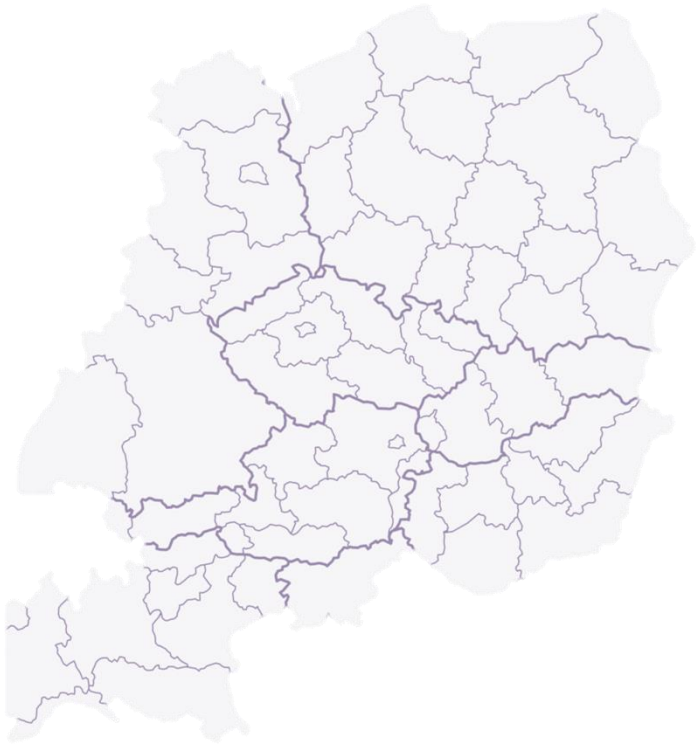
This project is implemented through the CENTRAL EUROPE Programme co-financed by the ERDF.

"NANOFORCE"
Nanotechnology for Chemical Enterprises -how to link scientific knowledge to the business in the Central Europe space



Book of recommendations for the European Commission - Longversion

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NANOFORCE, December 2013

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CONTENT

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Executive Summary

The European regulatory framework is growing slowly but steadily, however available regulations and guidance documents miss some details regarding nanotechnological aspects. An established legal advisory board for chemical enterprises starting in nanotechnology provides information on existing safety and nanotech related regulations within the European region including information and guidelines on endpoint measurements for nanomaterials. Within the aim of the Central Europe project NANOFORCE the general objective is to connect public and private organizations, to carry out collaborative and interdisciplinary research on nanomaterials, and to turn the most promising laboratory results into innovative applications or products.

NANOFORCE is providing a set of recommendations collected for the European Commission in order to evaluate the applicability of the available regulations in the European Union. In the light of the revision of the REACH regulation in 2014 the NANOFORCE recommendations should support the European Commission in order to evaluate the current state of guidance for research and industry on nanotechnology implementation. NANOFORCE therefore has collected samples of three nanomaterials of great interest for marketability and provided a data sets of lab analysis which will lead to safety data sheets showing how the tested nanomaterials can be produced and professionally used conforming to safety and users guidelines. Furthermore recommendations are being given on how to adapt a regular bulk material safety data sheet to the special requirements of a nano-product focusing on the correct implementation of nano-derived products and market placement.

Results are generated by standardized in vitro testing methods for human toxicity and ecotoxicological testing of nanomaterials like nano-silver, zinc oxide and titanium dioxide. A set of recommendations provided will focus on nano specific information for adaption of safety data sheets. Additionally to these recommendations the safety data sheet and exposure scenarios are examples published to show how to classify material, provide data for in depth life cycle analysis relevant for the end user and additionally provide a draft of qualitative exposure scenarios.

An excerpt of the recommendation for the European Commission is available on www.nanoforceproject.eu and by the corresponding author: office@bionanonet.at

1 Introduction

The 'EU Strategy 2020' outlined in a proposal of the European Commission in November 2011 identified "*nanotechnology as one of the Key Enabling Technologies that will promote smart, sustainable and inclusive growth throughout the European Union*" (EU-Horizon 2011). It is expected that nanotechnology applications, including the use of many different engineered nanomaterials will intensify in several industrial sectors in the near future.
The EU-Commission Staff Working Paper on 'Types and uses of nanomaterials' that has been presented last year (EU-COM 2012) highlighted the positive contributions of nanotechnology:

> *"in many areas, nanomaterials can significantly contribute to mastering the challenges of the future and the objectives of the EU 2020 Strategy, such as smart growth, developing an economy based on knowledge and innovation, and sustainable growth, promoting a low-carbon, resource-efficient and competitive economy. They can provide essential contributions to green technologies and environmental protection (e.g. sensors for smart electricity grids, filters for drinking water). They can also contribute to inclusive growth by providing new employment and keeping jobs in the EU … "*

But some of the properties of engineered nanomaterials (ENMs) that are the cause of technological benefits - such as: high reactivity, physical strength, electrical conductivity - may also cause harm when they come in contact with living organisms: *"nanomaterials differ from their macro counterparts not just physically and chemically, but also in their behaviour and effects in living organisms and the environment"* (SRU 2011). The key consideration in this regard is *"that knowledge concerning macroscale materials is not applicable to nanomaterials and thus their environmental and health impacts need to be assessed separately"* (Caliess 2012).

Prof. Kai Savolainen of the Nanosafety Research Center at the Finnish Institut of Occupational Health gave this short summary:

> *".. the small size of these particles is often associated with the potential to cross biological barriers and the ability to enter almost any organ or cell in the body. Through inhalational exposure they are able to enter the alveolar wall and thus have ready access to systemic circulation, and in turn to the body's organs and cells ... in addition, it has been demonstrated that for example manganese oxide nanoparticles are taken up by the olfactory nerve ending in the olfactory epithelium, allowing access to the olfactory bulb at the bottom of the forebrain, which in turn provides a pathway to other parts of the brain ..."* (Barents 2012).

These observations have given rise to concerns about ENM-risks. They are relevant for the public and the regulators, and also for the industry that intends to use these materials. The report that the EU-Joint Research Center (JRC) and the European Academies Sciences Advisory Council EASAC published two years ago on the 'Impact of engineered nanomaterials on health' (JRC 2011) pointed out that the uncertainties related to the safety of ENM represent a major obstacle to marketing and innovation based on these technologies.

It is therefore important to ensure that timely policy development takes these issues into consideration, because "*uncertainty about safety may lead to polarised public debate and to business unwillingness to invest further in nanotechnology*" (JRC 2011).

The potential risks resulting from exposure to nanomaterials are of special relevance to those who produce or use engineered nanomaterials at their workplaces in research facilities or in industry. Several reports from French and U.S. - authorities in charge of workers' health - (AFSSET 2008), (IGAS

2013) and (NIOSH 2013) - have highlighted the importance of a safe and healthy work environment for producers and users of engineered nanomaterials.

Following the introduction given in chapter N°. 1, a short description of the NANOFORCE project is presented in chapter N°. 2. A short overview of nanotech applications is the topic of chapter N°. 3, and the following chapters - N°. 4, 5 and 6 - describe the present regulations covering chemicals and nanomaterials and outline some deficiencies of the regulatory framework in the EU.
Chapter N°. 7 contains a description of the work of the scientific partners of the NANOFORCE project on several commercial available nanomaterials in a number of countries (Germany, Italy, Slovenia and Poland) and the design of the toxicity test. The major results with respect to Safety Data Sheets (SDS) and Exposure Scenarios (ES) are presented in Chapter N°. 8.
General recommendations and suggestions for further nanosafety research can be found in chapter N°. 9 and 10; a recommendation for a future 'Road Map' is the topic of chapter N°. 11.
The literature used for this report is listed in chapter N°. 12.

