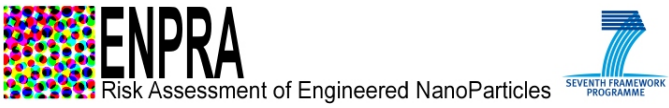

J R C T E C H N I C A L R E P O R T S

Safety Issues and Regulatory Challenges of Nanomaterials

A Symposium organized by
four EU FP7 Projects and the JRC
3-4 May 2012, San Sebastián, Spain

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Safety Issues and Regulatory Challenges of Nanomaterials

Summary of a Symposium organized by four European FP7 Projects
(HINAMOX, NANOPOLYTOX, NEPHH, ENPRA)
and the Joint Research Centre,
San Sebastián (Spain), 3-4 May 2012

Editors: Juan Riego Sintes (JRC), María Blázquez (EKOTEK), Sergio Moya (CIC Biomagune), Socorro Vázquez (LEITAT)

INTRODUCTION

This document represents a summary of the presentations and discussions of the Symposium on Safety Issues and Regulatory Challenges of Nanomaterials organized by four European FP7 Projects (HINAMOX, NANOPOLYTOX, NEPHH, ENPRA) and the Joint Research Centre and held in San Sebastian (Spain) on the 3 and 4 May 2012.

The symposium intended to

- Present to a broad audience the latest results and progress of the European FP7 Projects **HINAMOX, NANOPOLYTOX, NEPHH** and **ENPRA**
- Present the state of the art and recent developments in the legislation and regulations in the EU and the world concerning nanomaterials
- Share knowledge and experiences about the critical issues specific for the risk assessment and LCA of nanomaterials in a regulatory context
- Identify needs and challenges for policy making and regulation of nanotechnology based materials
- Trigger discussions and networking among experts in the different fields of nanosafety.

The Symposium included scientific presentations from very well known scientists from different disciplines involved in nanosafety and included addressed materials and new technologies, immunology/genotoxicity, exposure, regulatory and policy making, risk assessment with an additional focus on regulatory issues along the life cycle of nanotechnology-based materials. The final agenda and the list of participants are included as annex to this document. A link to the presentations can be found at: http://ihcp.jrc.ec.europa.eu/our_activities/nanotechnology and http://www.leitat.org/nanoLCA/index.htm

DAY 1. Thursday 3rd May

Session 1. Four different projects: Four different ways to approach nanosafety

(Chair: Sergio Moya)

In the first session the coordinators of four European FP7 Projects, HINAMOX, NANOPOLYTOX, NEPHH and ENPRA, presented to the audience the aims and latest results and progress in their respective projects.

Summary of Presentations

HINAMOX. Sergio Moya (CIC biomaGUNE, San Sebastian)

The project **H**ealth **I**mp**a**ct of Engineered **M**etal and Metal **Ox**ide Nanoparticles: Response, Bioimaging and Distribution at Cellular and Body Level (HINAMOX), focuses on metal and metal oxide NPs as potentially dangerous to biological organisms. Metal oxide and metal NPs are widely used in various industrial processes and common products. Some examples of these are TiO2 and ZnO as catalysts and UV protectors, CuO in anti-fouling paints, Al_2O_3 as a surface protector, CeO_2 in polishing, indium-tin oxides forming anti-electrostatic coatings and various rare earth oxides in electronics manufacturing. The above mentioned industrial applications highlight the technological and economical importance of these NPs spanning the chemical industry, cosmetic industry, paint industry, electronics manufacturing industry and waste treatment.

The integrated study of NP health effects in this project involves the following steps:

1) Characterization of commercially available NPs, and the fabrication and characterization of NPs with specific properties and with either fluorescence or radioactive labelling.

2) Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) for the analysis of the uptake, distribution and release of NPs in vivo.

4) Quantification and distribution studies at cellular level, by Ion Beam Microscopy (IBM), Electron Microscopy (EM) and Confocal Laser Scanning.

4) Understanding the interaction of NPs with cellular and extra-cellular components.

5) Determination of physiological effects of NPs in vitro.

6) Risk of exposure and toxicological effects of metal and metal oxide NPs.

The projected work in HINAMOX encompasses in this way a complete approach to understanding the safety and human health implications of NPs and nanotechnology based

materials. This approach addresses aspects concerning hazard characterization, human exposure, occupational exposure, and the inflammatory and toxicological response to NPs. The HINAMOX project is particularly strong with respect to the monitoring of NPs in cells and their biodistribution in animal bodies, employing techniques such as IBM and PET/SPECT, which have been little used up to now for studying the fate of NPs in biological systems. In order to achieve this task, a complex and innovative work of engineering and labelling of NPs is proposed. Cellular and body distribution studies together with biodurability tests will enable to understand the biological fate, transport and transformation of NPs within biological entities.

Aspects such as the behaviour, fate, bio-persistence, bio-kinetics, exposure and behaviour of NPs are addressed by HINAMOX, aiming at providing significant knowledge beyond the state of the art.

