not been proven safe must be undertaken to protect the public and workers.
4) **Environmental Protection**: A full lifecycle analysis of environmental impact must be completed prior to commercialization.
5) **Transparency**: All nano-products must be labelled and safety data made publicly available.
6) **Public Participation**: There must be open, meaningful, and full public participation at every level.
7) **Inclusion of Broader Impacts**: Nanotechnology's wide-ranging effects, including ethical and social impacts, must be considered.
8) **Manufacturer Liability**: Nano-industries must be accountable for liabilities incurred from their products.

[http://www.icta.org/nanotech/index.cfm http://www.nanoaction.org/nanoaction/index.cfm]

4.5.3.6. Friends of the Earth (FoE)

Friends of the Earth (FoE) International is a federation of environmental organisations, with member groups in over 72 countries. Using its words it challenges "*the current model of economic and*

corporate globalization, and promote solutions that will help to create environmentally sustainable and socially just societies."

FoE is one of the NGOs most active in the debate on nanotechnology. It has published various reports and positions papers on the subject, in particular :

- Nanomaterials, Sunscreens and Cosmetics: Small Ingredients, Big Risks, May 2006.
- Out Of The Laboratory And On To Our Plates: Nanotechnology in Food & Agriculture, April 2008.
- Mounting evidence that carbon nanotubes may be the new asbestos, August 2008

These reports are based on a in depth analysis of the market diffusion of products using nanomaterials, of warnings from authoritative scientific sources on potential risks of these nanomaterials, and of regulatory instruments applying along the lifecycle of these products.

They underline the current uncertainty on risks posed by some of these nanomaterials and the lack of specific regulation able to evaluate, prevent or limit the marketing of products for which there is not substantial evidence about their safety.

They also emphasise the fact that despite the gaps in the current regulatory framework to deal with nanomaterials are generally known and recognized since some years (also by regulatory authorities and policy makers), no specific regulatory provisions have been set up so far.

Each of these reports give a particular emphasis on specific products, but in all cases the approach suggested for the regulation of nanotechnology is the one clearly expressed also in the NanoAction Petition (see above).

It is worth to mention, for their implications some of the conclusion on their last report on carbon nanotubes. Given that some scientific studies indicate the potential for nanotubes to cause asbestos-like diseases or acute toxicity, FoE call for:

- Immediate moratorium on the commercial use of CNT and nano-related products using CNT, until research can demonstrate whether or not there is any safe level of exposure to them.
- Specific regulation to protect workers, the public and the environment, before further commercial use of CNT, development of new nanotechnology, including:
    - nano-specific safety assessments for nanotubes and all other manufactured nanomaterials;
    - requiring full physico-chemical characterisation and a comprehensive range of safety tests.
- Use of appropriate metrics for nanomaterials (i.e. particles surface area and number of particles rather than mass).
- Definition of new, clearly enforceable, permissible exposure levels.
- Development of cost-effective, reliable technologies for routine occupational exposure measurement before commercial production of nanotubes can proceed.

Currently, FoE actively participates in the NanoAction initiative.
[http://nano.foe.org.au/node/60]

4.5.3.7. Greenpeace

Greenpeace is an independent global campaigning organisation very vocal in asking for actions aimed to protect and conserve the environment. It has been one of the first NGOs calling for public consultation on nanotechnology development, and to underlain the socio-political concerns related to its development.

In 2003 Greenpeace published the report "Future Technologies, Today's Choices"[50] and participated in several event and initiatives related to nano regulation. In a position paper published in February 2007, highlighting that no regulatory framework has yet been developed , they called for:

- A moratorium on nanotech, in absence of any established regulatory framework.
- The development of a comprehensive national and/or international regulation specifically addressing EHS issues and the broader social and ethical issues related to nanotechnology, based on a strict precautionary approach.

Currently their position is expressed in the NanoAction petition.
[http://www.greenpeace.org/raw/content/denmark/press/rapporter-og-dokumenter/nanotechnology-policy-positi.pdf]

4.5.3.8. International Union of Food Workers (IUF)

The International Union of Food Workers is a federation grouping 336 trade unions, representing over 12 million workers in 120 countries. In March 2007, IUF called for a moratorium on the use of nanotechnology in food and agriculture. In addition to health and environmental risks of nanomaterials, IUF expressed concern about the social and economic implications of nanotechnology in food and agriculture.
[www.iuf.org - http://nano.foe.org.au/node/195]

4.5.3.9. Legambiente

Legambiente is an Italian, non-profit association created in 1980 for the safeguard and the sound management of the environment and for the promotion of sustainable lifestyle, production systems and use of resources. Legambiente is the most widespread environmental organisation in Italy, with more that 1000 active local groups and 110,000 members.
The Association is a partner of the EU project Nanocap (Nanotechnology Capacity Building) and has recently published its position on nanotechnologies.
Legambiente aims at a responsible development of Nanotechnologies through a complete tracciability of their life cycle (research - production – consumption). Countries and industries must invest in research activities to avoid any risk for workers and consumers. Meanwhile, they must adopt the precautionary principle, waiting for the results of toxicological studies. Countries and EU must also adopt rules and laws to ensure safety for humans and environment.
REACH regulation covers nanomaterials because it deals with substances in whatever size, shape or physical state. Therefore, under REACH manufacturers, importers and downstream users have to ensure that their nanomaterials do not adversely affect human health or the environment. This is a good regulation but we think that EU and Countries should enforce it with a specific nanotechnology legislation.
The European Code of Conduct is based on the precautionary, accountability and sustainable principles. Enterprises could assume more responsibilities and contribute to the risk assessment but it's a volunteer code and could not replace the legislation.

[http://www.legambiente.org
http://www.legambiente.org/section.php?p=document_cat&cat=Convegno+Nanotecnologie%2C+20%2F11%2F2008&id=14]

4.5.3.10. Natural Resources Defence Council (NRDC)

The Natural Resources Defence Council is an international not for profit environmental organization, based in the USA, with more than 1.2 million members and online activists.

On May 2007 it published a report devoted to nanotechnology (Nanotechnology's Invisible Threat Small Science, Big Consequences , NRDC, May 2007[51]), asking with other CSOs (including ETC,

[50] http://www.greenpeace.org.uk/files/pdfs/migrated/MultimediaFiles/Live/FullReport/5886.pdf

[51] http://www.nrdc.org/policy/reports.asp?more=1

Greenpeace, FoE, ICTA), EPA to fully disclose the potential hazards of nanomaterials. It underlined that voluntary program (such as the EPA Nanomaterials Stewardship Programmme) without a mandatory regulatory component will not be able to really address potential risks.

NRDC propose a regulatory framework based on a precautionary approach, which:

- prohibits the use of untested or unsafe nanomaterials;
- requires full life cycle EHS assessment before commercialisation;
    - fosters public and workers participation in the decision-making processes.

NRDC underlines also the importance of placing the burden on industry to provide assurances of safety (instead of the current government approach "no data means no risk").
[http://www.nrdc.org/policy/ -
http://switchboard.nrdc.org/blogs/jsass/tags/showtag.php?tag=nanotechnology]

4.5.3.11. Soil Association

The Soil Association is a charity organisation, UK's leading campaigning and certification organisation for organic food and farming, developing standards for organic integrity. Their symbol can be found on over 70% of Britain's organic produce.