1.1 Overview of Nanotech – Applications

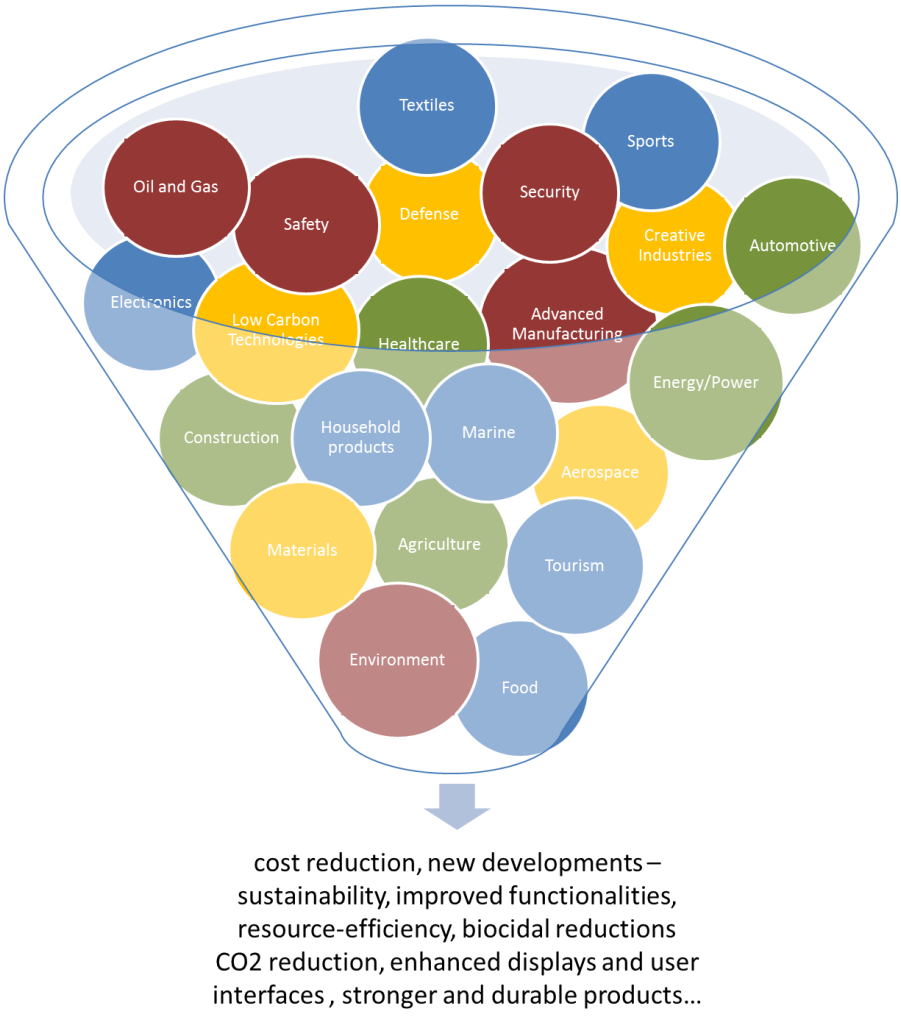

Figure 1 Examples for Nanotechnologies Applications, modified from http://www.nanopro.biz/index.php?option=com_content&view=article&id=53&Itemid=16

1.1.1 Types of nanomaterials

A short overview on the types and the uses of nanomaterials can be found in the 'Commission Staff Working Paper' (EU-COM 2012). This document cited estimates from SRI consulting on global production volumes - with carbon black (9.6 milion t), synthetic amorphous silica (1.5 million t) as the most widespread commodity nanomaterials. Aluminum oxide (200 000 t), barium titanate (15 000 t), titanium dioxide (10 000 t), cerium oxide (10 000 t), zinc oxide (8 000 t), and nanosilver (ca. 20 t) are also being used in industry.
Reliable detailed data about the types and volumes of nanomaterials produced and processed in European countries have not been published, but a French report by the IGAS, the 'inspection générale des affaires sociales' (IGAS 2013) allows an estimate. The data given by IGAS are based on a targeted survey of more than 400 French enterprises carried out on behalf of the French Ministry for Industry. A presentation of these surveys given at workshop of Netherlands Ministry of Social Affairs (MSA-NL 2011) indicated that the exposed population in French industry consisted of 700 people (in production) and 3 200 (in processing). The nanomaterials that were identified by the enterprises were TiO_2, Al_2O_3, CeO, Fe_2O_3, SiO_2, $CaCO_2$ (with CNT and Nanotalc under development); they had been produced / processed in quantities between 10 and 50 000 tonnes.

1.1.2 Uses of nanomaterials

The Commission Staff Working Paper gave a short overview of the uses of nanomaterials - "*from commodity applications in everyday goods to highly specialised low-volume technical applications, e.g. in electronics or biomedicine*" (EU-COM 2012).
The biggest use by far are - according to this paper - "*carbon black nanoparticles that serve as reinforcing agent for rubber in tyres and other rubber goods, followed by functional fillers in polymers (mainly synthetic amorphous silica, in lower quantities also other metal oxides). In the electronic industry, nanomaterials serve as fine abrasives (mainly colloidal synthetic amorphous silica) for the preparation of electronic components and are elements of multi-layered ceramic capacitors (mainly $BaTiO_3$). "*
In cosmetics, the most important nanomaterials are synthetic amorphous silica, titanium dioxide and zinc oxide. Among biomedical applications, gold nanoparticles in medical diagnostics and silver nanoparticles (e.g. in hospital textiles) seem to be the biggest applications in terms of market value.
In addition to those applications, there is use of a wide range of nanomaterials in paints and coatings, catalysts, solar and fuel cells, etc.

The economic sectors with highest use of nanomaterials are (EU-COM 2012):

- aerospace (e.g. lightweight materials, resistant paints and coatings for aerodynamic surfaces);
- automotive industry and transport (e.g. scratch-resistant paints and coatings, plastics, lubricants, fluids, tyres);
- agrifood (e.g. sensors to optimise food production);
- construction (e.g. insulation, stronger building materials, self-cleaning windows);
- energy generation (e.g. photovoltaics) and
- energy storage (e.g. fuel cells and batteries);
- environment (e.g. soil and groundwater remediation);
- cosmetics (e.g. sunscreens, tooth paste, face creams);
- health, medicine and nanobiotechnology (e.g. targeted drug delivery);
- information and communication technologies,
- electronics and photonics (e.g. semiconductor chips, new storage devices and displays);
- security (e.g. sensors to detect biological threats); and
- textiles (e.g. protective clothing, stronger, self-cleaning or fire resistant fibres).

1.2 EU-Regulations concerning Nanomaterials – REACH

All products that are produced in EU-countries or are imported are subject to a standard authorization procedure guided by the EU directive on general product safety, which determines the security measures that must be applied to products prior to market placement.
The high importance that is now being assigned to the topic of 'chemical safety' grew out of the rising concerns about a wide variety of chemicals and their possible effects. After discussions at the EU-Environmental Council in 1998, the four then existing regulations for chemical substances were evaluated, and in 2001, the European Commission proposed a revised framework - the 'White Paper: Strategy for a Future Chemicals Policy'.

In 2003, an early version of a new EU-regulation - REACH [= Registration, Evaluation, Authorization and Restriction of Chemicals] was proposed. It was - and still is -

> "*an innovative approach to chemicals regulation which required the registration, evaluation, authorization and restriction of chemicals …… one of the most controversial legislative proposals in the history of Community law-making.*
> *Among the regime's main features are, first and most importantly an explicit responsibility that is placed on producers and importers for both producing information and for insuring their products do not adversely affect human health or the environment …* " (Fisher 2008).

REACH - EC-Regulation No. 1907/2006 - demands substance-specific information from manufacturers and importers of chemical substances. These data form the basis for the regulation and restriction of hazardous substances; they are conveyed to the European Chemicals Agency (ECHA) that is charged with risk assessments and authorization or restriction procedures.

REACH, as a general provision on chemical substances, applies regardless of the sector and also to nanomaterials which can be seen as a *"specific embodiment of chemicals"* (Calliess 2012). REACH has, in comparison to other and older regulations covering chemicals, a distinct advantage by addressing the deficit of information on the multitude of old 'existing' chemicals that have in the past not been subject to strict registration and testing requirements [in the United States, the proposed 'Chemical Safety Improvement Act' is expected to bring major changes to the old chemical regulation TSCA that are similar to the basic tenets of REACH: "*new chemicals would have to first pass safety screening before entering the market. Chemicals already in commerce would also undergo safety evaluations, which would be prioritized based on the substance's risk to human health and the environment, and high-priority chemicals would undergo further safety testing*" (Verdant 2013).

The framework of REACH covers all chemicals substances - and the definition for those is *"a chemical element and its compounds in the natural state or obtained by any manufacturing process, including additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition."* This wide definition includes - at least in principle - also nanoscale substances. Whether this coverage is also "*enough to cover issues related to nano-technologies, nanosciences and the potential risk for health and the environmen*t" (ETUI 2010) is a controversial topic. The key consideration in this regard has been described recently in a European Law Journal (Calliess 2012) which explained *"that knowledge concerning macroscale materials is not applicable to nanomaterials and thus their environmental and health impacts need to be scientifically assessed separately."* This is due to the fact that the predominant forces ruling the behaviour of small nanoparticles result in different optical, electrical and magnetic properties than those the bulk material possesses. In addition, the surface of nanoparticles displays a greater number of atoms or

molecules, which can increase surface reactivity, and their tiny dimensions enable them to interact with the body's cells and molecules.
Since a number of years, new scientific and technological developments have given rise to concerns to many citizen and stakeholders. In the wake of *"several high-profile regulatory failures of the EU - such as the BSE-crisis of the 1990s, the 'bovine spongiform encephalopathy - a crisis of public confidence and legitimacy emerged"* (Flear 2012). Early on, the European Commission recognised the particular properties of nanomaterials and the resulting need for regulation of risks from nano-technologies also. In its 'Communication on Nanotechnologies' (EU-COM 2004) it stated:

> "*appropriate and timely (nanotechnology) regulation in the area of public health, consumer protection and the environment is essential, also to ensure confidence*
> *from consumers, workers and investors. Maximum use should be made of existing regulation. However, the particular nature of nanotechnologies requires their re-examination and possible revision. A proactive approach should be taken ...* "

Several publications have dealt with evaluations and suggested nano-specific revisions of the chemical regulation REACH - a list is contained in the Annex. Many of them stressed the importance for a 'precautionary approach' when dealing with unknown chemical risks.
The 'precautionary principle' is the basis of Article 191(2) of the Treaty on the Functioning of the European Union; as well as Article 20a of the German Constitution. The international principle of sustainable development and precaution is also part of the 'Rio Declaration' (UNEP 1992), where Principle N$^{O.}$ 15 states: *"In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."*

A 2011 report by the German Advisory Council on the Environment (SRU) on 'Precautionary Strategies for Managing Nanomaterials' has emphasized that it is necessary to close the widening gap between technological advancement and knowledge of risk. Up to now, the institutions and dialogue forums have reached only a relatively small group of experts - *"... as a result, the discussions concerning the risks and regulation of nanomaterials continues to advance generally out of the broader public eye"* (SRU 2011). The SRU-experts recommended to *"extend the existing dialogue activities to a broader cross-section of society, and to ensure that all communications processes operate transparently, that they address risks and opportunities in equal measure, highlight important details, and include non-experts such as consumers and the interested public ... "*

1.3 Discussion of the coverage of REACH for Nano-Regulation

REACH has already brought many changes to the regulation of chemicals in the EU. The EU-Commission concluded in its 'Review on REACH' in June 2013 *"that REACH functions well and delivers on all objectives that at present can be assessed. Some needs for adjustments have been identified, but balanced against the interest of ensuring legislative stability and predictability, the Commission will not propose any changes to the enacting terms of REACH."*

With respect to the coverage of 'nanomaterials', the Commission has expressed its conviction that *"a) current legislation covers in principle the relevant risks relating to nanomaterials, and b) that the protection of health, safety and the environment needs mostly be enhanced by improving implementation of current legislation"*.

The position of a number of stakeholders is different – among them the majority of the European Parliament (EU-Parliament 2009), the Parliamentary Committee on Environment (EU-Parliament-ENVI 2013) and several NGOs (CIEL 2012, EEB 2012, etc.) as well as national Governments, such as France, several governmental agencies (UBA 2013) and advisory boards (SRU 2011). The report of the SRU, the 'German Advisory Council in the Environment' on 'precautionary strategies for managing nanomaterials' concluded:

"Existing chemicals legislation is not sufficient for precautionary regulation of nanomaterials as the nanoform of chemicals. This is partly because it is often unclear how nanomaterials should be dealt with under the law. By definition they are substances and as such are generally subject to regulation but – with few exceptions – they are legally not considered separately from their macroscale counterparts. This is not justified given that they can potentially have modified properties and nano-specific features. Nanomaterials should therefore generally be treated as separate substances in their own right. " (SRU 2011, p.18).

Prof. Kai Savolainen, Director of the Nanosafety Research Centre at the Finnish Institut of Occupational Health in Helsinki, remarked in an article published in Spring of 2012 concerning 'responsible development of nanotechnology' that the risk management approaches in the EU are generally based on the REACH regulation, but that *"this novel regulation does not provide reliable or sufficiently practical guidance on how to assess the potential risks on engineered nanomaterials, and hence, the support of REACH for engineered nanomaterial risk management and governance is limited …"* (Barents 2012)

1.4 Short Summary of the main issues concerning REACH & Nanomaterials

Several documents and scientific publications have dealt with the topic of the adequacy of REACH with respect to the regulation of nanomaterials [a list of the most relevant of these publications can be found in the Annex 'REACH and the regulation of nanomaterials'].
These publications address a multitude of regulatory tropics and of unresolved questions.
Three main issues are expressed in most of them:

① a sense of urgency:
"we still lack a fundamental understanding of how nanomaterials interact with living systems and thus, we are not yet in a position to assess the relevant end-points for nonmaterial-toxicity. At the same time, we are faced with a tsunami of new materials for which testing or screening of toxicity is required...." (FIOH 2013, p. 9);

② the desire for more transparency and pro-active regulation for nanomaterials:
"Parliament has called for the clear labeling of all ingredients present in the form of nanomaterials in substances, mixtures or articles ... and we reiterate our call on the Commission to proactively address nano-specific regulatory issues throughout all Union legislation relevant for application of nanomaterials with potential health, environmental or safety impacts over their life-cycle ..." (EU-Parliament-ENVI 2013);

③ the need to adapt the REACH-directive with respect to nano-specific areas:
"we call on the European Commission to publish without delay a proposal or an appropriate mix of effective measures that should include – (1) a solution to the current lack of a

definition within REACH, (2) a review of the current tonnage levels that determine which information is required for nanomaterials, (3) shortening the period within which information must be obtained, (4) introducing specific requirements for nanomaterials such as characterisation and testing ..." (Atsma 2012).

The recent publication by Christian Calliess and Heidi Stockhaus (Calliess 2012) explains in detail that the 'precautionary principle' that forms the basis of the REACH regulation is - due to technical details and specifications - not always of relevance for nanomaterials: a 'substance' is (in Art. 3(1)) defined as *"a chemical element and its compounds in the natural state or obtained by any manufacturing process"* . Therefore, when substances - such as nanomaterials - differ from their macroscale counterpart solely in terms of size, they do not qualify as substances in their own right.

But all the obligations under REACH are linked to 'substances' - the registration procedure, the obligation to submit a chemical safety report on the properties of the material, the publication of a SDS-safety data sheet. In all those cases where the macro counterpart of a substance has already been registered, the nano-version of the same substance is, basically, not subject to the requirements of REACH:

"but ... in view of the difference between nanomaterial properties and those of the counterpart bulk material and the possibility that this difference also translates into an altred risk profile, it is unjustified to give the nano version of a bulk material a free pass simply because its macro counterpart has been on the market without raising any health or environmental safety concerns ..." (Calliess 2012).

2 NANOFORCE – Activities and Results

2.1 Short Description of the NANOFORCE – Project

The project NANOFORCE is a cooperation of several national and regional chemistry associations and R&D Centres of the Central Europe area [www.nanoforceproject.eu]. It has been co-financed by the ERDF, the 'European Union Regional Development Fund' and intends to foster innovative nanotechnology-sector networks across Central Europe regions and to improve the knowledge about environmental, health and safety issues related to new nanomaterials.
NANOFORCE brings together public and private organizations in the regional areas of Austria, Bavaria, the Czech Republic, Lombardy, Poland, Slovakia, Slovenia, and the region of Veneto.
Through collaborative and interdisciplinary research several nanomaterials - TiO_2, ZnO, nano-Ag - have been characterised and tested in the frame of REACH Regulation; their potential health and environmental hazards have been determined.
These findings - together with the data gained through NANOFORCE-questionnaires about the existing safety procedures in industry - form the basis for general recommendations for toxicological testing and for suggestions for a future 'Road Map' on nanosafety research.
An excerpt of 'NANOFORCE State of the Art Report on Existing Safety Procedures and Nanotechnology related Legislation' concluded:

"The State of the Art Report on Existing Safety Procedures and Nanotechnology related Legislation provides an analysis and evaluation of the current regulations for nanomaterials in the European Union. The risks and benefits of nanomaterials are currently being assessed by many research groups, mainly because of the specific effects resulting from their shape, morphology, size, surface area, functionalization, atomic structure and particle chemistry […] To standardize the identification of nanomaterials and open new perspectives on risk assessment and safety regulations, a recommended definition of nanomaterials was presented by the European Commission in 2011[…] Regarding the regulatory framework for the management of chemicals, REACH is the main legislation in nanotechnology for the overall monitoring of production processes […]."

The report can be made available by the partners of NANOFORCE on contact, please visit www.nanoforceproject.eu for details. Furthermore a publication on the main findings of regulations has been published in Falk et al. 2013.

2.2 Description of the activities of NANOFORCE – research groups in the field of characterization and testing of nanomaterials

The scientific partners of the NANOFORCE project partners selected several nano-materials that are already commercially available or that will be shortly introduced into the market. They have been provided by suppliers within the member countries Germany, Italy, Slovenia and Poland.
The purpose of these tests was to collect data on their toxicity that could be used for adaptions of Safety Data Sheets (SDS) and Exposure Scenarios (ES).

By performing toxicological tests and characterisation methodologies NANOFORCE provides amendments to existing SDS and propose recommendations for the evaluation of those documents.

In the following section the nanoparticles tested are being presented with respect to the partner involved within the testing.