Project website: http://www.hinamox.eu/

NANOPOLYTOX. Socorro Vázquez-Campos (LEITAT, Barcelona)

NANOPOLYTOX (**Tox**icological impact of **nano**materials derived from processing, weathering and recycling from **poly**mer nanocomposites used in various industrial applications) aims at addressing a number of questions related to the safety of composites that contain polymers and nanomaterials. In general, a composite is a bulk substance consisting of two or more distinct, structurally complementary substances. In the past two decades, polymer nanocomposites, reinforced polymers with low quantities of nanosized organic or inorganic ingredients dispersed into a thermoplastic or thermoset polymer, have emerged as a new class of materials. The use of engineered nanomaterials –ENMS- in composites production offers enormous advantages over traditional macro- or micro-particles including increased tensile strength, modulus and heat distortion temperature, flame retardancy and barrier and anticorrosive properties –amongst other- and applications across a wide range of sectors are currently on the market.

To date, limited know-how presently exists on the environmental and human health risks these materials pose from a life cycle perspective since most of the research activities related with toxicological evaluation of Nanotechnology have been focused on ENMs synthesized at laboratory scale or directly supplied from industrial providers, which represent the most relevant form of exposure in production facilities.

With a fast growing, the consequent exposition to human and environment to these novel materials will undoubtedly increase, not only in the production phase but all throughout the life cycle of nanocomposites based applications: from ENMs manufacturing, to their surface modification for a better dispersion in the polymer matrix to the production of a variety of consumer products that undergo different end of life processes after usage stage. Therefore, the evaluation of the plausible release of ENMs embedded into solid matrixes through the

different life cycle stages and the associated toxicological and ecotoxicological impact of released materials is fundamental for risk assessment and this is what NANOPLYTOX intends to address.

Project website: http://www.nanopolytox.eu/

NEPHH. María Blázquez (EKOTEK, Bilbao)

NEPHH (**N**anomaterials Related **E**nvironmental **P**ollution and **H**ealth **H**azards Throughout their Life Cycle) aims to identify and rate important forms of nanotechnology-related environmental pollution and health hazards that could result from activities involved in silicon-based polymer nanocomposites throughout their life cycle, and to suggest means that might reduce or eliminate these impacts.

The generated knowledge contributes to better understanding the human health and environmental impacts of the selected nanomaterials. The project results set a basis for the establishment of required actions for the efficient management and minimisation of risks. NEPHH also contributes to the acceptance of nanotechnology by the wide public, by helping to ensure its safe and sustainable introduction into the market.

Project website: http://www.nephh-fp7.eu/

ENPRA. Lang Tran (IOM, Edinburgh)

The principal aim of ENPRA is to develop and implement a novel integrated approach for **E**ngineered **N**ano**p**articles (ENP) **R**isk **A**ssessment (ENPRA). This approach is based on the Exposure-Dose-Response Paradigm for ENP. This paradigm states that exposure to ENP of different physico-chemical characteristics via inhalation, ingestion or dermal exposure is likely to lead to their distribution, beyond the portal-of-entry organ to other body systems. The cumulative dose in a target organ will eventually lead to an adverse response in a dose-response manner. Our approach intends to adapt the traditional Risk Assessment approach to ENP and l covers: Hazard Identification; Dose-Response Assessment; Exposure Assessment and Risk Assessment, Management.

The specific objectives of ENPRA are: (i) for Hazard Identification: To characterize a panel of commercially available ENP carefully chosen to address the relevant hazards, properties and potential mechanisms[1]; (ii) for Dose-response Assessment: To assess the hazards of these ENP by means of in vitro toxicology tests based on five body systems: (1) pulmonary; (2)

[1] *The ENP selected represent a subset from a panel of ENP chosen as reference materials for testing in a UK government (DEFRA) funded project and is very likely to be fed into the OECD plan for reference materials testing. The samples were chosen with contrasting properties on size/surface area (TiO2), charge (silica), shape (MWCNT) and surface chemistry (silver, iron).*

hepatic; (3) renal; (4) cardio-vascular and (5) developmental, and five endpoints: (a) oxidative stress; (b) inflammation and immune-responses; (c) genotoxicity; (d) fibrogenicity and (e) developmental toxicity; (iii) To verify the in vitro findings with in vivo models; (iv) for Exposure and Risk Assessment: To use data from this project and other sources (including US data) to: (1) model exposure and the exposure-dose-response relationships by means of mathematical modelling such as PBPK and QSAR-like methods, and extend these deterministic models into probabilistic models (2) to conduct the risk assessment with uncertainty analysis; (v) for Risk Management: To develop and implement a strategy for dissemination to maximize the anticipated high impact of our findings.

Project website: http://www.enpra.eu/

Session 2. Regulatory testing of ENMs and an international perspective

(Chair: Juan Riego Sintes)

In the second session an overview of the current status of the regulatory framework in the EU and the associated research as well as other international activities were presented.

Summary of Presentations

Which nano-EHS strategy for Europe? Giorgios Katalagarianakis (EC, DG RTD)

The past, current and foreseen development of EU funded research related to nanosafety was presented, also in context of nanotechnological development and regulatory needs in particular in the Horizon 2020, where nanotechnology is one of the six key enabling technologies included in the industrial leadership part. Horizon 2020 intends to allow for smart, sustainable and inclusive growth for the EU. Regarding safe development and application of nanomaterials, the intention is to advance scientific knowledge of their potential impact on health or on the environment for pro-active, science-based governance of nanotechnologies, and to provide validated scientific tools and platforms for hazard, exposure and risk assessment and management along the entire life cycle of nanomaterials and nanosystems.
Under FP7 the Commission has already invested more than 100 MEuro on projects dealing with the nanosafety of nanomaterials within ca twenty five projects.