Basing on warnings from the scientific community on risks of nanomaterials, and on the fact that the UK Government acknowledged the risks since some years but did not take action to impose controls, the Association decided in January 2008 to ban the use of man-made nanomaterials. Thus, on a precautionary basis, all Soil Association certified organic products (organic foods, health products, sunscreens and cosmetics, textiles) will have to avoid the use of engineered nanomaterials.
In the view of the Association, commercial release of nanomaterials should be stopped until there is a sound body of scientific research into all the health impacts.
[http://www.soilassociation.org/web/sa/saweb.nsf/librarytitles/1EC7A.HTMl/$file/Nanotechnology.pdf]

4.5.3.12. WHICH? (or Consumers's Association)

Which? is an independent UK consumer body, the largest consumer organisation Europe.
In September 2007 it published a position paper on nanotechnology (Nanotechnologies Small scale, big impact), identifying 10 key priorities regarding government actions to ensure consumer protection. Among them: Apply the precautionary principle to products on the market using nanotechnology, ensuring transparency and clear information about risks of nanomaterials to consumers and other stakeholders, define clear guidances on regulation and regulatory gaps, increase funding on EHS research.
[http://www.which.co.uk/about-which/press/campaign-press-releases/other-issues/2007/09/nanotech--small-scale-big-questions.jsp]

5. CONCLUSIONS

The study has analysed initiatives, opinions and results from a wide range of key stakeholders, researchers, policy makers, businesses, civil society organisation, at international level, in an attempt to provide a structured view of the debate on regulation and governance of nanotechnologies.

The investigation has confirmed, in fact, that nanotechnologies are seen as exciting new opportunity capable of revolutionising entire industrial sectors and the quality of life. At the same time, their responsible development is considered fundamental for their success.

The concern about potential harmful effects of nano-related products is at present pinned essentially on manufactured nanomaterials, but no specific regulation exist yet to deal with them for risk assessment. The attitude is to use available provisions, such as REACH, in Europe, and TSCA, in USA, and follow a precautionary approach. Nevertheless gaps in the scientific knowledge challenge the reliability of these measures.

Together with the diversity of materials and applications, the lack of data characterising nanomaterials, lack of standardisation in nomenclature and metric, knowledge of the impact of nanomaterials on human health and the environment challenge the responsible development of these technologies.

Besides the need to address the above said issues, also the implications of nanotechnologies respect to ethical, legal and social issues (ELSI) are considered a crucial point that must be taken into account for the proper governance of nanotechnology.

The adoption of dedicate actions is advocated from several parts, which to be effective requires an inclusive approach.

The fact that nanotechnologies are still at an early stage of development can give the opportunity to tackle on time the challenges deriving from their use, but the fact that nano-related products are already hitting the market in increasing number makes the solution of the problem urgent.

The activity and the attention on these themes, particularly in the last 3/4 years, has flourished and it has prompted a demand for dialogue and debate amongst the interested stakeholders.

International authoritative working groups (of OECD and ISO in the first instance) are widely recognised has the converging points of on-going activities regarding risk management and standards. The results of their work will be very likely widely adopted.

These groups are working also on regulatory issues (analysis of existing regulation and voluntary measures in relation with nanotechnologies), and governance (social, economical and commercial issues affecting the development of nanotechnologies). On these aspects there could likely be disagreements and different choices amongst the various Countries and economies and to avoid this international cooperation is considered fundamental. Several initiatives have been activated to this end.

Civil society organisations are rather critic about the way nanoregulation has been handled till now and generally ask for initiatives aimed to deepen and answer scientific technical issues and clarify regulatory aspects of nanotechnologies. Some of them require the application of a strict precautionary approach.

Their request is to reach scientific evidence on safety, have adequate regulatory instruments in place and possibly agreement/confidence on ethical/social concerns *prior* to commercialisation.

In light of uncertainties and novelties related to nanotechnologies, they also asks for classification of nanomaterials as new substances, labelling of nanoproducts, ensuring safety data are made publicly available, foster an open, meaningful, and full public and workers participation in the decision-making processes.

On their view, the fact that nanotechnology-related products are already on the market and their number is expected to increase during the next years, raising the risks for researchers, workers and consumers, makes the implementation of trusty procedures and regulatory options mandatory.

This positions are countered by policy makers and regulatory bodies on the base that a strict precautionary approach, besides the difficulties to enforce it, can also hinder the scientific development, and, most of all, they think that there are not enough scientific data to justify changes in legislation. Industry/businesses, are also in favour of adopting existing regulation saying that it already puts strict controls on safety (of products in general).

REACH is considered as one of the most compelling instruments to deal with nanomaterials, able to consider almost all nanomaterials as new substances and asking for detailed risk assessment reviews of substances. This, in the view of some observers, could become even an over-regulation example, placing a too costly procedure in the use and production of nanomaterials.

In spite of the differences, there is in any case a general agreement on the necessity of increasing the efforts to thoroughly understand the impact of nanotechnologies on EHS and ELSI implications and develop an action plan to govern the development of nanotechnologies which takes into consideration all these issues. Public engagement is essential to gain public acceptance.

Voluntary measures, such as risks management systems and Code of Conducts, are somehow a trade-off or a temporary action in between the establishment of a firmer scientific evidence for specific regulatory/policy decisions. Being voluntary, their effectiveness will of course depend on the level of application and of the instruments, mainly scientific, to comply with them.

6. References

References to articles, reports and other documents are reported hereafter, references to websites and news are generally reported as footnotes within the text of the report.
References are divided by paragraphs, some documents can be reported more than once if used in different paragraphs.

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- **Annex 7.1 Proposed and Existing Strategies and Action Plans**

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7. Annexes

7.1. Proposed and Existing Strategies and Action Plans[52]

In this annex, are presented strategic programmes and Action Plans which have a direct impact on the development of nanotechnologies in the corresponding country or region, e.g. via allocation of money or via the definition of future research projects, and it must exhibit an integrating or framing nature, by coordinating different activities on a superior level.

They include, with a different degree of commitment, aspects of framing future regulatory actions that will foster the responsible development of nanotechnology. Certainly, the existence of a Strategic Plan, focusing and coordinating the efforts, can favour an approach aimed to the responsible development of nanotechnologies.

7.1.1. European Action Plan 2005-2009 (EC)

On 12 May 2004 the Commission adopted the *Communication Towards a European Strategy for Nanotechnology*[53] in which a safe, integrated and responsible strategy was proposed. This aims to reinforce the Union's leading position in nanoscience and nanotechnology (N&N) research and development (R&D) and innovation while addressing any environmental, health, safety and societal concerns upfront. Based on this communication, the Commission has prepared an Action Plan [1], which defines a series of articulated and interconnected actions for the immediate implementation of a safe, integrated and responsible strategy for N&N. The Action Plan has been adopted by the European Commission in June 2005, and in September 2007, the first implementation report to the Action Plan has been released, summarising the actions taken and the progress made between 2005 and 2007[54].

The Action Plan is structured into eight main areas, each one with specific actions the European Commission and its member states will take to promote R&D in N&N.

1. RESEARCH, DEVELOPMENT AND INNOVATION: EUROPE NEEDS KNOWLEDGE

Reinforce and promote N&N R&D in the European Union's seventh framework programme (FP7), with specific support for European Technology Platforms (nanoelectronics, nanomedicine) and collaborative R&D into the potential impact of N&N. Therefore, public investment shall be increased and effective coordination among the different stakeholders shall be established.

2. INFRASTRUCTURE AND EUROPEAN POLES OF EXCELLENCE

Support interdisciplinary R&D infrastructure and "poles of excellence", reinforce cooperation between industry and academic R&D and advance transnational networking. Some areas of N&N R&D would particularly benefit from such integration include nanotoxicology and nano-ecotoxicology, as well as nano-metrology.

3. INTERDISCIPLINARY HUMAN RESOURCES: EUROPE NEEDS CREATIVITY

Promote networking and disseminate best practices for education and training in N&N and encourage the development of supporting activities. Training programmes should also be targeted specifically at SMEs, who often lack the necessary 'in house' expertise or resources. Interdisciplinary R&D in N&N goes beyond traditional concepts and a greater awareness amongst these groups of entrepreneurship, ethical, health, safety (including in the workplace), environmental, and social issues is needed.