2.3 Results of the NANOFORCE - experiments

2.3.1 Material : NanoAg (powder and varnish)

The company 'Veneto Nanotech (VN)' supports technology transfer of nanotechnology applications to the Italian companies. VN is involved in research projects addressing from definition of nanosafety research strategy, to tests standardization, to exposure and toxicological assessment. VN actively develops new nanotechnology applications, and is working in the voluntary certification of the responsible use of nanomaterials.
A new product, a NanoAg-powder, and a Nano-Ag-varnish that can be applied on plastic tiles was investigated. The experimental plan included the characterization of both products, the determination of human cytotoxicity for the powder, and release and ecotoxicity for the varnish.
To evaluate the silver (Ag) release from commercially available paints containing nano-Ag, painted tiles were exposed to aging processes, in order to simulate the fate they could underwent under indoor and outdoor conditions. The toxicity of Ag powder was carried out on lung cell cultures, while the ecotoxicology was tested on crustacean Daphnia magna and on plant seeds.

The Experiment
Two nanomaterials were characterized: 1) Tecstar AgNPs (powder) and 2) Tectstar AgNPs (water based additive) and their size distribution was determined. No strict standardized tests were followed during the measurements.

AgNPs (1) were analyzed using DLS and TEM. The aggregation of nanoparticles (as a 20 ppm nanoparticle suspension in cell culture medium) was assessed by DLS. TEM based size distribution was obtained by observing a 100 ppm aqueous suspension of AgNPs (1) on carbon coated 300 mesh copper grids. Images were recorded on a side-mounted Olympus Morada CCD camera at magnifications ranging from 67000 to 150000×. Image processing and particle size distribution was made using ImageJ software and involved image resampling, filtering, thresholding, particle identification and characterization. The diameter of each particle was estimated from the particle area assuming a perfectly circular particle. AgNPs (2) were analyzed using TEM as a 40 ppm aqueous suspension on 300 mesh copper grids. Images were recorded on a side-mounted Olympus Morada CCD camera at magnifications ranging from 30000 to 220000×. Image processing and particle size distribution was made using ImageJ software and involved image resampling, filtering, thresholding, particle identification and characterization. The diameter of each particle was estimated from the particle area assuming a perfectly circular particle.

Potential release of Ag from two different kinds of lacquers containing Ag nanoparticles was estimated by simulating their use in outdoor and indoor conditions in static leaching bath. For outdoor exposure, atmospheric precipitations, sun light and seasonal variability were contemporary mimicked by acid leaching solution, UV light and warm-cold turnover respectively. For indoor exposure a cleanup procedure was simulated by sprinkling an all-purpose degreaser on painted boards. The concentration of total Ag (both nanoparticles and ions) was evaluated by analysing all leachate samples by ICP-MS; the release of Ag from painted boards was calculated by considering the final volume of the leachate and the surface of the tested boards. When significant release of total Ag was detected, A4F analyses were performed to investigate the presence of nanoAg. No standradized tests were used.

Ecototoxicity tests were carried on terrestrial plants (OECD, 2003) (seedling elongation as endpoint, acute) and freshwater crustaceans (UNI EN ISO 6341:1999) (immobilization as endpoint, acute). With terrestrial plants (Sinapis alba, Sorghum saccaratum and Lepidium sativum) a 5 ml aliquot of leachate water was added to a polystyrene Petri dish (B 100 mm) fitted with a Whatman No. 1 ashless filter

paper. Ten seeds were placed in each dish (three replicates for each sample). The plates were incubated at 25 °C in the dark for 72 h. Controls (three replicates) were prepared in which seeds were treated with distilled water only. Boric acid was used as reference toxicant.
With crustaceans, acute (48 h) toxicity tests were conducted with Daphnia magna. A 10 ml aliquot of leachate water was added to multiwell plates with lids. Five organisms were placed in each well (four replicates for each sample). The plates were incubated at constant temperature (20 ± 2 °C) and 16 h light/8 h dark cycles. Controls (four replicates) were prepared in which daphnids were treated with clean freshwater water only. Copper sulphate was used as reference toxicant.

The effective concentrations causing 50% effect on the exposed population (EC50) as well as their associated 95% confidence intervals (95% CI) were determined whenever possible as well as the maximum effect. The US EPA Probit Analysis Program (version 1.5) was used to determine EC50 values. In required cases, statistical analyses were carried out using standard ANOVA techniques, followed by Tukey's significant difference test.

For the toxicity assessment, characterized AgNPs were administered to cells in vitro, with the purpose to evaluate their potential toxicity. Cytotoxicity assays were performed upon treatment of epithelial A549 cells, a human cancerous cell line originated from lung carcinomatous tissue and widely used as in vitro model for the analysis of compounds whose major route of exposure is through inhalation. Assays for the induction of pro-inflammatory cytokines were performed on NR8383 cell line, an alveolar macrophage cell line from the lung of rat, which is used in vitro to study macrophage related activities and provides a homogenous source of highly responsive alveolar macrophages. Each assay was preceded by an evaluation of interferences of the AgNPs and the components of the assay, with the aim to avoid false results.
A549 cells were treated with a wide range of AgNPs concentrations for 3 incubation times (6, 24 and 48 hours), and cytotoxicity assays MTS and LDH assays were performed. While LDH assay resulted inappropriate for the evaluation of these AgNPs due to assay interferences, MTS assay was able to detect a dose-dependent and time-dependent toxicity.

Ag powder is actually classified, and the main issue was that Ag as metal has a classification, AgNO3 has a classification. So the decision was to adopt the classification of those forms, which are relevant for the mode of action of nano Ag, and which are confirmed by a paper as reported in the SDS. Concerning the ES, there is no availability for an ES because in the use phase, it is all done in closed or semi-closed systems, with appropriate protections for workers. In addition, no release to the environment is expected due to working systems. The PNEC would not apply but was still calculated to a value of 0.04 µg/L, by applying a AF of 1000 to the lowest short term effect data which was Daphnia pulex 0.04 mg/L.
Ag varnish is not classified is the mixture as such. Within NANOFORCE the classification of both main components, as deducted from the SDS of the two products (Ag and KOH) was merged into two classifications according to CLP guidance. The classification of KOH is obliged in that concentration range by the CLP guidance. The release from the applied varnish under stressful conditions outdoor is negligible, while there is a higher release by using a degreaser as cleaner (indoor use). The leachate is very toxic to Daphnia (with uncertainty it is due to Ag or for other varnish components), and cause bio-stimulation in seedlings.

Nevertheless results were not compared to other published results, nor with other research groups nor NANOFORCE partners. Concerning toxicity, we have tested other nano Ag particles, using the same tests, and those were the term of comparison for the NANOFORCE material. Comparison of release or ecotoxicity was not possible because the tested product (painted tile, additive) was unique.

2.3.2 Material : NanoAg (paint)

SDS and ES for nanoAg (paint)

For the German evaluation a report has been prepared by Dipl.-Chem. Helmut Schmid (Fraunhofer ICT, Pfinztal, Germany). The reports describe the assessment of three nanoproducts (Bioni Perform, Bioni Nature and Bioni Hygienic) according to the following five categories. Each category consists of several criteria that are evaluated on a scale between 1 (poor degree of fulfilment) and 3 (high degree of fulfillment). From the sum of the individual criteria a total degree of fulfillment of the nanoproduct is derived. The product has been evaluated as a real nanoproduct with benefits in e.g. sustainability effect or substitution of more toxic chemicals, that are obtained by using the nanoproduct. To provide a holistic approach to the assessment of nanoproducts also ethical, social and economic consequences are considered. The assessment of the products and a comprehensive review of current legislation are developed further into exposure scenarios, a nano-safety roadmap (i.e. recommendations for further studies).

2.3.3 Material : TiO_2 Nanoparticles

SDS for TiO_2 Nanoparticles

The researchers at the University of Nova Gorica have performed a number of analyses of commercially available TiO_2 (P25 from Evonik Degussa and PC500 from Cristal Global): cytotoxic tests (acute and chronic MTT tests), genotoxic tests (H2A.X histone phosphorylation test) and ecotoxic tests (Lumistox) using three different dispersion protocols.

In the second part of these experiments, the toxicity of water leached from paints containing nanoparticles (TiO_2, ZnO) was tested under different conditions including different leaching regime (washing to imitate rain or immersion), different exposure to solar radiation (0, 14 and 30 days) and deposition of paints on different materials.

Several characterization analyses were performed including Fourier Transform Infrared Spectroscopy, Atomic Absorption Spectroscopy, Dynamic Light Scattering, Nanoparticle Tracking Analysis, SEM, Analytical ultracentrifugation, Particle-Induced X ray Emission, as well as ecotoxicity and cytotoxicity tests. The results showed that washing released much less nanoparticles from paint than immersion, leading to no increase of toxicity in the former case, while after immersion of paints in water ZnO was found to have higher effect on toxicity than TiO_2. However, the toxicity was reduced with time of UV exposure.