Currently, from a R&D perspective, materials characterisation is well advanced for the most common nanomaterials; although some difficulties remain and the hazards are mostly understood, also with some difficulties remaining as quantification, combination, long term, special cases. However, there is some delay regarding ecotoxicity and exposure monitoring advances fast and there remain the problems of unclear metrics, release from matrix, fate, etc. While Life-Cycle Analysis seems progressing well, faster progress is needed for risk evaluation risk communication and eventually risk reduction.

However, from a regulatory nanosafety perspective, data on materials characterisation are insufficient to underpin Risk Assessment, hazards identification and quantification is not standardised, the exposure monitoring and metrics reliability is low, there is a need for in-situ characterisation techniques, the current data from Life-Cycle Analysis are inadequate and there is a need of criteria for Risk evaluation/acceptance. In addition comprehensive costs-benefits analyses are not really available and risk communication is still challenging.

In order to secure sustainable innovation on nanotechnologies, it is necessary to build on on-going work, so to provide the necessary mass of data on materials and their behaviour and

input them to e.g. the OECD-WPMN. This can be done with a combination of public and private funding, or contribution of resources both from FP-7, the MS, industry and other stakeholders, to establish an international network of laboratories that work together with a compulsory obligation to communicate and share results.

A vision document (what will be the safety requirements in 10 years?) and a strategic agenda (to be updated every 4-5 years) have been developed and presented for the EU leadership in nanosafety. A nanosafety research pillar has been established (the nanosafety cluster) within the nanoFUTURES European technology platform, complemented by national platforms. An implementation plan will follow with particular attention to the European situation.

EU regulatory perspectives on Nanomaterials safety assessment and testing. Henrik Laursen (EC, DG ENV)

The presentation started by addressing the hot topic of the Commission recommendation for a Definition of nanomaterial and its application. Laursen explained that this recommendation is addressed to Member States, EU Agencies and industry so they can integrate it where regulatory provisions exist or are in preparation. Such integration may involve some adaptation to the scope of the field of interest. He recognised the difficulties in implementing its thresholds and mentioned the JRC work on appropriate measurement methods. This definition is the first step to arrive to an appropriate definition for the regulatory context. It is based on science but it has to be implementable in the regulatory arena. He recognised that currently there is not enough information, to make a fully comprehensive definition for all types of variations of nanomaterials. In addition, he commented that by 2014 this recommendation should be reviewed and probably improved; the review will involve e.g. re-examination as appropriate of the size range and the threshold for the size distribution. Another example for possible examination is whether materials with internal structure or surface structure in the nanoscale such as complex nanocomponent nanomaterials including nanoporous and some nanocomposite materials should be included in an improved definition.

Then, he mentioned the REACH Implementation Projects on Nanomaterials RIPoN, particularly the reports on “Information requirements” and “Chemical Safety Assessment” whose advice ECHA is going to incorporate in an update of the on-line Guidance.

The 2nd Regulatory review of Nanomaterials, following-up on the 2008 Communication is imminent and will address an in-depth assessment of key legislation (REACH, ENV legislation etc), scientific development and practical implementation and an assessment of and information on nanomaterials on the market, including safety aspects. Also the REACH Review Communication, due in June 2012, that addresses obligations from REACH and other broader issues will also include issues relevant for nanomaterials as e.g. substance identification, registration and evaluation.

Finally, coming back to other European Commission and ECHA activities, the workshop on REACH and nanomaterials to be held in Helsinki on 30 – 31 May and the establishment of the group assessing already registered nanomaterials under ECHAs committees were announced.

WPMN work on the Safety of Manufactured Nanomaterials. Presented by Tom van Teunenbroek on behalf of Mar González (OECD)

After introducing the main objectives of OECD's programme on Environment, Health and Safety are (protect humans and the environment; gain efficiencies in chemicals management; and avoid non-tariff trade barriers) and their implementation via international harmonisation, co-ordination / co-operation and outreach activities; the presentation focused on the Programme on the Safety of Manufactured Nanomaterials which is implemented by the Working Party on Manufactured Nanomaterials (WPMN).

In particular two projects under WPMN were highlighted: the Safety Testing of a Representative Set of MNs and the Manufactured Nanomaterials and Test Guidelines (TG). They converge through the Sponsorship Programme for the Testing of Manufactured Nanomaterials (Testing Programme).

Preliminary conclusions of a 2009 review of the OECD collection of TGs, indicate that most of them are applicable to nanomaterials, although some need to be adjusted. A key guidance on Sample Preparation and Dosimetry (GNSPD) was published in 2010 and a revised version is to be published in 2012. Preliminary recommended priority has been given to work on test guidelines No: 209, 302B, 310, 316, 403, 412, 413, 436.

The Sponsorship Programme is an international effort to share the testing for 59 endpoints of an agreed set of 13 manufactured nanomaterials of which 12 have a lead sponsor. This Programme intends to obtain an understanding of the kind of information on intrinsic properties that may be relevant for exposure and effects assessment. It is divided in two phases. The first one, focused on testing, will be partially completed in June 2012 with variations on completeness depending on the material. The second phase will involve three steps: integration workshops, evaluation of results, and an additional experimental programme.

The following integrating workshops are foreseen:

- ✓ December 2012, Korea: Toxicokinetics and mechanistic issues.
- ✓ 29-30 January 2013, Berlin: Ecological fate and toxicity.
- ✓ March 2013, TBC: Physical-chemical properties.
- ✓ March-June 2013, TBC: Nanogenotoxicity.
- ✓ May 2013, TBC: Groping of chemicals, Nanomaterials.