4. INDUSTRIAL INNOVATION: FROM KNOWLEDGE TO THE MARKET

[52] References to this annex are included in the general report references (section 6)

[53] ftp://ftp.cordis.europa.eu/pub/nanotechnology/docs/nano_com_en.pdf

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Due to the enabling character of N&N, advances can be made in virtually all technology sectors. Excellence in N&N R&D shall be translated into commercially viable, inherently safe products and processes by fostering knowledge transfer, standards development and best practice for commercialisation of N&N. Patent monitoring and harmonisation will be adapted. Standards provide a level playing field for markets and international trade and are prerequisites for fair competition, comparative risk assessments and regulatory measures.

5. INTEGRATING THE SOCIETAL DIMENSION: ADDRESSING EXPECTATIONS AND CONCERNS

Ethical issues and health, safety and environmental aspects shall be integrated into the technological development of N&N and an effective dialogue with all stakeholders established, informing about progress and expected benefits, and taking into account expectations and concerns (both real and perceived) so to steer developments on a path that avoids negative societal impact.

6. PUBLIC HEALTH, SAFETY, ENVIRONMENTAL AND CONSUMER PROTECTION

Risk assessment related to human health, the environment, consumer and workers should be integrated at all stages of the life cycle of the technology. Safe and cost-effective measures to minimise exposure of workers, consumers and the environment to manufactured nano-scale entities should be promoted, including the development of terminology, guidelines, models and standards for risk assessment. Inventories of use and exposure will be fostered.

Adaptations of EU regulations will be proposed paying particular attention to (i) toxicity thresholds, (ii) measurement and emission thresholds, (iii) labelling requirements, (iv) risk assessment and exposure thresholds and (v) production and import thresholds.

7. INTERNATIONAL COOPERATION

International cooperation will intensify dialogue at international level with a view to adopting a declaration or a 'code of good conduct' for the responsible development and use of N&N. Industry shall be invited to adhere to these principles. Issues of common nomenclature, metrology, approaches to risk assessment and the establishment of a dedicated database to share toxicological and data, and also the support for N&N R&D in less developed countries are promoted.

8. IMPLEMENTING A COHERENT AND VISIBLE STRATEGY AT EUROPEAN-LEVEL

Coherent and coordinated action is proposed to monitor and oversee the implementation of the Action Plan in regard to conformity and coherence with Commission policies and related initiatives, and to generate appropriate visibility and effective communication. A useful, beneficial, profitable and consensual exploitation and application of N&N in the EU shall be promoted e.g. via dedicated 'horizon scanning' activities, pro-active and responsive dialogue with the public and ad-hoc initiatives at international level.

7.1.2. Denmark Action Plan

The Action Plan *Technology Foresight on Danish Nanoscience and Nanotechnology* since 2004 [2] focuses on a series of recommendations:

1. Prioritise technology areas
2. Create interplay between nanotechnological research and the development of high technology in industry
3. Establish nanotechnology centres for strategic research and innovation
4. Produce more university graduates and researchers
5. Spread nanotechnology widely to Danish enterprises
6. Give attention to hazards and health, environmental and ethical considerations.

The prioritised technology areas have been chosen on the basis of their industrial and social relevance in addition to national and international research strengths and/or potential. The prioritised areas are nanomedicine and drug delivery, biocompatible materials, nanosensors and nanofluids, plastic electronics, nanooptics and nanophotonics, nanocatalysis, hydrogen technology and similar, plus nanomaterials with new functional properties.

According to the Action Plan, besides supporting the research and development of nanotechnologies in Denmark, attention to hazards and health, environmental and ethical considerations should be given, but except for this general indication, no specific work programmes or projects on this matter could be found

7.1.3. Finland: FinNano 2005-2010

Finland's first investments in nanotechnology date back to the period of 1997–1999. Finland decided to increase public investment in nanoscience and nanotechnology in 2004 by starting the National Nanoscience and Nanotechnology Programme, FinNano. The total volume of the programme is approximately €70 million, and the duration is five years (2005 – 2009). FinNano is carried out in close collaboration with Academy of Finland's *Nanoscience Research Programme*.
The aim of the programmes is to strengthen research, support national and international networking, promote the effective use of infrastructures and encourage enterprises to see the potential of nanotechnology in the focus areas of

1. innovative nanostructure materials
2. nanosensors and nanoactuators
3. new nanoelectronics solutions

The FinNano programme does neither mention environmental, health or safety effects nor ethical, legal and social implications of nanotechnologies. However, Tekes (the Finnish Funding Agency for Technology and Innovation) and FinNano programme have identified the need to clarify and coordinate the field of nanosafety research in Finland. Therefore, a survey [3] has been dedicated to clarify the relevant research, authoritative and business actors and their roles in the field of nanosafety in Finland.

The nanosafety study included a web-based survey that was directed to nanotechnology researchers. According to the survey, nanosafety research is oriented towards basic research and covers, for example, product life cycles only partially. From the HSE point of view, especially the environmental effects have not been included in the ongoing research activities. The existing risk management methods and tools, legislation and the public risk management procedures were considered inadequate for managing nanotechnology related risks. Furthermore, the report concluded that public discussion on nanosafety has been scarce in Finland.

7.1.4. Germany: Nano-Initiative - Aktionsplan 2010

After a strategic reorientation in 2002 the Federal Government has published the extended Nano-Initiative Aktionsplan 2010 [4], bundling research in nanotechnology and its dissemination.
The action plan is intended to provide a single framework for action that goes beyond individual government departments, and which brings together goals and plans for nanotechnology. The seven Federal Ministries for Labour and Social Affairs (BMAS), Environment, Nature Conservation and Nuclear Safety (BMU), Food, Agriculture and Consumer Protection (BMELV), Defense (BMVg), Health (BMG) and Commerce and Technology (BMWi) together with the BMBF have laid the foundations to

- speed up the transfer of nanotechnology research results into innovations and to introduce further industrial sectors to nanotechnology. To achieve this, nanotechnology must be brought from the laboratories into the firms. As an appropriate measure, BMBF and BMWi initiate industry dialogues to inform about the use of nanotechnology, fund new lead innovations, and support SME in the use of nanotechnology;
- remove innovation obstacles and improve conditions through early coordination of different fields of politics. To this end, the coordination of the departments is improved, young talents as well as standardisation activities are supported;
- lead an intensive dialogue with the public on the opportunities of nanotechnology including its risks. To this end, possible effects on health and the environment will be analysed, a common strategy on environmental risks of insoluble nanoparticles developed, and modern means of information and participation of the public applied.

To exploit market potentials and employment growth through nanotechnologies, four leading innovation areas have been funded: *NanoMobil* for the automobile industry, *NanoLux* for the optical industry, *NanoFab* for electronics and *Nano for Life* for life sciences. Further lead innovation areas include production technology, textile industry, construction industry, medicine, measurement technology, plant engineering and construction, micro/nano integration, environment and energy.