The experiment

All experiments on toxicity of titania nanoparticles in commercial powders were performed using three different dispersion protocols of these powders in water (sonication with protein stabilizer, sonication without a stabilizer and simple stirring) to determine their impact on toxicity and to enable comparisons with several previous results of other researchers. Dispersion protocol indeed importantly affected results, despite toxicity of titania was in general very low.

In toxicity analyses we used two standardized methods: MTT test and Lumistox.

In H2A.X histone phosphorylation test we applied fluorescence antibodies to determine the extent of activation of DNA repair systems and the overall number of cells. Final absorbance (optical density) of the solution was measured at 570 nm using Tecan Infinite 200 Automated microplate reader specrophotometer. In genotoxicity assay (H2A.X histone phosphorylation test) we also used fluorescence antibodies to obtain information about cell number, proliferation and survival, and extent of activation of DNA repair systems in different experiments. Results were measured using automated Zeiss fluorescence microscope equipped with appropriate filters ('green' Filter: EX BP 470/40, BS FT 495, EM BP 525/50; 'Dapi' Filter: set EX G 365, BS FT 395, EM BP 445/50).

Lumistox was used to determine acute toxicity on luminescent bacteria in accordance with DIN EN ISO 11348-3. The test system measured the light output of the luminescent bacteria after being

exposed to the testing sample and compared it to the light output of a control (reagent blank) with no exposure to the testing sample. A difference in light output between the sample and the control is attributed to the effect of the sample on the organisms. We used Glass cuvettes 50x12 mm (REF 916 912), freeze-dried luminescent bacteria in accordance with DIN EN ISO 11348-3, Biofix Lumi reconstitution solution, Biofix Lumi Medium for freeze-dried luminescent bacteria (REF 945 608), and LANGE LUMIStherm+LANGE LUMIStox 300 instrument.
For simulations of solar radiation we used SUNTEST XLS+ (daylight (300-800 nm) exposure for 14 and 30 days, irradiance of 750 ± 5 W/m^2, BST = 25°C ± 5 K).

2.3.4 Material : Nano-Ag and ZnO Nanoparticles (powder)

SDS and ES for NanoAg and ZnO (powder)
The Institute of High Pressure Physics (IHPP), also known as 'UNIPRESS', it is a member of the Polish Academy of Sciences. The IHPP investigated two nanosubstances: nano-Ag manufactured by a polish producer and nano-ZnO that had been synthesized in the 'Laboratory of Nanostructures'.
Both materials are available on the market as commercial products. Comprehensive structural investigations of nanopowders were realized in the Laboratory of Nanostructures. Moreover, extensive literature study concerning toxicological and eco-toxicological properties of Ag and ZnO in nano-forms was also performed.
The Experiments
The applied tests are not standardized for materials in their nano-form, but all of them are recommended by EC or OECD for nanomaterials characterization. The eco-toxicity of Ag and ZnO nanopowders was tested in collaboration with Slovenian partner University of Nova Gorica. Standardized method for acute toxicity: LUMISTOX DIN EN ISO 11348-3 was used. The inhibition of the luminescence emitted by the bacteria Vibrio fischeri indicated that NOEL and NLEC of Ag nanoparticles was at least 5 ppm. For ZnO sample NOEL and EC50 reached 5 ppm and 52 ppm, respectively. It should be noted that presented eco-toxicity pa-rameters characterize only particular Ag and ZnO nanopowders and can't be treated as a universal data. Results were compared with many articles form scientific journals (see Markelj A., 2012; http://www.ung.si/~library/diplome/OKOLJE/107Markelj.pdf).

2.3.5 Conclusions

Conclusions – Experiments on SDS and ES
Chemicals in their nanoparticle form can interact differently with biological systems than their conventional forms. Moreover, nanosubstances may present different toxicological properties, that depend on the size of nanoparticles. This is due to the fact that structural parameters of nanoparticulate substances can influence material properties stronger than their chemical composition. Therefore, in the case of nanosubstances, important variables relate to particle size, shape, chemical composition, surface reactivity, bio-persistence etc. Nanomaterials need to be well characterized using standardized procedures.

When using different measurements methods, it should be taken into consideration that nanoparticles interact with environment much easier that bulk samples. Such interaction can influence detected parameters. Therefore, the method should be very well documented and described, including the statistical data of the measurements.

Several stages of the life cycle of nanoparticles can result in the danger of human exposure. Each physical form (powder, embedded in a solid matrix or attached to a substrate) has its own exposure pattern and should be characterized throughout the product lifecycle.

The transfer of nanoparticles from one medium to another can also affect nanoparticles and influence its toxicity. It is an open question how long nanomaterials will keep their properties during storage: the influence of aging and of moisture during storage should be considered. The method of exposure e.g. via inhalation, ingestion or skin contact, as well as the response and susceptibility of the cells exposed, are significant additional factors.

Troubles/pitfalls/difficulties during the tests

The main difficulties occurred during the release and characterization study and were related to the lack of standardized methods and reference materials, and the instability of test material in samples to be tested. These troubles create a lack of reproducibility in the obtained results and the need to repeatedly perform the characterization tests to estimate this variability. General guidelines for DLS and TEM analysis of nanoparticles are available but defined, standardized methods are lacking. Therefore such measurements necessarily differ from one group to another leading to scarce reproducibility. Specific guidelines/SOPs/methods are mandatory for integrated nanoparticle characterization. REACH guidelines do not define specific SOP, they give only indication of the recommended techniques, which we actually used. There are projects underway at European level to define those characterization and testing standards. Additionally problems arouse with the lack of data on precise composition of tested products; Lack of information on what happens with nanoparticles in physiological solution; Complexity of results and the need of specific evaluations tools (statistical programmes as well as databases for results).

3 Recommendations

3.1 Considerations and Responsible Conclusions

We are living in the nanotechnology era. The total marked of nano-enabled products is in the range of the GNP of Germany and will further dynamically grow. For many countries (e.g. South Korea) nanotechnology is the main driving factor of the economy. Frontiers of research are now shifting to the sub-nanometer (picotechnology) dimensions control range, and to organized nano-structures of high order. Nanometrology, nanosafety and nano-regulatory issues are an important topic. This is typical for a technology that spreads widely in industry. It is also important for policy makers, since public acceptance is crucial for wide applications and for support of research in this area.

The arguments to support nanotechnology development are very strong. It is creating jobs. It contributes to balanced national budgets, what is especially important in the time of economic slowdown. Robust health care systems are possible only in countries with a strong economy, and this is not possible without nanotechnology. Further, nanotechnology offers important solutions for key societal needs. Wellbeing and improved products is very important for an attractive industry offer. Low cost solar energy and green transport will contribute to a clean environment and improved health of citisens of the planet. Improved antibacterial nano-technologies will reduce risk in hospitals, swimming pools, etc., and reduce risks with food consumption or reduce food waste. New cancer therapies, diagnostics tools, and nano-tech based regenerative medicine will radically improve health care, reduce its costs, and spread medical care to developing countries. Nanotechnology based water filters may help water supply in countries with water shortage. Thus slowing down nanotechnology development brings about tremendous risks for citizen's safety and health.
On the other hand, implementing new technologies brings about inevitable risks. History teaches us about many cases health and safety of citizens' was impaired due to new technologies. Sometimes the negative side effects had been discovered many years after the technology was introduced. Thus there are strong requests to slow down introduction of new technologies until possible safety risks are recognised. In the case of nanotechnology, such requests are strengthened because nanotechnology is difficult to understand, and also was a used to attract audience in many horror books or films. Thus nanotechnology public perception is an important issue. There may be strong political pressures from various lobbies in favour of one or other kind of decisions. Regulatory risk is a factor negatively affecting economic growth based on nanotechnology.

Even though the fundamental question is not new, nanotechnology imposes unknown before challenges on regulatory institutions. This is due to the very nature of nanotechnology. In the past, regulations were mainly dealing with materials, or chemical substances. In the case of nano-materials, it is the shape and size that determines their properties. For instance, a gold nanoparticle 100 nm in diameter, 50 nm in diameter, 10 nm in diameter, in form of nano-sized star or triangle or film or sphere, may have completely different properties. Further, the properties will depend on the chemical composition of one mono – layer of molecules attached to the surface of the particles. The existing regulations are not prepared to handle such a situation. Furthermore, it is not any more the total production weight per year that is important, but perhaps the total specific surface or chemical activity measured by various methods, which is important. Testing the structure of nano-objects requires expensive equipment and experienced staff. Thus regulatory organisations are under unknown before pressure from two sides: how to avoid having negative impact on economy and citisens health by introducing too stringent regulations, and at the same time how to satisfy society the need for safety of products on the market or technologies in the working place.
What is the solution for the above dilemma: invest in nanotechnology to improve human health and safety and use "precautionary principle" in the sense not to stop an activity that can bring big

benefits" , or slow down nanotechnology development until potential negative side effects are recognized, and use "precautionary principle" in the sense "stop a new technology since it may bring health and safety risk?"