Research for Regulatory needs. Tom van Teunenbroek (VROM, The Netherlands**)**

The process from hazard identification to risk assessment, followed by risk management, mitigation, and avoidance, forms the only acceptable route for evaluating MNMs. The proposed NanoReg project (a common European approach to the regulatory testing of nanomaterials) seeks to provide legislators with a set of tools for risk assessment and decision making instruments for the short to medium term, to develop for the long term, new testing strategies adapted to a high number of nanomaterials where many factors can affect their environmental and health impact; and to establish a close collaboration among authorities and industry with regard to the knowledge required for appropriate risk management.

NanoReg will collect and evaluate all existing data, from ongoing and completed national, EU and international sources; define its own boundaries of this project; make a gap analysis to identify those nanomaterials where regulatory and testing input is needed either just to give additional guidance, or to make modifications to existing testing schemes, or for where new methodologies are needed; agree on test methods based on relevant data.; establish a forum to decide how to implement changes to the guidance and guidelines; agree the data storage and management from the project and, finally, ensure open and transparent dissemination of results. An initial set of regulatory questions to be addressed by NanoReg has been defined.

For the success of the project, that is, for ensuring a sustainable development of applications of nanomaterials and nanotechnologies, it is essential a close cooperation between, and decided commitment from, the main players: industry, science, risk assessors, and policy makers. Only by attaining this cooperation we will be able to shift from the current (unsustainable in the long run) situation in which risk and safety considerations are made at the time (or after) the placing on the market of nanomaterials, to a situation where these considerations are already integrated in the research development, innovation and pre-marketing stages of the products of nanotechnologies.

Present developments in nanosafety research and regulation in Brazil: A nanomedicine perspective. Paulo César de Morais (University of Brasilia, Brazil)

Prof. de Morais first gave an overview on the nanosafety initiatives in Brazil. The present stage of nanosafety in Brazil includes the activity of ABNT (Associación Brasileña de normas técnicas) one of the ISO members for the ISO TC229 launched in November 2005, a private and non-profit Brazilian organization, officially in charge of the standardization in the country and the Brazilian representative in many international organizations such as ISO, IEC, COPANT and AWN.

Then, he presented the research pursuit at the Brazilian Institute of Bionanotechnology, of which he is co director. The Institute coordinates research activities taking place at several

universities located in different states of Brazil. While the main issues in the Institute are concerned with the development of therapies on the base of nanomaterials for the treatment of complex diseases and especially cancer by means of photodynamic therapies, the institute also tackles nanosafety issues related to their nanoparticles and nanomaterials under study.

De Morais informed about the next symposium in Sao Paulo, Brasil (17-18 of May): Nanotechnology in cosmetics.

Nanosafety, nanomedicine research in China: Experiences from the participation in EU programs. Zhengwei Mao (Zhejiang University, China)

This presentation first provided an overview of Chinese nanotechnology and nanosafety research. Nanotechnology is one the seven “priority” fields in the mid- and long term development plan for science and technology of China (2006-2020). During the period 2006 to 2010, research efforts have concentrated on aspects such as toxicology of manufactured nanomaterials; fate, transport, and transformation in cell and human body; human exposure and bioavailability; transport, transformation and influence of nanomaterials in environment; and risk assessment of manufactured nanomaterials in working places. It includes a network on nanosafety research of more than twenty institutions and two hundred scientists. Also a relevant number of standardisation activities are also implemented. All these in addition to the high level of funding (that is going to be doubled in the period 2011-2015) has produced a dramatic increase in publications citations and patent applications since 2008. Dr. Mao reminded the opportunities for international cooperation grants between China and European countries provided by the Ministry of Science and Technology of China (MOST) and the National Nature Science Foundation of China (NFSC).

Dr. Mao summarised research related to interactions of nano and colloidal particles with cells in terms of cellular uptake progress, localization inside cells, exocytosis, cytotoxicity, genotoxicity and potential influences on cell cycle, functions and phenotypes after particles uptake.

Finally, Dr. Mao announced the next Spring World Congress on Engineering & Technology (SCET 2012). To take place in Xian, China (26–29 May 2012).

Discussion Panel

The presentations and subsequent discussions recognised the activities and progress in knowledge about the safety aspects of nanomaterials made within the FP7 projects and other international initiatives as the OECD Sponsorship Programme. However there are still relevant scientific information gaps and uncertainties in the Nanosafety area that difficult regulatory decisions making.

The example of substance identification, i.e. determining when a material is different or equal to another one and when changes to that material mean that it is no longer the same material from a regulatory perspective was presented as a paradigmatic stumbling block for regulators.

The many yet unanswered questions risk more and more to hinder the appropriate and sustainable deployment of nanotechnologies and to take the benefits it promises to deliver. Safety concerns on some nanomaterials are a serious obstacle to acceptance of the whole range of materials and products from nanotechnologies. In order to avoid hindering innovation and technological progress and ensuring the continued economic development of the nanotechnology industry an important boost of research on Nanosafety is needed and already in course of implementation by the EU.