7.1.5. Dutch Nano Action Plan

In 2006 the Dutch government has launched a 'Cabinet's View Nanotechnologies: From small to great'. This document describes both opportunities and risks of nanotechnologies and resulted in a Dutch Action Plan Nanotechnology [5] concentrating on ethics, risk research, and innovation and development. The action plan includes proposals on managing risks, research and innovation, the communication of the technology with the wider society and legal aspects and is in line with the European action plan described in annex 7.1.1. For elaboration and implementation of the action points, an interdepartmental working group has been formed.
The Dutch Action Plan focuses on various types of actions. In relation to risks the most significant actions are:

- Proposal of a new strategic research agenda in summer 2008 from the research community. The research budget should include annual investment of at least 15% for risk research during at least 5 years.
- A Knowledge and Information point Risk of Nanotechnology (KIR nano). RIVM is, as described in the Cabinet's View, already hosting such a point since 2007. They have published a first assessment in autumn 2008: Nanotechnology in perspective [6].
- Participation in OECD sponsorship programmes
- A dialogue with relevant parties, initiated by the Dutch Department of Housing, Spatial Planning and the Environment.
- Furthermore, a broad societal committee will be formed advising the government on ethical aspects, societal dialogue and communication.

In terms of the current legal position on the technology, the Dutch government has concluded that at present no new legislation is needed to govern nanotechnology. The Commission is in agreement with the Dutch government that current legislation is adequate; however it wants to ensure that this remains the case (see also 4.3.4).

7.1.6. Norway:National Strategy for Nanoscience and Nanotechnology

The Research Council of Norway has since 2002 has a research program called "Nanotechnology and new materials, nanoscience and integration" (NANOMAT [7] [55]). In the period 2007-2016 NANOMAT will focus on:

- Thematic areas (order of priority): Energy and the environment, ICT including microsystems, health and biotechnology, ocean and food
- Expertise areas (alphabetical order): Bio-nanoscience and bionanotechnology; Ethical, legal and social aspects (includes health, environment, safety/security, risk); Fundamental physical and chemical processes at the nanometre level; Interface and surface science and catalysis; Components, systems and complex processes that exploit nanoST; New, functional and nano-structured materials
- Infrastructure and coordination of tool platforms with advanced scientific equipment

The work programme belonging to NANOMAT is based on the foresight study "Advanced Materials Norway 2020", "The National Strategy for Nanoscience and Nanotechnology (nanoST, adopted 2006)" and "Nanotechnologies and New Materials: health, environment, ethics and society – national research and expertise requirements". The present plan, with a time perspective from 2007 to 2016, contains a drastic revision of the original work programme, which had a time perspective from 2002 to 2006.
For the years of 2007-2008, an Action Plan has been approved by the Divisional Board in December 2006, with more specific areas of action and priority orders.

55 http://www.forskningsradet.no/servlet/Satellite?cid=1088796688084&pagename=nanomat%2FPage%2FHovedSideEng

7.1.7. The Spanish National Plan for R&D and Innovation 2008-2011

In September 2007 the Ministers Council approved The Spanish National Plan for Scientific Research, Development and Technological Innovation 2008-2011 (R&D&I) [8] [56] with a very significant increase of the budget. The Plan has underlined five strategic objectives, with nanoscience / nanotechnology being one of them.

Although topics related to nanotechnologies' potential impact on human health and the environment are among their lines (e.g. nano-ecotoxicity), the focus of the programme clearly lies in fostering research, industrial development and commercialisation of nanotechnologies rather than supporting research on EHS and ethical, legal and societal issues.

7.1.8. Swiss Action Plan on Manufactured Nanomaterials

In spring 2006, the Federal Office for the Environment (FOEN) and the Swiss Federal Office of Public Health (SFOPH) started a project to develop an Action Plan called "Risk Assessment and Risk Management for Manufactured Nanomaterials 2006-2009" in order to show what endeavours are required in Switzerland to fill the knowledge gaps. It is based on a comparable EU Action Plan from June 2005.

In the context of the first phase of the Action Plan, the principals for the assessment of the need for action had to be worked out in collaboration with a professional committee of experts in a comprehensive basis report [9] which the federal offices BAG and BAFU published in summer 2007.

In the second phase, a detailed Action Plan describing several areas of measures has been presented in autumn 2007 and adopted by the Government after consultation [10]. The implementation of the proposed measures is provided for the time between 2007 and 2009. The plan lays out guidance for responsible long term development of nanotechnology and sets out a differentiated public dialogue on its risks and benefits. This includes

- providing a summary of the **uses** of nanoparticles in Switzerland and developing **exposure scenarios** (comparison with the existing emissions in the ultrafine range e.g. diesel exhaust particulates);
- conducting a **dialogue** with the relevant stakeholders (scientists, trade associations, offices, insurers, politicians, investors, general public);
- devising **scientific principles** for danger and risk assessment;
- drawing up harmonised **definitions**, **measurement methods** and validated **test guidelines** for the danger and risk assessment in cooperation with the *OECD*, *EU*, *ISO*;
- motivating the research and business communities to develop and apply **self-regulation-measures**;
- adapting existing **legislation** if this is needed to guarantee the safety;
- introducing **immediate measures** to protect employees in industry and research.

With the adoption of the plan of action on synthetic nano-materials, the House of Parliament addresses issues surrounding the potential risks of nanotechnologies, and answers the parliamentary inquiry of the Green Party, who demand a legal adjustment for synthetic nano-materials. In addition, the action plan submits a concept whereby despite existing scientific gaps, the risks of synthetic nano-materials can be recognized and controlled in the context of the existing legislation.

Besides the Action Plan, in November 2007 the Parliament made the decision to launch a national research program (NFP) with an aim to extend knowledge in the area of risks and benefits of nanotechnologies. These projects will complement the actions taken resulting from the Action Plan

7.1.9. Nanotechnology Action Plan for Russia - 2015

Russia has announced a "Nanotechnology Action Plan for Russia – 2015" at the OECD Tour de Table Meeting in Paris (November 2007) which would contain a special subprogramme covering nanosafety and potential impacts of nanomaterials on health and environment. However, no specific information on such an Action Plan could be found on the internet.

[56] http://www.plannacionalidi.es/documentos/Plan_ingles_web.pdf

7.1.10. USA- National Nanotechnology Initiative (NNI)

The National Nanotechnology Initiative is a strategic program established in Fiscal Year (FY) 2001 to coordinate Federal nanotechnology R&D. The NNI provides a vision of the long-term opportunities and benefits of nanotechnology. By serving as a central locus for communication, cooperation, and collaboration for all Federal agencies that wish to participate, the NNI brings together the expertise needed to guide and support the advancement of this broad and complex field. Including the NNI budget requests for FY 2009 of $1.5 billion, the total NNI investment since its inception in 2001 is nearly $10 billion.

Given the dynamic nature of the field, the NNI Strategic Plan is periodically reexamined. The 21st Century Nanotechnology Research and Development Act of 2003 calls for the NNI Strategic Plan to be updated every third year; the most recent plan of December 2007 updates and replaces the December 2004 plan. The 2007 NNI Strategic Plan [11] describes the vision, goals, and priorities of the NNI.

Goal 1: Advance a world-class nanotechnology research and development program

Goal 2: Foster the transfer of new technologies into products for commercial and public benefit

Goal 3: Develop and sustain educational resources, a skilled workforce, and the supporting infrastructure and tools to advance nanotechnology

Goal 4: Support responsible development of nanotechnology

Besides the more R&D oriented objectives, goal 4 aims to maximise the benefits of nanotechnology and at the same time to develop an understanding of potential risks and to develop means to manage them. The NNI pursues a program of research, education and communication focused on environmental, health, safety and broader societal dimensions of nanotechnology development.

As in the earlier strategic plan, this NNI Strategic Plan identifies major subject areas, or program component areas (PCAs), in which investments are needed to ensure success of the initiative. The two PCAs related to societal effects are titled “Environment, Health and Safety” and “Education and Societal Dimensions”. In the latter, education-related activities such as development of materials for schools, undergraduate programs, technical training, and public communication, including outreach and engagement are provided. Research directed at identifying and quantifying the broad implications of nanotechnology for society, including social, economic, workforce, educational, ethical, and legal implications.