In our opinion new regulations should be based on a deep knowledge of nanotechnology. Nanotechnology needs nano-science based regulations.
It is clear that, if particle dimensions are less than 100 nm there may be a need for special regulations. Additional factors: surface layer chemical composition, real average size, size distribution, specific surface, shape, gradients of chemical composition inside the particles become perhaps more important than the material the nanoparticle is build off. Thus, for nanoparticles less than 100 nm, there may be a need for special regulations before market entry is allowed.
Direct implementation of the above recommendation will however paralyse the nanotechnology market, since methods to analyse nanostructures in an industrial scale are at their infancy, are quite expensive, or not possible yet at all. Application of standard protocols used in the community of environment and health protection experts, is not suitable for nanotechnology, because the nano-aspects of the investigated objects will not be taken into account. A standard protocol is to subject some living organisms to a dose of a substance, and investigate its effect on life time or reproduction ability of the organism. A nanotechnology based approach will take into account the nanoparticles size, size distribution, shape and surface capping layer on toxicity. However, it will take first of all into account the specific characteristic of nanoparticles, which is their extraordinary physico-chemical activity, which depends on their specific surface area (total area of one gram the nanoparticles) and surface capping layer. Thus taking into account factor alone the that the particle size is less than 100 nm is a big error, since beyond that shape there is a myriad of nanostructures, which may have a beneficial or harmful health effect. Further, the attraction force between nanoparticles is tremendous. Two nanoparticles may attract each other with a force per unit area in the range of 1 GPa. This leads to strong agglomeration. For instance in water encountered in typical environmental conditions (soil water, see water, river water), ZnO nanoparticles 20 nm in diameter will agglomerate and form micron sized agglomerates. Thus any living organism will interact with micron sized particles, not any nano-particles. Further, if the nanoparticles are embedded in a matrix (e.g. polymer) and are chemically bonded with the polymer, removing them from the matrix would require pressures also in the range of GPa, that means extremely strong forces. Finally, nanoparticles are thermodynamically unstable. Thy will tend to reduce energy by reducing specific surface (e.g. bond to a matrix or dissolve and precipitate as large particles). Finally, the nanoparticles will dissolve, and concern will be with the toxicity of the ions released in the environment and not with the nanoparticles themselves. Thus, our knowledge of nano-science leads us to following conclusions:

- Standard tests for toxicity of materials or chemical substances are not suitable for nano materials. New test have to be developed
- Nano-science will help to develop new tests for nano-products
- Nano-products environmental and health impacts must be evaluated case by case.
- Present knowledge of nano-science tells us that in most cases nanoparticles will agglomerate and or dissolve, and not act on humans or animals as nano-objects.
- Precautionary principle is to be regarded from the point of view of the possible negative impact of new regulations in the field of nanotechnology on citizens' health and safety , since they may prevent to implement important new technologies

One key message is that the approach to toxicity studies is currently particle-based; it needs to be shifted towards a product-based approach. The results include safety data sheets of the products and are supported by a comprehensive list of references and review of relevant literature. Guidelines provided by different research institutions such as ITS Nano or ISO and OECD as well as guidance provided by REACH could help to determine the most appropriate testing methods, appropriate safety measures and appropriate concentrations to be applied in each experiment. Additionally they

could help to design experiments in more appropriate way to enable further comparisons of research results.

The size of the nanomaterials can have a major influence on their interactions with nano/bio interfaces - very small particles can easily penetrate through boundaries inside the body, while big agglomerates can have toxicological impact because of their surface chemistry.

To ensure that complete and real effects of nanomaterials and nanomaterials in the environment are well taken into consideration, several effects of nanomaterials should be tested:

- their effects on bacteria, different cell types, arthropods (especially detritivores), mammals, algae and plants. Lethal as well as sublethal effects should be evaluated (including effects on reproduction);

- all experiments should draw clear distinctions between different dispersion protocols and different media (deionized water, physiological solution, water with peptides, marine water…);

- the effects and the fate of nanomaterials on/in the cells;

- the fate of nanomaterials in the soil and in the water bodies (distribution between water and bottom, possibilities for further resuspension, effects on organisms in and on the mud).

For all nanomaterials that are used in the form of dust, the amount of leaking into the surrounding air and impact area needs to be considered. For these nanomaterials, the effects on respiratory, and olfactory and digestive systems, as well as on skin and eyes are extremely important.

For all nanomaterials that are used in the form of solutions, it is important to evaluate the toxicity effects of the (pure) solutions. Moreover, their effect on freshwater and marine ecosystems should be evaluated, together with their effects and fate in cells (tissue cultures).

For nanomaterials which are used as coatings, paints or new solid materials, it is essential to evaluate the degree of leakage of these nanomaterials into the environment in different conditions (water, temperature, sun radiation, acid/alkaline environment, ageing, etc.), the fate of these leached nanomaterials in the environment and their toxic effect on different non-target organisms.

In order to produce a meaningful SDS, it is necessary to have the specific information for the product. One of the benefits of nanomaterials is their wide applicability within different fields of application. Following the sections of an SDS, NANOFORCE suggests that the uses to be reported are realistic uses and are linked to the actual use of the product, and not all the possible uses than can be foreseen.

As far as classifications and labeling are concerned, it could be possible to use the same classification as that used for of the bulk substance. Concerning all points mentioned to be taken into consideration for a nano safety data sheet, the preparations of a nano exposure scenario has to relay on the data gained within the process of testing a nanomaterial.

Concerning the Physical-Chemical characteristics, the last IUCLID5 version includes also the 13 nano-specific endpoints recommended by OECD. Those endpoints should also be specifically measured for the product in question and included in the SDS. The endpoints are: Agglomeration/aggregation; Crystalline phase; Crystallite and grain size; Aspect ratio / shape; Specific surface area; Zeta potential; Surface chemistry; Dustiness; Porosity; Pour density; Photo catalytic activity; Radical formation

potential; Catalytic activity. Not all parameters are relevant to all materials. In our opinion, the minimum set of parameters that should be reported for all materials are size distribution, aspect ratio/shape, surface area, surface chemistry, dustiness (for powder), crystalline phase (for nanomaterials with different crystalline phases). Especially important for nanomaterials is the waste management and the disposal phase. This part should be carefully evaluated, collecting scientific evidences to suggest the best way to dispose of the wastes and of the final product.
In order to produce a useful ES, the actual exposure in realistic conditions should be measured. This is because the available exposure models are not specific for nanomaterials, and the final result will be not precise, and overestimated most of the time for the precautionary principle application (e.g. release of nanosilver from a treated surface assumed 100%). This assumption can greatly reduce the applicability of nanomaterials.

3.2 Recommendations based on the NANOFORCE testing results

Suggestions for thorough revisions of REACH have been presented by NGOs (CIEL 2012), (EEB 2012) and by several Governments and Agencies (KEMI 2013), (UBA 2013). These suggestions and first experiences from the REACH registrations (Aschberger 2013) were discussed at a workshop in Brussels in Spring 2013. In summary, NANOFORCE has revised the positions of the Stakeholders and furthermore commented the major issues with respect to possible knowledge gaps:

a) Uniform definition
b) “Case by Case” approach for nanomaterials
c) Standardized methods and reference material (particles in relevant media) as well as reports on safety and exposure assessment for registered nanomaterials
d) Life-Cycle approach in consideration of the precautionary principle

Within the project NANOFORCE research groups have been carrying out characterization and toxicity tests on three nanomaterials (TiO_2, nanoAg, nanoZnO) within the aim to evaluate possible knowledge gaps in risk assessment.

a) Uniform definition

There is the need of a proper definition of nanomaterials including their classification and differentiation into natural, incidental and engineered nanomaterials. Additionally a definition should demand on revealing information on size and characteristics of nanomaterials especially for further registration and labelling purposes (Bleeker et al., 2013).

b) 'Case by Case' approach for nanomaterials

Despite the considerable amount of work and resources in the nanosafety domain, there are still many unanswered questions that have to be addressed to achieve a safe and sustainable development of nanotechnology in commercial applications. The “Second Regulatory Review on Nanomaterials” suggests that the risk assessment of nanomaterials should still be performed on a case-by-case basis; however, while this approach still is crucial to fill several knowledge gaps that are still existing in the whole nano-risk assessment procedure, a strategy to achieve the possibility of a read-across between results achieved into different projects has to be promoted (European Commission, 2012).
This strategy starts from the better use of existing results. Several initiatives, represented for instance by FP6 and FP7 projects, or the OEDC WPMN sponsorship programme, have provided significant amount of data on different classes of nanomaterials. This data represent a valuable source of information, and should be deeply analysed to understand and identify the real knowledge gaps to be addressed in the future research and to develop a science based regulation. Another possible outcome of the analysis of these data is the generation of rational grouping and modelling

approaches, which should be encouraged with the aim of focussing the testing requirements for companies producing and developing nanomaterials.