Once again, it was stressed that the classical substance by substance testing and assessment approach will not be able to provide the required information in a time span that does not block innovation. Accordingly additional momentum has to be given to approaches such as read across and grouping of substances. However, these or even large scale testing (including high throughput) might be unable to solve the problem of regulatory testing needs. In combination with classical testing and integrated testing strategies, they will undoubtedly be the essential tool for generating the critical mass on knowledge and data to understand the nanomaterials behaviour. But, instead of using this kind of "a posteriori" approaches, a better way to enhance safety, while ensuring innovation and technological development, might be using the data generated by those approaches to identify the set of undesirable characteristics of nanomaterials that determine adverse effects and incorporate ("a priori") this knowledge already in the early design of the nanomaterials.

Session 3. Challenges in nanosafety research: New materials and technologies

(Chair: Sergio Moya)

In the third session the speakers presented future challenges related to new nanomaterials and technologies.

Summary of Presentations

Tailoring Morphology and Surface Chemistry in Gold Nanoparticles. Luis Liz Marzan (University of Vigo/ CIC BiomaGUNE, Spain)

Among the various model systems that have been used to study the properties of nanomaterials, gold nanoparticles offer the great advantage of an outstanding chemical stability, which allows not only a long lifetime but also a high degree of control during their synthesis and surface modification. Therefore, a wide variety of nanoparticle shapes, sizes and surface compositions are currently available, which can be reproducibly synthesized with no need for sophisticated equipment or extensive training. In addition, the aim of this research is to identify the most relevant parameters that affect nanoparticle growth, and in turn morphology and selected properties.

Radiolabelling of NPs and Biodistribution studies. Jordi Llop (CIC BiomaGUNE, San Sebastián, Spain)

The assessment of the biodistribution pattern of labelled metal oxide NPs and inflammatory response after single-dose exposure using Positron Emission Tomography (PET) was presented. Metal oxides are commonly used bulk materials due to their ease of manufacturing, low cost and unique physicochemical properties. There are different applications depending on the particle size. The unique properties of nanoparticles have promoted a massive growth in the nanotechnology sector leading to increased production of nanoparticles. Therefore, many concerns related to the health and environment impact have grown.

In addition, for a proper *in vivo* risk evaluation of nanoparticles, the determination of their biodistribution properties following administration by different routes and the assessment of the inflammatory response after exposure are needed.

Metal oxide nanoparticles: Al_2O_3, ZnO and TiO_2 enriched with ^{18}O were synthesized and activated by bombardment with high energy protons. The activation generated radioactive ^{18}F at the place of ^{18}O. The irradiation process did not introduce significant changes in particle size and crystal structure. The final amount of radioactivity was sufficient to perform whole body in

vivo biodistribution studies in rodents. NPs were administrated to the rodents intravenous, orally and topically. Animals were scanned in the PET device at different times after exposure to the NPs PET experiments were performed for each labelled NP and for each of the administration routes mentioned the biodistribution pattern depends on the nanoparticle size and chemical composition, as well as, the administration route. In addition, PET has been applied in vivo evaluation of the inflammatory response after acute exposition to metal oxide nanoparticles, in this case the NPs are not labelled but the organs of the animal.

Methodologies for proper dose quantification of NPs at cellular level. Irina Estrela (University of Leipzig, Germany)

Understanding the mechanisms of uptake and distribution of nanomaterials in cells and organs is essential for assessing the risk of existing and new nanomaterials for human health and ecology.

Due to their small size, the nanoparticles may influence physiological and biochemical processes in cells and tissues in specific ways causing toxic effects. Knowledge of actual doses of nanomaterials in cells and tissues is thus of pivotal importance as this dose is the central link between exposure and toxicity. Once it is known, the different exposure scenarios can be compared and the toxic effects can be directly related to the doses actually present in cells and organs.

Ion Beam Microscopy (IBM) and Confocal Raman Microspectroscopy were used as novel means for determining doses of nanomaterials and visualization of their distribution for cell culture based in vitro test methods and tissues. These methods are unique and powerful tools for spatially resolved elemental and chemical analysis with submicron resolution.

IBM can be applied for studying authentic (meaning as used industrially and without a labelling) nanoparticles and other nanomaterials.

The study presented addresses the relationship between the applied dose on nanoparticles and their genuine intracellular concentration. In parallel, intracellular dose dependent toxicity studies were conducted by means Flow Cytometry.

The intracellular concentration can be considered as a key endpoint, which is a function of the physic-chemical parameters of the nanomaterials under consideration as a function of their surface functionalisation. This provides the basis for systematic and comparable intracellular dose dependent toxicity studies. Relationship between material features and biological effects could thus be established by using this innovative endpoint.

By means of Raman spectra disconsolation and subsequent cross-correlation analysis, the co-localization of nanoparticles with different intracellular environmental, such as lipid rich regions,

cytoplasm and nucleus was quantified. Their changes can be used as an indicator of the toxic effect of nanoparticles. Studies with nanomaterials as carbon nanotubes, surface engineered with lipids and polyelectrolytes showed that the nature of the surface of nanoparticles and their modifications in biological fluids is crucial for uptake and toxicity.

Polymer nanocomposites: NM-matrix compatibility issues in industrial production processes. Loredana Mercante (LATI, Italy)

Loredana Mercante, from LATI, Italy, presented the polymer nanocomposites: NM-matrix compatibility issues in industrial production processes.

Since the science and technology of nanocomposites has produced great enthusiasm in plastics world, nanoscale particles embedded in a polymer matrix give physical and structural properties cannot be achieved by ordinary synthesis methods.