In the April 2008 assessment of the NNI by the President’s Council of Advisors to Science and Technology [12], the panel concluded that at present, nanotechnology does not raise ethical concerns that are unique to the field. Rather, concerns over implications for privacy and for equality of access to benefits are similar to concerns over technological advances in general. Furthermore, the panel is concerned that public opinion is susceptible to hype and exaggerated statements (both positive and negative) and the NNI should therefore “expand communication and outreach efforts, particularly with respect to real and perceived benefits and risks associated with nanotechnology” as well as integrate societal and ethical aspects of nanotechnology with technical R&D.

7.1.11. Australia: National Nanotechnology Strategy (NNS)

The National Nanotechnology Strategy (NNS) aims to establish the environment that allows Australia to capture benefits of nanotechnology while addressing the issues impacting on successful and responsible development of nanotechnology [13]. It complements other Australian Government initiatives (for example, CSIRO Niche Manufacturing Flagship) and existing research, innovation and industry policies that promote the development of enabling technologies and facilitate greater coordination of policies affecting nanotechnology. The NNS includes specific initiatives to:

- address the health safety and environmental (HSE) impacts of nanotechnology on regulations and standards;
- establish a nano particle metrology capability at the National Measurement Institute;
- facilitate a whole of government approach to nanotechnology through establishing the Australian Office of Nanotechnology.

A key activity in the Strategy includes analysis of the impact of nanotechnology on regulatory frameworks. Funds are being provided under the Strategy to the Australian Federal Departments of Health and Ageing, DEWR, and the Environment and Water Resources to ensure regulatory systems adequately address the health, workplace and environmental implications of nanotechnology. An independent report completed in September 2007 entitled "A Review of the Possible Impacts of Nanotechnology on Australia's Regulatory Framework" is currently being considered by government agencies.
As part of the NNS, a coordinated Public Awareness and Engagement Program is to be developed and implemented. The program is aimed to raise awareness and develop knowledge of the opportunities and potential of nanotechnology, and to encourage an informed debate based on balanced and factual information, therefore it intends:

- increase awareness and understanding among the general public about nanotechnology and its potentials;
- enable an informed public debate through improved awareness and understanding of social and ethical issues regarding the use of nanotechnology;
- understand the publics' knowledge, concerns and aspirations for nanotechnology, provide the Australian public with timely updates on the Government's response to emerging nanotechnology issues;
- create public awareness and understanding of Australian regulatory bodies and practices concerning nanotechnology and related health and safety issues.

The Public Awareness and Engagement Program will arrange public forums, promotional materials, conference events and mobile exhibitions with targeted publicity in metropolitan, regional and rural media to support these initiatives. Industry surveys were undertaken in 2005 and 2006 to gauge the level of awareness and understanding of nanotechnology issues among targeted firms with a potential interest in nanotechnology; and public awareness studies undertaken in 2005 and 2007 surveyed the community on their understanding of nanotechnology related issues.
The current NNS will cease in June 2009.

7.1.12. China

In China, although being one of the foremost countries in terms of publications regarding nanotechnologies, no specific action plan exists with the aim to frame the development of nanotechnologies in terms of ethical, legal and societal aspects, and public investment into nanosafety research is very low [14].

In 2004 a meeting on EHS issues was organised by the Chinese Governments, with the participation of the Ministry of Science and Technology (MOST), the National Natural Science Foundation of China (NSFC), the Ministry of Education (MOE) and CAS (Chinese Academy of Sciences), and certain framing activities in the field of health and safety have been dedicated to a research institution for "Bio-Environmental Health Sciences of Nanoscale Materials" at the CAS.

In 2006, the National Center for Nanoscience and Technology (NCNST) decided to establish a nanosafety lab focusing on the economic, environmental and societal aspects of nanotechnologies. Although its mission clearly lies in the research of the properties and health and safety effects of nanomaterials, the drafting of standards and regulatory frameworks for research and industrial activities is also one point of activity.
Currently about 30 research organizations in China have started activities related to toxicological and environmental effects of nanomaterials/ nanoparticles [16].

7.1.13. Japan

Nanotechnology research is promoted in Japan through the Science and Technology Basic Plan, which is currently active in the third version starting in April 2006 for five years. New in this revision, the topic of "public confidence and engagement", which, among others, emphasises responsible actions in terms of ethical, legal and societal issues, reinforcements of accountability

and public relations of science and technology activities. The strategy also includes R&D on the social acceptance of nanotechnology.
Besides various programmes to promote research on health impacts of nanomaterials, in 2004, a first multi-stakeholder dialogue on the health, environmental and societal aspects of nanotechnology called “Nanotechnology and Society” has been organised in Japan. This led to subsequent governmental projects in 2005 and 2006 which resulted in policy recommendations for public research institutes, the private sector and the government.
Besides these activities, a series of international meetings and workshops on the topic of health, environmental and societal issues of nanotechnology were held in Japan and abroad [15,16].

chemicals regulatory area on health and environmental safety aspects of manufactured nanomaterials.

7.2. Ongoing Research Projects

The following list of current and recently completed research projects give a brief overview on the topics addressed in national and international research programmes. The selection of projects is not conclusive. It is only intended to give some examples of the broad variety of topics and specific subjects. The initiatives are ordered by country/region of origin.

7.2.1. European Union

EC Research Framework Programmes (FP)
The Action Plan "Nanosciences and Nanotechnologies: An Action Plan for Europe 2005-2009" defines a series of elements to ensure a safe, integrated and responsible strategy for nanosciences and nanotechnologies. The elements also include funding activities in research, development and innovation under the Research Framework Programmes. For a detailed description of the EU Action Plan see annex 7.1.1.

Framework programmes have been the main financial tools through which the European Union supports research and development activities covering almost all scientific disciplines. The most recent programme is the FP7 which has started in 2007 and will last until 2013. FP7 bundles all research-related EU initiatives together under a common roof. The broad objectives of FP7 have been grouped into four categories: Cooperation, Ideas, People and Capacities. For each type of objective, there is a specific programme corresponding to the main areas of EU research policy. All specific programmes work together to promote and encourage the creation of European poles of (scientific) excellence. Two recent reports give a detailed list of projects on EHS and ELSI both from the European Commission and at National level in Europe**:**

- EU nanotechnology R&D in the field of health and environmental impact of nanoparticles (EHS), 2008, European Commission [57][58]
- European activities in the field of ethical, legal and social issues (ELSA) and governance of nanotechnology, 2008, European Commission

The first document counted 106 projects on EHS, 14 of them from EC framework programmes and the other 92 from EU Member States. The second illustrates 27 projects on various ELSI funded by FP5, FP6 and FP7. Some of these projects are briefly reported below.
All the FP projects may be accessed via the CORDIS Search platform:
http://cordis.europa.eu/search/index.cfm?fuseaction=search.advanced
Cellnanotox: Cellular Interaction and Toxicology with Engineered Nanoparticles. The objective is unraveling the correlation between the physicochemical characteristics of NPs and their toxic potential on various organs of the human body.
Website: http://www.fp6-cellnanotox.net/index.html
Dipna: Development of an Integrated Platform for Nanoparticle Analysis to verify their possible toxicity and the eco-toxicity, basic knowledge on the interaction between nanoparticles and cells, and identification of the modes of NP-cell interaction.
Website: http://dipna.eu/
Atbest: This project developed a process approach, with corresponding tools, for the management of new and emerging science and technology, where uncertainty is great, but hoped-for potential is great as well. This project builds on what has been learnt already, so as to characterize assessment approaches and corresponding tools that address the new challenges.
Website: http://latts.cnrs.fr/site/p_lattsperso.php?Id=864