Explanation of particle properties which are important for the characterisation of nanomaterials can be found in the table below (table 1). The NANOFORCE project group has selected a set of parameters to test the nanomaterials based on the selection provided by several research and working groups (such as OECD WPMN).

Table 1 Specific physiochemical properties and characterization of nanomaterials – Literature Study and experience on recommendations for parameter-selection

Parameter	Sources
Agglomeration/aggregation	(OECD, 2010) (SCENIHR, 2009) (Pettitt & Lead, 2013) (Tiede et al., 2008) (Pronk et al., 2009)
Crystaline phase	(OECD, 2010) (SCENIHR, 2009) (Pettitt & Lead, 2013)
Crystallite size	(OECD, 2010) (SCENIHR, 2009) (Bleeker et al., 2013) (Pettitt & Lead, 2013)
Dustiness	(OECD, 2010)
Representative TEM picture/s	(OECD, 2010) (Tiede et al., 2008)
Particle size distribution	(OECD, 2010) (SCENIHR, 2009) (Bleeker et al., 2013) (Tiede et al., 2008) (Pronk et al., 2009)
Specific surface area	(OECD, 2010) (SCENIHR, 2009) (Bleeker et al., 2013) (Tiede et al., 2008) (Pronk et al., 2009)
Surface chemistry	(OECD, 2010) (SCENIHR, 2009) (Pettitt & Lead, 2013) (Tiede et al., 2008) (Pronk et al., 2009)
Shape	(SCENIHR, 2009) (Tiede et al., 2008)(Pettitt & Lead, 2013) (Pronk et al., 2009)
Catalytic or photocatalytic activity	(OECD, 2010) (SCENIHR, 2009) (Pettitt & Lead, 2013) (Pronk et al., 2009)
Pour density	(OECD, 2010) (SCENIHR, 2009)
Porosity	(OECD, 2010)

In addition the method selection should be depending on the planed use of the nanomaterials and the methods used should be well described documented and preferably standardized. It is necessary to test nanomaterials in different media due to changes in physio-chemical properties and toxicity (Tiede et al., 2008). Furthermore tests have to be performed on nanomaterials concerning their life cycle (environmental fate, storage, etc.) (Bleeker et al., 2013).

Using different methods of measurements we should take into consideration that nanomaterials interact with environment and can change their properties (Pettitt & Lead, 2013).

c) Standardized methods and reference material (particles in relevant media) as well as reports on safety and exposure assessment for registered nanomaterials

- Toxicity assessment of nanomaterials should include the same steps as toxicity assessment of other substances. Special attention has to be taken to test effects of nanomaterials on different organisms that feed on organic matter in/at the bottom of the water bodies and in/on the soil (impacts on their metabolism, reproduction, accumulation etc.). This is especially important in studies of toxicity in the sea and in other waters with considerable ion content.
- Non standardized test, including in vitro test and toxicogenomics approaches should be considered when validated protocols are available, according to Reg EC 1907/2006 Annex 11
- Determination of toxicity of nanomaterials themself (not aggregates) is important in studies of transportation through membranes and accumulation within cells (study of cell-lines). Here we propose the use of sonication with the addition of a protein stabilizer. In the majority of other cases we recommend tests which will study conditions, which appear in the nature (without sonification etc. of the final test solution).
- For photo-active substances it is needed to include studies of toxicity under/after irradiation.
- For substances including nanomaterials it is important to test their release from these materials under different conditions they will face with during their life-time. For example paints should be tested on leaching of their substances under rain and immersion, include effects of UV radiation).

Most results are related to toxicity studies of pure nanomaterials based on *in vitro* and *in vivo* experiments. Undoubtedly, this basic research is essential. But at this point the question must be answered, how these results should be treated. Since these are particle-based individual results, they may not be used for general statements and warnings, especially if no practice-relevant exposure conditions were selected. Otherwise, the public may be confused in general. Concerning hazard testing, a shift in the toxicology testing is required. Toxicology testing shall indeed take an increasing advantage of 21st century tools, in particular High-Content and High-Throughput tools, to have a faster and more informative description of the toxicological feature of each material, with also the perspective of reducing the costs.[1]

To ensure the possibility to read across, a crucial step is that data are achieved with common protocols; a recently published document published by the Danish Environmental Protection Agency (The Danish Environmental Protection Agency, 2013) reviews several of the endpoints used for the regulatory registration of chemicals and the applicability of the test methods used to achieve them to nanomaterials. In addition, several ongoing research initiatives in Europe, for instance the MARINA and NANOVALID research projects, are still validating research tests, to develop standard operating procedures (SOPs) to be adopted also for regulatory testing. The use of harmonised protocols is of paramount importance for the achievement of data that is comparable for the development of grouping and modelling approaches. It is important to point out that such grouping approaches can go beyond the traditional grouping according physicochemical characteristics, but should include exposure routes and toxicological behaviours. The goal is to assess the increased or decreased hazard given by the nano implementation during the product life cycle, and find commonalities between different products. This work would allow the performance of life cycle risk assessment (always linked to a product or a group of products) and to allow an appropriate risk management of end of life phases, and an effective risk communication.

Finally, effective risk communication strategies are to be developed, taking into account safety documents. This aspect is especially relevant for downstream users, consumers, and organisations dealing with recycling and disposal. There is an issue of communication of potential safety problems linked to nanomaterials use. For example, it is important to give all relevant information, and consumers should be advised about the appropriate use of nanoproducts, and disposal

[1] http://www.ncbi.nlm.nih.gov/pubmed/23879741

requirements. There are projects starting to deal with these issues, but results should be used to implement a nano communication strategy.

d) Life-Cycle approach in consideration of the precautionary principle

It is important, both for research and regulation of nanomaterials, to be more product-oriented. The mean to achieve this is the development of a testing strategy that covers the whole life cycle of the nanomaterial, hence applying a cradle-to-grave approach. As indeed highlighted into several documents and scientific papers, both the usage and wasting conditions, and the activity of environmental stressors, are able to modify the physicochemical characteristics of nanomaterials, hence potentially influencing their environmental fate, and their toxicological behaviours. Therefore, while regulation should address this issue, research in parallel should identify when modifications during the life cycle are enough to trigger the necessity of a novel risk assessment.[2]

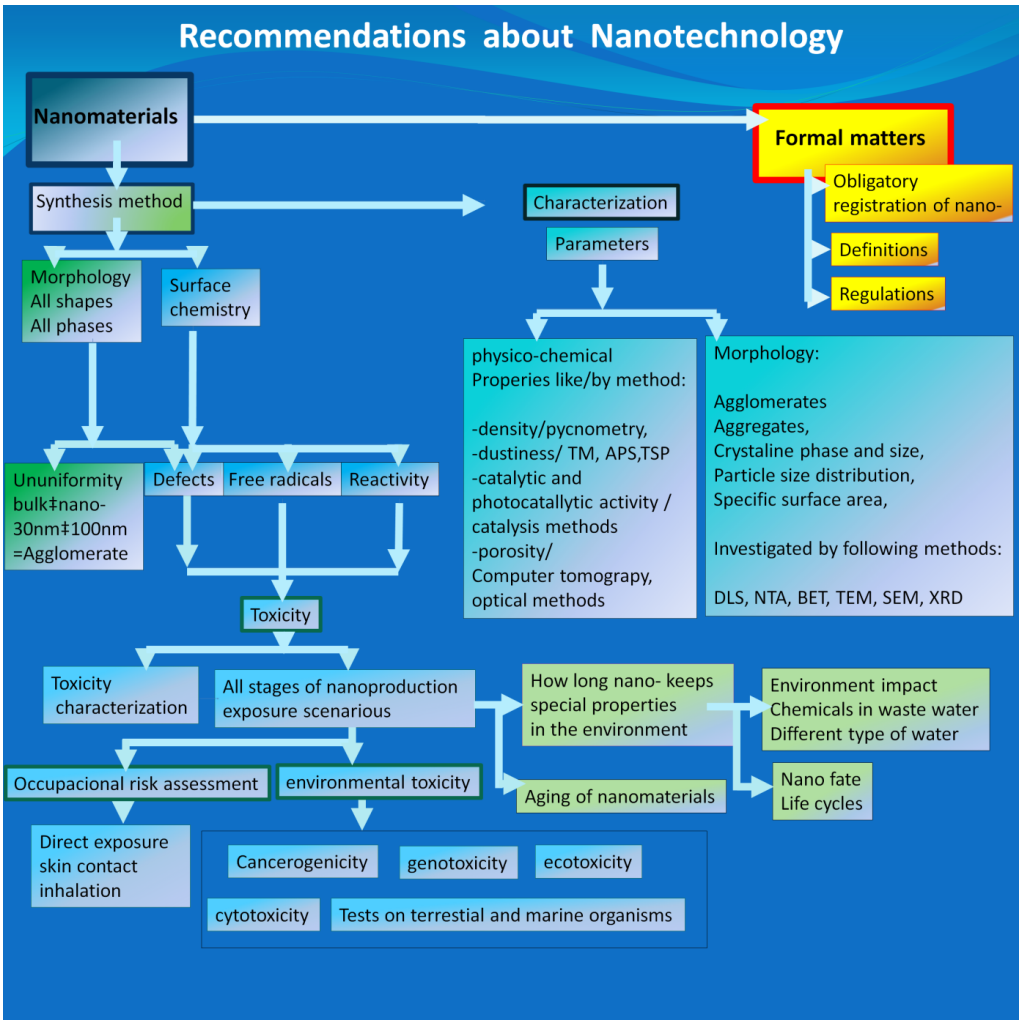

Figure 2 NANOFORCE - Recommendations on future Research Development with respect to current regulations (NANOFORCE project 2011-2014)