The extraordinary properties are becoming reality in many practical uses since mechanical resistance, flame retardancy, etc. can be improved. One of the demonstrated benefits of adding nanofillers to polymers is a large increase in stiffness or elastic modulus, per unit mass of reinforcement. This also translates into higher tensile strength as for the PP in figure; hardness and/or scratch resistance.

The leading nano-scale fillers in common industrial projects are nanoclays and carbon nanotubes. Both must be chemically modified by the mean of surface treatment in order to achieve a good dispersion and/or better adhesion with the polymer, as necessary to get substantial benefits.

After some studies, both of these nano-fillers have promoted evident improvements in structural, thermal, barrier, and flame-retardant properties of plastic.

The research has confirmed as well the potential of different types of surface treated nanofillers (nanoclays, nano-metal oxides and NWCNT) in very common polymeric substrates (PA, PP, EVA). In addition, important improvements in the mechanical characteristics of the compound were obtained with nanoclays and carbon nanotubes.

However, there are no clear guidelines regarding safety and toxicological aspects of these nanofillers.

Discussion Panel (New perspectives for ENM)

The scope of session 3 was first to give a general overview of the developments in nanotechnology, in the development of new materials with unique properties due to their

nanoscale structure, and for the fabrication of complex mixtures where the nanomaterials are mixed polymers. Many challenges in nanosafety come from continuous generation of new materials at lab scale. Due to the anticipated further developments, material science, scientists will have to tackle as well nanosafety issues if they want to lead to their commercialization.

The second important issue was to present the state of the art and advances in the study of the fate of nanomaterials “in vitro” and “in vivo”. Very much associated with the study of the fate is the quantification of the real dose of nanomaterials, which is the dose present in the organisms or cells after exposure. The knowledge of the real dose is in fact necessary to understand the mechanisms of action of nanomaterials in biology and to develop a predictable toxicological model for nanomaterials.

After the presentations the discussions focused on the chemistry of new materials at the nanoscale. Several questions were addressed to Prof. Liz Marzan related to the control of optical properties of gold nanoparticles. Then, Dr. Estrella Lopis was asked about the use of Raman microscopy for NP visualization at cells.

Session 4. Nanomaterial interactions with living systems

(Chair: Socorro Vázquez Campos)

In the fourth session the speakers presented some issues related with nanomaterial interactions with living systems.

Summary of Presentations

A methodology shift in safety assessment of nanomaterials for nanomedicine and release in the environment. Marcelo Cacace (National Council of Research, Italy)

Dr. Cacace described nanotechnology as one of the technologies that are envisaged to bring revolutionary changes to our society (together with biotechnology, information technology and cognitive science).

Despite of the fact that the number of nanobased products that reach the market is rapidly increasing, many methodological challenges in the safety assessment of nanomaterials remain. He suggested that current toxicological tests should be refined to incorporate a larger spectrum of bio-interactions. For example, immune networks, epigenetic and cell cycle-related effects. In addition, exposure data on humans and environment should also be generated. At the moment, insufficient knowledge is available to identify systematic rules that govern the toxicity of nanomaterials. For this reason, the risk assessment should be done case by case.

Some projects related to nanomaterials were launched in the 7th FP and other projects on nanosafety/regulatory issues have been or are in the process of being launched. However, Dr. Cacace expressed his opinion that a stronger sense of urgency should be felt in enforcing the program. Besides, it is also essential to have a full public discussion about the social and ethical dilemmas which nanotechnology and the new technological wave will bring.

The needs of strong governance and regulated norms recapitulate the two main obstacles in the route to safe implementation of nanotechnologies. From one side, the definition, characterization and control at the production stage present a formidable challenge to materials scientists. From the other side, there needs to be consensus on unequivocal endpoints and tests to investigate biological effects of nanomaterials.

Safety assessment of novel polymer-silicon composites - from LCA prospective. Huijun Zhu (Cranfield University, UK)

As part of the NEPHH project, this study applied the LCA concept aiming to identify hazardous airborne nanoparticles (NP) that could be released during the development and application of

novel products, focusing on polymeric-silicon composites in recognition of their attractiveness for a wide range of industries, including construction, engineering, automotive and aerospace.

Objectives of the study:

- Characterization of NP for toxicity study.
- Investigation of *in vitro* toxicity of raw SiNP.
- Assessment of toxicity of NP released from silicon-polymer composites.

Under drilling conditions, it was shown the differences in the level of nanoparticles release between polyamide 6 (PA6) based and polypropylene (PP) based polymeric composites and toxicity potency between the polymer-based nanoparticles and the raw silica nanoparticles, suggesting that LCA of the release ad toxicity of nanoparticles could result in more reliable outcomes informing safety evaluation of novel products. Further studies are needed to assess the safety of novel products under scenarios representing all life stages from raw materials sourcing to final product disposal and recycle.

Nanostructures and immune system. Africa González (University of Vigo, Spain)

This presentation highlighted the importance to understand the possible immune reactions to Nanostructures.

Nanomedicine is giving hope to many patients (possibility of new cures or treatments, better methods of diagnosis, reliable medical devices, etc.). However, it is crucial to know the behaviour of nanomedicines on biological systems in order to ensure their safety.

In contrast to some industrially used nanomaterials, such as carbon nanotubes, that have high aspect ratios and are insoluble, nanomedicines are usually biodegradable and relatively biocompatible. In these cases, one of the main issues regarding possible adverse effects is the immune response to these nanomaterials. In fact, although many nanomedicines do not show direct cell toxicity or genotoxicity, they have been shown to induce immune responses, mostly allergic or pseudo allergic reactions. Moreover, macrophages recognize and internalize the majority of their potential therapeutic activity. Specific production of antibodies directed against some nanomaterials has also been reported.