[57] ftp://ftp.cordis.europa.eu/pub/nanotechnology/docs/elsa_governance_nano.pdf

[58] ftp://ftp.cordis.europa.eu/pub/nanotechnology/docs/final-version.pdf

NanoBio RAISE: This EU funded project aims to anticipate the societal and ethical issues likely to arise as nanobiotechnologies develop and to use the lessons from the GM debate to respond to the probable public concerns.
Website: http://nanobio-raise.org/
NanoDialogue: This EU funded specific support action aims at provoking and facilitating social dialogue between the research community, citizens and other stakeholder organisations. The project ended with the final conference in February 2007.
Website: Only via Cordis (http://cordis.europa.eu/fp6/projects.htm)
Nanologue: This EU funded specific support action aims at facilitating a dialogue on the social, ethical and legal benefits and potential impacts of nanotechnology. The project is finished.
Website: http://www.nanologue.net
Nanointeract: Nanointeract aims at developing a platform and toolkit for understanding interactions between nanoparticles and the living world. It creates a fundamental view of how engineered nanoparticles interact with living cells, and a knowledge-based and rational approach that underpins the development of nanotoxicology.
Website: http://www.nanointeract.net/
Nanosh: Inflammatory and genotoxic effects of engineered nanomaterials are the topic of this project. Better understanding of the characteristics, behaviour, and toxicity of nanoparticles, as well as the development of useful methods to assess exposure to and health effects of nanoparticles.
Website: http://www.ttl.fi/Internet/partner/Nanosh/
Saphir: The general objective of the project is the safe, integrated and controlled production of high-tech multifunctional nanostructured products including their recycling, ensuring competitiveness.
Website: http://www.fos.su.se/page.php?pid=176
Nanocap: Nanotechnology capacity building NGOs. To develop recommendations to enable public authorities to address the health, safety and environmental risk issues related to the rapid introduction of nanotechnology into society. Nanocap intends to give industry the tools to introduce a "responsible nanotechnology".
Website: http://www.nanocap.eu/Flex/Site/Page.aspx?PageID=3493&Lang=UK
Nanotest: The main goal of this proposal is to develop alternative high-throughput testing strategies using in vitro and *in silico* methods to assess the toxicological profile of nanoparticles used in medical diagnostics.
Website: Only via Cordis (http://cordis.europa.eu/fp6/projects.htm)
Impart: Improving the understanding of the impact of nanoparticles on human health and the environment. This NMP coordination action will foster communication links between numbers of regional, national and international initiatives in order to reduce duplication of effort, pool expertise and facilitate co-operation between networks.
Website: http://www.impart-nanotox.org/
NanoDerm: Quality of Skin as a barrier to ultra-fine particles. This FP5 research project aims at applying and developing different methods for analysing the quality of skin as a barrier against nanoparticles and to investigate the nanoparticles activity and the skin response. The project has been completed.
Website: http://www.uni-leipzig.de/~nanoderm/
Nanosafe2: Nanosafe2 follows Nanosafe and focuses on safe production and use of nanoparticles. This NMP integrated project will establish processes to detect, track and characterise nanoparticles.
Website: http://www.nanosafe.org/
Particle Risk: Risk Assessment for Particle Exposure. This NEST research project is developing methods to assess the dangers posed by new kinds of particulate matter being developed by modern science and technology. The project was completed in Spring 2008.
Website: Only via Cordis (http://cordis.europa.eu/fp6/projects.htm)
Decide: This project aims at involving the public in political decision making in nanotechnology with the help of the PlayDecide nanotechnology kit. Next to nanotechnology, other controversial liefescience issues discussed are: HIV-Aids, neuroscience, preimplementation genetic diagnosis, stem cells and xeno-transplantation.
Webiste: http://www.playdecide.org/

WomenInNano: This project aims at allowing high-level women scientists working in Nano-science to act as Ambassadors for Women and Science in order to raise awareness of gender issues in science (more specific, in Nano-Science) and to provide role models for girls and women, with a view to encouraging them to consider studies and pursue careers in scientific fields. The project was completed in March 2008.
Website: http://www.womeninnano.de/
Observatorynano: Observatorynano aims at developing appropriate methodologies to link scientific and technological development of nanotechnologies with socio-economic impacts. It is intended to be a European observatory for science-based and economic expert analysis of nanotechnologies, cognisant of barriers and risks, to engage with relevant stakeholders regarding benefits and opportunities. The project started in April 2008.
Website: http://www.observatory-nano.eu/
NanoImpactNet: The objective of the NanoImpactNet, funded under FP7, is to create a scientific basis to ensure the safe and responsible development of engineered nanoparticles and nanotechnology-based materials and products, and to support the definition of regulatory measures and implementation of legislation in Europe. It includes a strong two-way communication to ensure efficient dissemination of information to stakeholders and the European Commission, while at the same time obtaining input from the stakeholders about their needs and concerns. Project start date: April 2008.
Website: http://www.nanoimpactnet.eu/object_class/nano_men_home.html
Nano2Life: The aim of Nano2Life is to merge existing European expertise and knowledge in the field of nanobiotechnology in order to keep Europe as a competitive partner of the US and Japan and to make it a leader in nanobiotechnology transfer in 5 years time. Nano2Life aims to set the basis of a virtual European Nanobiotech Institute, focused on the understanding of the nanoscale interface between biological and non biological entities, and its possible application in the area of complex and integrated novel sensor technologies, for health care, pharmaceuticals, environment, defence, food safety, etc.
Website: http://www.nano2life.org/
Besides the EU framework programmes, in which also non-EU organisations may participate, a series of national research programmes exist that complement these activities. In the following, a short selection of such national nanotechnology research initiatives is listed.
Deepen (Deepening Ethical Engagement and Participation in Emerging Nanotechnologies)
Development of a deepened ethical understanding of issues related to emerging nanotechnologies through an interdisciplinary approach utilising insights from philosophy, ethics, and the social sciences.
Website:http://www.geography.dur.ac.uk/Projects/Default.aspx?alias=www.geography.dur.ac.uk/projects/deepen
Nanostrand: Standardization related to Research and Development for Nanotechnologies. Goal of the project was to roadmap future European standardisation activities for nanotechnology which relate to pre-normative research work in order to support European organisations to play an active role in worldwide development of nanotechnology standards.
Website: http://www.nanostrand.net/
Nanotransport: Behaviour of aerosols released to ambient air from nanoparticle manufacturing. NANOTRANSPORT is an EU research project addressing the occupational health risks associated with aerosols released during manufacture of nanoparticles. The objective of NANOTRANSPORT was to investigate physical changes which nanoparticle aerosols undergo after release into the workplace environment under specific scenarios.
Website: http://research.dnv.com/nanotransport/

7.2.2. Czech Republic

Project: Study of transport of inhalated nano-sized particles (Ag, Pb, Cd) and their allocation in organs. The research gives more information for a proper understanding of risks of technologies producing Ag, Cd and Pb nano-sized particles as well as their oxides, which can have health impact for animals and humans or the impact on the environment.

A delegate of the Czech National Institute for Public Health represents the Czech Republic in the Working Party on Manufactured Nanomaterials of OECD (http://www.szu.cz/) and a delegate of the Ministry of Education, Youth and Sports represents the Czech Republic in the Working Party on Nanotechnology of OECD (http://www.msmt.cz/)

7.2.3. Denmark

In Denmark, the National Research Centre for the Working Environment's (NFA) programme of work[59] focuses on integrating research on nanoparticles, aerosol science and molecular biology. The Technical University of Denmark is leading on some research covering metrology, exposure and human health.