[2] http://www.efsa.europa.eu/en/efsajournal/doc/958.pdf

3.3 Recommendations concerning future nano-safety research

Insufficient knowledge on the effects of nanomaterials has led to concern over the environmental, health and safety risks potentially associated with nanotechnology and nanomaterials. They can interact differently with biological systems than their conventional counterparts and exhibit different toxicological, ecotoxicological and exposure features. Whilst a number of general approaches to the risk assessment, safe handling and control of nanomaterials have been published including detailed methods[3, 4, 5, 6] currently, there is no single piece of guidance which can provide a definitive, step-by-step approach. Scientific community as well as international organizations should work on methodologies for assessing risks associated with nanomaterials. Priority has been given to developing horizontal standards for terminology and nomenclature, measurement and characterization, health, safety and the environmental (HSE) and nanomaterial characterization[7].

The future research should focus on exposure assessment, both via experimental activity and modelling, for groups of products, activities, and uses. In this area there is the need to have standardized methods, and different SOPs, to be able to compare the different scenarios. Another issue is the grouping of nanomaterials for testing and eventually forecasting nanomaterials toxicity and properties. This can simplify the CLP activity and the estimation of DNEL and PNEC.

i. Future research projects should be more standardized to improve comparability of results.
ii. The long-term studies of toxicity should be continued.
iii. The possible interaction of different types of nanomaterials should also be examined more closely.

3.4 Outline and Roadmap

Recommendation in the time of Horizon2020 in order to foresee the development within the next three- four years until 2016, when most of the question marks would be solved, regulations and nanomaterials registration principles would be worked out according to recent scientific findings. All the projects under supervision of OECD and European Union will be completed and all legislation work will be finished. Simultaneously the most important research investigations hopefully result in standards of characterization methods, standard of toxicological methods and availability to created databases of SDS, ES, characterization and toxicological tests.

[3] UK, the Control of Substances Hazardous to Health Regulations (COSHH).
[4] BSI PD 6699-2:2007 Nanotechnologies: Guide to safe handling and disposal of manufactured nanomaterials.
[5] BSI PD 6699-3:2010 Nanotechnologies. Guide to assessing airborne exposure in occupational settings relevant to nanomaterials.
[6] OECD ENV/JM/MONO (2009)16 Emission Assessment for the Identification of Sources and Release of Airborne Manufactured Nanomaterials in the Workplace: Compilation of Existing Guidance.
[7] ISO/TC 229 Business Plan (Date: 12/01/2011), Version: Draft 4.

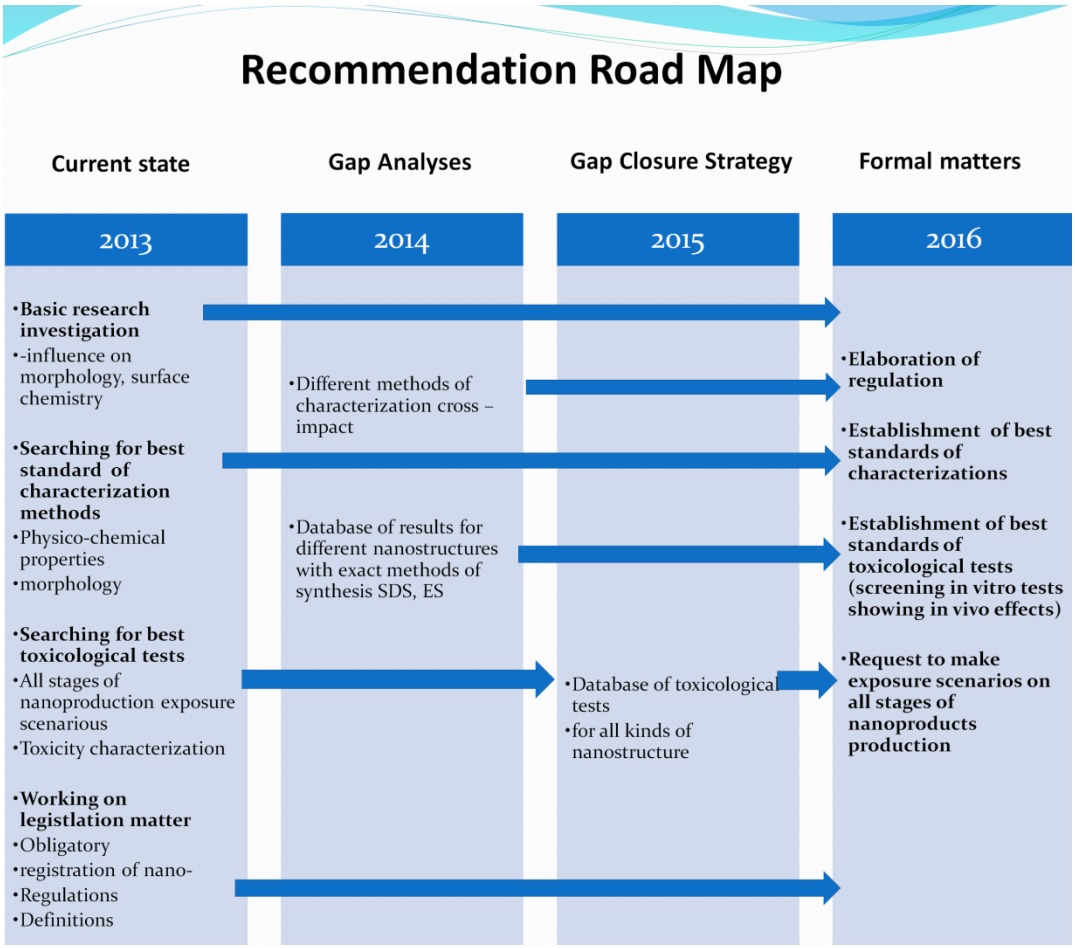

Figure 3 NANOFORCE Recommendation Roadmap for future Nanotechnology-R&D with respect to regulation (NANOFORCE project 2011-2014)

4 Annex : » REACH and the regulation of nanomaterials «

Relevant publications are:

Older publications concerning EU-REACH and nanomaterials

German Environmental Agency - Umweltbundesamt (UBA):
Legal appraisal of nano technologies, Report No. 10/07 (March 2007),
http://www.umweltdaten.de/publikationen/fpdf-l/3198.pdf

SCCP - Scientific Committee on Consumer Products,
EU-Commission, DG Health & Consumer Products, (Dez. 2007) :
'Opinion on Safety of Nanomaterials in Cosmetic Products',
http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_123.pdf

Scientific Committee for Emerging and Newly-Identified Health Risks (SCENIHR):
'Opinion on the appropriateness of the risk assessment methodology …
for assessing the risks of nanomaterials' (29. March 2007),
http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_004c.pdf

Centre For Business Relationships, Accountability, Sustainability and Society (BRASS),
Cardiff University, Working Paper Series No. 48 :'Nanotechnology and the Regulatory Environment - A Synopsis' (2008),
http://www.brass.cf.ac.uk/uploads/wp/WP48FullPaper.pdf

European Parliament resolution of 24 April 2009 on regulatory aspects of nanomaterials (2008/2208(INI)),
http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P6-TA-2009-0328+0+DOC+XML+V0//EN

SCENIHR (Advisory Body to DG Health): 'Scientific Basis for the Definition of the term "nanomaterial" ',
(08.Dec. 2010),
http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_032.pdf

Health and Environment Alliance - NGO (30. June 2011):
'Parliament backs NGOs' call for tighter controls on nanotechnology',
http://www.env-health.org/news/latest-news/article/parliament-backs-ngos-calls-for

European Association of Consumers (BEUC), Newsrelease (19.10.2011) :
BEUC welcomes adaption of nano-definiton, but calls for proper regulation of safety risks,
http://www.beuc.org/Content/Default.asp

EU-Commission Recommendation of Oct. 18, 2011 on the Definition of Nanomaterial, OJ L 275/38 ff.,
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:EN:PDF

Publications dealing with the EU-REACH and the REACH-review

REACH Implementation Project: Substance Identification of Nanomaterials (RIP-oN 1),
Advisory Report (March 2011) AA N° 070307/2009/D1/534733 between DG ENV and JRC,
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