Different approaches to decrease the immunogenicity of nanostructures were presented, such as coating silica nanoparticles with PEG (that practically eliminates its toxicity) or sterilization or even, in future, covering the nanoparticles with proteins able to make them invisible to the immune system..

The importance to understand the immunogenicity of nanomaterials and the need to generate new in vitro methods to study these interactions was clearly demonstrated.

NANOPOLYTOX: Effect of nanoparticle surface functionalisation and accelerated ageing on *in vitro* toxicity. Gemma Janer (LEITAT, Spain)

The surface modification is a common practice to improve compatibility of nanomaterials with embedding matrices and/or to improve their functional properties. In addition, transformation of nanomaterials may also result from other processes that take place during their use and end of life (EOL) stages. For these reasons, the Nanopolytox project evaluates the impact that some of these transformation processes have on nanomaterials cytotoxicity and cell internalization. The comparative cytotoxicity of nanomaterials with and without surface modifications and before and after accelerated weathering processes was presented. In addition, the differences in cell internalization between pristine and functionalized nanomaterials were also discussed.

The conclusions of the talk were the detected minor effects of MWCNT and TiO_2 nanoparticles, regardless of functionalisation or ageing. For other types of nanomaterials, such as SiO2 and ZnO nanoparticles the cytotoxicity depended on the functionalisation and the ageing process. Nanoclays were cytotoxic due to the effects of the organic modifiers. These functionalisations were not lost during the ageing process and, accordingly, their toxicity was similar before and after the ageing process.

Changes in cell internalization were observed after some functionalisation processes. These differences seemed to be related to the changes that the functionalisation caused in the agglomeration / aggregation pattern of the nanomaterials.

In vitro models of dose-response to ENP. Vicky Stone (Heriot Watt University, Edinburgh, UK)

This talk presented different in vitro approaches to evaluate toxicity of nanomaterials. In the absence of any real evidence that engineered nanomaterials are harmful, there is a need to predict the potential toxicity of nanomaterials. The long term goal is to be able to predict toxicity on the basis of property-activity relationships, however, in the short term, a combination of animal and *in vitro* systems for both healthy and disease models will be needed.

The limitations of current in vitro protocols were highlighted and some efforts to develop more sophisticated in vitro systems were presented.

The results of the ENPRA project were presented. In this project, in vitro and in vivo models were used. One of the main conclusions was that the *in vitro* approach predicted broadly well the outcome *in vivo* but there was one false positive (out of four types of nanomaterials: MWCNT, ZnO NPs, TiO_2 NPs, and Ag NPs).

The data from the in vitro experiments with the ENP as well as their characterisation were combined to QSAR analysis to be performed by the JRC.

Finally, the ITS-Nano project was presented. The objective of the project is to develop an Intelligent-Testing-Strategy for Engineered Nanomaterials. This will be done by the ITS-Nano consortium in consultation with international experts in Nanosafety.

Use of Toxicogenomics in the characterization on risk associated with nanomaterials. Sabina Halapannavar (Health Canada)

For hazard assessment, the microarray data can be examined to identify specific biological processes affected. One of the main challenges in using Toxicogenomics for risk assessment is that LOAEL and NOAEL values will need to be established. As an alternative to the NOAEL approach, the BMD (Benchmark dose) approach could be applied to microarray data, by selecting the genes for which statistical significant differences are identified.

As a conclusion, the genomic tools could significantly increase the efficiency of toxicity testing of nanomaterials, be useful in identifying mode of action, and even be used to derive reference doses.

Discussion Panel (Challenges in Hazard Evaluation of ENM)

The understanding of the relevant dose metric for in vitro and/or in vivo studies was subject of discussion. The participants realised that there is currently not a consensus on the most representative dose metric for in vitro systems. Different degree of aggregation and precipitation of NM during the in vitro experiment are regarded as stumbling blocks for comparing different studies. These factors determine the real exposure of cells to NM. In this sense, it may have different consequences for cells that adhere to the plate surface and cells that grow in suspension. Also the degree of dissolution is one of the factors that condition dose for NM that are highly soluble (such as Zn or Ag NPs). There is currently a Qnano toxicology group that is developing a consensus document on how to express dosing for in vitro studies.

Currently, surface area seems to be the best dose metric for low solubility low toxicity NM (such as polystyrene and TiO2 NPs). However, this parameter is not sufficient to describe toxicity of other more complex NMs. So, NMs for which solubility, surface charge, crystal structure and other properties have an important contribution to toxicity, surface area may not be the most appropriate dose metric. In the lack of overall consensus on the most relevant dose metric, studies should present their results using in the dose metric that they consider most relevant, but should provide sufficient information for the future transformation of this parameter to other units to facilitate the comparison among studies.

A specific discussion point was the prediction of nanotube toxicity. Frustrated phagocytosis is a shared mechanism of toxicity by asbestos and CNTs. However, only some asbestos types are carcinogenic, and the question remains on whether CNTs would or not also be carcinogenic. The characteristics that seem to determine the pathogenicity and carcinogenicity of these types

of nanomaterials are: 1) length and aspect ratio, 2) biopersistence /dissolution /biodurability of the NM, 3) bioavailable ion contents. Long straight CNTs are more pathogenic than short-entangled CNTs in terms of frustrated phagocytosis, and in vivo lung inflammation. The coating of NM is also a modulator of its toxicity. The pathogenicity of reactive NM is reduced when they are coated with a nonreactive layer.