Project: Nanoparticles in the paint- and lacquer industry. Exposure and toxic properties.
The project is financed from national resource.
Website:
http://www.arbejdsmiljoforskning.dk/Aktuel%20forskning/Nanopartikler_i_farve_og_lakindustrien_-_NANOKEM_hovedprojekt.aspx

Project NANOPLAST: Nano-technological materials and products in the plastics industry: Exposure assessment and toxicological properties.
The aim is to investigate physical, chemical, and toxicological properties of nano-technological materials that will obtain massive use in the future production of plastic products. The project focuses on polymer nano composites (PNCs) that consist of a polymer matrix containing a uniformly dispersed nano-technological material that can be nanoclay, carbon nanofibres (CNFs), or carbon nanotubes (CNTs).
Website:http://arbejdsmiljoforskning.dk/Aktuel%20forskning/Nanoteknologiske%20materialer%20og%20produkter%20i%20plastindustrien%20NANOPLAST.aspx

Project NANOPACK: Biopolymer nanocomposite films for use in food packaging applications.
It is a research project funded by The Danish Council for Strategic research, The Danish Research and Innovation Agency, with partners from: Risoe DTU, National Food Institute (DTU), Faculty of Life Sciences (KU), Faerch Plast A/S and Danish Meat Association.
Website:http://www.risoe.dk/Research/sustainable_energy/bioenergy/projects/NanoPack.aspx/

Project SUNANO: Risk assessment of free nanoparticles
The project is financed from The Danish Strategic Research Council, Programme Commission on Nanoscience, Biotechnology and IT (NABIIT).

7.2.4. France

The National Institute for Industrial Environment and Risjs (INERIS) and the National Institute for Research and Security (INRS) are working to develop a research programme on EHS study of nanotechnology.
Website: http://www.ineris.fr/ - http://en.inrs.fr/
Commissariat a l´Energie Atomique (CEA) is coordinator of the FP6 integrated project **Safe production and use of nanomaterials - Nanosafe 2** (2005 – 2009).
Details on France strategy on the development and regulation of nanotechnologies are reported in paragraph 4.2.2

7.2.5. Germany

With the Nano-Initiative - Aktionsplan 2010, the German Federal Government established a framework under the national high-tech strategy in order to coordinate the national activities in research in nanotechnologies and their dissemination. For more details on the Nano-Initiative see annex 7.1.4.

NanoCare (2006-2009): NanoCare is the leading project supported by the German BMBF to elucidate potential health effects of manufactured nanoparticles. NanoCare aims at developing measurement methodologies and results allowing the early assessment of the effects of nanomaterials on health

[59] http://www.arbejdsmiljoforskning.dk/?lang=en

and the environment. The results of the project, which is jointly conducted by industries and research institutions, are available to the public in an internet database.
Website: www.nanopartikel.info

Two other projects on health and safety effects of nanomaterials (**INOS** and **TRACER**) are as well supported by BMBF.

7.2.6. Italy

NANOSH Italia: is a project co-funded by the Italian Ministry of Health and the National Institute for Occupational Prevention and Safety (ISPESL). Main objective is to develop an innovative methodology for assessing and preventing risks related to nanomaterials, in an integrated approach for workers' health and environment. The project involves some of major institutional bodies in Italy active in this research area, as ISPESL, "Salvatore Maugeri" Foundation of Pavia, the National Institute of Physics (INFN), the University of Rome "Tor Vergata" and the University of Parma.
Website: www.ispesl.it
ECSIN: European Center for the Sustainable Impact of Nanotechnology. The center aims at carrying out researches and studies to evaluate the effects due to the exposition to nanoparticles and/or nanomaterials on the human and environmental health. Moreover, the Center will analyze the impact of nanotechnology on society, through the benchmark analysis, in order to improve the comprehension and the social acceptability of nanotechnology.
Website: http://www.ecsin.it/

7.2.7. The Netherlands

Since 2003, the **Rathenau Institute** has been playing a major role in the construction of a public debate on nanotechnologies in The Netherlands and in Europe by encouraging an open dialogue between scientists, government departments, the private sector and the general public. This independent organisation, set up by the Netherlands Ministry of Education, Culture and Science, and managed as a unit of the Royal Netherlands Academy of Arts and Sciences (KNAW2) has conducted a series of framework projects including e.g. **Nanotechnology II: Nano in Focus**. This project is focused on nanotechnology applications expected to enter the market before 2015 and on their risks.
Websites: http://www.rathenauinstituut.com/
http://www.rathenau.nl/showpage.asp?steID=2&ID=2108
NanoNed, the Nanotechnology network in the Netherlands, is the nanoinitiative of eight research institutes and Philips. It clusters the nanotechnology Dutch industrial and scientific knowledge infrastructure in a national network and enables a knowledge leap through strong research projects, an infrastructure investment programme and economically relevant dissemination of the knowledge and expertise. The NanoNed TA programme aims at understanding and improving the interaction between science, technology and society. The NanoNed's TA projects deal with a broad spectrum of N&N specific issues. For instance, Social aspects of nanotechnology in the life sciences focuses on the exploration of societal and ethical questions and a search for meaningful dialogue between researchers and NGOs, and Risk and responsibility tackles how governance of nanotechnology will be shaped through concrete issues like risk of nano-particles.
Website: http://www.nanoned.nl/TA/
Dutch strategies regarding Nanotechnology research and regulation are reported in detail in paragraph 4.2.5 and annex 7.1.5.

7.2.8. Switzerland

In Switzerland, besides the Swiss Action Plan on Manufactured Nanomaterials (see annex 7.1.8), a National Research Programme on Opportunities and Risks of Nanomaterials has been proposed and approved by the Federal Council. It will be launched in 2009.

The NFP will be tightly coordinated with the National Center of Competence in Research (NCCR) Nanoscale Science. From the NCCR "Nanoscale Science" the Swiss Nanoscience Institute (SNI) developed. It constitutes a priority program of the University of Basel, which combines basic science with application-orientated research. In various projects researchers focus on nanoscale structures and aim at providing new impact and ideas to the life sciences, to the sustainable use of resources, and to information and communication technologies.
Website: http://www.nccr-nano.org/nccr/

7.2.9. UK

Environmental Nanoscience Initiative: The Environmental Nanoscience Initiative was set up by NERC (Natural Environment Research Council), Defra (Department for Environment, Food and Rural Affairs) and the Environment Agency (EA) to begin to answer some questions of basic nanosciences research, ecotoxicology and ecological effects of engineering nanoparticles.
Website: www.nerc.ac.uk/research/programmes/nanoscience
Environment and Human Health Programme: This is a joint three-year inter-disciplinary capacity-building programme supported by NERC, EA, Defra and other institutions focused on how the natural environment contributes to people's health through the quality of air, food and dringing water
Website: http://www.nerc.ac.uk/research/programmes/humanhealth/
Nanotechnology Engagement Group (NEG): The NEG was established in 2005 to document the learning from a series of groundbreaking attempts to involve members of the public in discussions about the development and governance of nanotechnologies. The NEG studied six UK projects that sought to engage members of the public
in dialogue about nanotechnologies. The project was completed in 2007 and resulted in a series of recommendations for future research and practice in this field.
Website: http://www.involve.org.uk/neg
Nanojury: The Nanojury was a collaborative project jointly initiated by independent citizens, The Policy, Ethics and Life Sciences Research Centre (PEALS), Newcastle University, Greenpeace, The Guardian Newspaper, the IRC in Nanotechnology and FRONTIERS Network of Excellence. NANOJURY members discussed during the spring and summer 2005 risks of nanotechnology and published recommendations asking first of all for broader democratic control over the development and global regulation of new technologies.
Website: http://www.nanojury.org.uk/
SafeNano: The Safenano Initiative is a venture by the Institute of Occupational Medicine. The initiative was designed to help industrial and academic communities to quantify and control the risks to their workforce, as well as to consumers, the general population and the environment, through both information provision and consultancy services.
Website: www.safenano.org
Details on UK strategy and plans for the development and regulation of nanotechnologies are reported in paragraph 4.2.2.

7.2.10. USA

The National Nanotechnology Initiative (NNI) is the US program established in fiscal year 2001 to coordinate Federal nanotechnology research and development. The 2007 NNI Strategic Plan describes the vision, goals, and priorities of the NNI. Financial support goes to the participating agencies' (Departments of Defense, Energy, Commerce, Health and Human Services, National Science Foundation, National Institutes of Health, EPA, NASA, etc.) individual research programmes or projects. For more information about the NNI see paragraph 4.2.9 and annex 7.1.10.
Website: www.nano.gov/html/about/strategicplan2004.html

Some specific agency research initiatives are listed in the following.

EPA National Center for Environmental Research: Based on the Nanomaterial Research Strategy (NRS), which guides the nanotechnology research program within EPA's Office of Research and Development, a series of strategic research projects with environmental relevance are conducted. The anticipated outcomes from this research program will be focused research products to address risk assessment and management needs for nanomaterials in support of the various environmental statutes for which the EPA is responsible.
Website: http://es.epa.gov/ncer/nano/research/index.html
NIOSH Research Programme: National Institute for Occupational Safety and Health (NIOSH) is the leading Federal agency conducting research and providing guidance on the occupational safety and health implications and applications of nanotechnology.
Website: http://www.cdc.gov/niosh/topics/nanotech/research.html
Center for Nanoscale Science and Technology (CNST): The Center for Nanoscale Science and Technology consists of a Research Program and the NanoFab, a shared-use facility. The CNST mission is to focus on solving nanoscale measurement problems that are encumbering the development of nanotechnology.
Website: http://cnst.nist.gov/index.html
Center for biological and Environmental Nanotechnology (CBEN): CBEN's mission is to discover and develop nanomaterials that enable new medical and environmental technologies. The Center is focused on fundamantal and engineering research of multifunctional nanoparticles, education programmes for teachers, students and also citizens, and on Innovative knowledge transfer that recognize the importance of communicating nanotechnology research to the media, policymakers, and the general public.
Website: http://cben.rice.edu/
Center for Nanotechnology in Society (at Arizona State University): CNS-ASU is one of two centers funded by the National Science Foundation to study nanotechnology in society; the other is at the University of California, Santa Barbara. It is designed as a boundary organization at the interface of science and society.
Website: http://cns.asu.edu/
Center for Nanotechnology in Society (CNS-UCSB) of the University of California: CNS-UCSB with the California NanoSystems Institute launched in April 2007 a series of events called NanoMeeter (also "Public Nano Café") to promote a debate about emerging nanotechnologies and their implications.
Website: http://www.cns.ucsb.edu/nanotechnology-society/
Center for Responsible Nanotechology: The Center for Responsible Nanotechnology (CRN) is a non-profit research and advocacy think tank concerned with the major societal and environmental implications of advanced nanotechnology. CRN engages individuals and groups to better understand the implications of molecular manufacturing and to focus on the real risks and benefits of the technology.
Website: http://www.crnano.org/speaker.cp.htm
NISE Nanoscale Informal Science Education Network: The US National Science Foundation has supported a 20 million dollars program over five years (2005– 2010) to promote a network of science museum to foster public dialogue on nanotechnology**.** The NISE organisation coordinates the activities of five science museums to organise a series of exhibitions and public forums (about 3 a years) to inform and engage the public about N&N its related societal and environmental impact.
Website: http://www.nisenet.org/

7.3. Standards organisations and nanotechnology

Following is a list of organisations worldwide involved in standards for nanotechnology. The list includes organisations developing formal standards (International Standard organisation, National Standard Bodies and regional standard organisation) and organisations developing informal standards, as SDOs (standard developing organisations).

International Standard Organizations

- International Organization for Standardization (ISO) – TC 229, Nanotechnologies
  Website: http://www.iso.org/iso/iso_technical_committee?commid=381983
- International Electrotechnical Commission (IEC) - TC 113, Nanotechnology standardization for electrical and electronic products and systems
  Website: http://www.iec.ch/dyn/www/f?p=102:7:0::::FSP_ORG_ID:1315

ISO is composed of the National Standards Bodies (NSBs), one per member economy. There are currently 28 Participating (P) Members and 8 Observer (O) members in ISO TC 229 on nanotechnology.
The IEC is composed of "National Committees", one per member economy. In some cases, the National Committee to the IEC of an economy may be the ISO member from that country or economy. There are currently 15 Participating (P) members and 14 Observer (O) members in IEC TC 113 on nanotechnology (full list of members are available in the each Committee websites). *NSBs reported below are all members of ISO TC 229 and some of them also of IEC TC 113.*

National Standard Bodies

Following a (partial) list of NSBs having specific Technical Committees or Commissions on nanotechnology.
The complete list is available on the ISO TC 229 website.

- American National Standards Institute's Nanotechnology Standards Panel (ANSI-NSP)
  Website:
  http://www.ansi.org/standards_activities/standards_boards_panels/nsp/overview.aspx?menu
- Japan Industrial Standards Committee - Council on Nanotechnology Standards in Japan (JISC/CNSJ)
  Website: http://www.jisc.go.jp/eng/pj/index.html
- Standardization Administration of China - Committee on Nanotechnology (SAC/TC279)
  Website: http://www.sac.gov.cn/
- Standards Council of Canada – Canadian Advisory Committee for ISO TC229
  Website. http://www.scc.ca/
- Korean Agency for Technology and Standards (KATS) - Materials and Nanotechnology Standards Division
  Website: http://www.kats.go.kr/

At European level:

- British Standards Institute – Committee for Nanotechnologies (BSI –NTI/1)
  Website: http://www.bsigroup.com/en/Standards-and-Publications/Industry-Sectors/Nanotechnologies/BSI-Committee-for-Nanotechnologies/
- DIN/DKE Deutsches institut fur Normung - Steering Committee on Nanotechnology
  Website: http://www.dke.de/dke/
- Association Française de Normalisation – Nanotechnologies (AFNOR- X457)
  Website : http://www.afnor.fr/portail.asp
- UNI – U22 - Italian Organization for Standardization CT U22-Nanotechnologies ….

Regional Standard Organisations

- CEN TC 352 . Nanotechnologies
  Website: http://www.cen.eu/cenorm/sectors/sectors/nanotechnologies/index.asp
- CENELEC – The European Committee for Electrotechnical Standardisation
- ETSI - European Telecommunications Standards Institute

Standards developing organizations (SDOs) [60]

Following a (partial) list of SDOs most involved in nanotechnology:

- ASTM Committee on Nanotechnology (ASTM - E56)
  Website: http://www.astm.org/COMMIT/COMMITTEE/E56.htm
- IEEE Nanotechnology council
  Website: http://grouper.ieee.org/groups/nano/
- SEMI - Semiconductor Equipment and Materials International
  Website: http://www.semi.org/
- VAMAS (Versailles project on Advanced Materials and Standards)
  Website: http://www.vamas.org/

[60] Whereas the term national standards body (NSB) is generally used to refer to the one-per-country standardization organization which is that country's member to ISO, the term Standards Developing Organization (SDO) generally refers to the thousands of industry or sector based standards organizations which develop and publish industry specific standards. Some economies feature only an NSB with no other SDOs. Large economies like the United States and Japan feature several hundred SDOs which are coordinated by the central NSBs of each country (ANSI and JISC in this case). [Wikipedia]

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