One main general conclusion of the presentations and the later discussions was that consensus on appropriate toxicology tests and dose metrics is urgently needed, and some specific proposals were given during the talks. In addition, the role of the immune system on both the toxicokinetics and the toxicity of some nanomaterials were highlighted. Finally, most of the talks highlighted the need to take into consideration the dynamic nature of the nanomaterials properties during their life cycle and also within the test systems.

DAY 2. Friday 4th May

Session 5. Exposure and Risk assessment of ENM

(Chair: Lang Tran)

Summary of Presentations

In vivo dose-response model for ENP. Håkan Wallin (NRCWE, Denmark)

Dr. Wallin presented the *in vivo* dose-response model for engineered nanoparticles.

Risk=exposure x potency

Toxicity=surface area × particle specific activity

Inhalation studies in rodents have been carried out to determine the effects of various substances through this route of exposure both for nanomaterials and for dusts released by sanding paints and lacquers containing nanoparticles. As conclusions, Wallin stated that the lung physiology and biology is complex and, as pathogenic effects that develop over time are poorly understood, there is still a need of animal studies. There is a need of more information related with the toxicity of nanomaterials during the whole life cycle, the toxicity of nanoTiO_2 is masked in paint, as well as, the toxicity of ZnO remains in glass treatment product and to conclude, the instillation and aspiration are alternatives to inhalation experiments.

Industry needs and Research Activities. David Carlander (NIA, Belgium)

As an important part of the responsible use and application of nanotechnology and nanomaterials, the nanotechnology industries are actively participating and supporting research related to the safe handling and use of nanomaterials. This in turn helps them innovate, develop and bring to market new nanoenabled products. However this is only sustainable and acceptable for consumers if we are able to balance the perception of the “data-gap”. The data generated in research projects needs to be useable for broad policy information, regulatory compliance, prioritisation of standardisation and in-house product development.

There is a need of a modification of current testing methods and development of new testing methods. Interference has to be addressed for each test protocol and for each nanomaterial.

Carlander, mentioned some important documents and tools to be taken into account in relation with the support of the research activities:

- The report from REACH Implementation Project on Nanomaterials (RIP-oN): Specific Advice on Fulfilling Information Requirements for Nanomaterials under REACH (RIP-oN 2).
- The European Chemicals Agency (ECHA) recently published three appendices to their "Guidance on information requirements and chemical safety assessment".
- The NANOhub: online database in support of globally harmonised tests and measurements of Representative Manufactured Nanomaterials.

From source to dose and the role of measurement devices and measurement strategies. Derk Brouwer (TNO, The Netherlands)

The assessment the health risks posed by nanomaterials requires accurate measurements and/or modelling of human exposure. There are many challenges in nano-exposure measurements. It is well known that factors as breathing patterns and lung anatomy can affect the actual dose deposited in the lungs and airways. On the other side current existing measurement devices suffer from limitations due e.g. the difficulty to characterise aggregation processes or how to distinguish/separate exposure to the targeted nanomaterials from the background particulate and aerosols.

There is still no general agreement on the appropriate metric to describe exposure. However, there is consensus that for a comprehensive health-relevant exposure assessment, a multimetric approach is needed, including total and size resolved surface area concentration and particle number concentration, mass concentration in nano and inhalable/respirable ranges as well as particle shape and agglomerate structure and composition and bioactivity. So far, these required measuring features are not met by a single device, so a suite of devices is needed. Currently, a range of devices are being developed that can assess breathing zone concentrations more accurately.

Exposure models may provide the appropriate concentrations in the breathing zone; however, much more information is needed for a dose estimate.

The project NanoDevice attempts to tackle some of these challenges, including the possible development of a portable measuring device for nanoparticulate material in the work place.

Mapping environmental risk across Europe from nanoparticles used in consumer products. Richard J. Williams (Centre for Ecology and Hydrology, UK)

Working in NanoFATE, a collaborative project supported by the European Commission, seeks to fill knowledge and methodological gaps currently impeding sound assessment of environmental risks posed by ENPs, examining post-production life cycles of key nanoparticles,

from their entry into the environment as “used products”, through the full range of waste treatment processes to their final fates and potential toxic effects.

Concentrations of nano ZnO and nano Ag have been estimated for all European surface waters using a version of the global water availability and assessment GWAVA (Global Water Availability and Assessment Model) that has been enhanced to model chemical contaminants derived from their use by people. The model allows predicting concentration in waters by taking into account e.g. rainfall runoff and human land use of water, the effects of waste treatment and loss through sedimentation.

Currently, in order to develop the risk assessment, they are calculating the percentage of Zn all over the world. It is an arduous task since there is not only Zn from artificial nano-applications but also from other applications such as construction, and probably the percentage of the last one is higher. In addition, to obtain the percentage of releases to water there is a need to know how much the society consumes, so they can calculate how much quantity of nanomaterial has been released.

As a conclusion, Williams stated that NanoFATE pretends to develop the understanding of the fate and behaviour of the nanoparticles in sewage treatment, soils and surface waters. Ecotoxicological studies will be undertaken at realistic environmental concentrations using a range of terrestrial and aquatic organisms. From this should emerge a robust risk assessment for these nanoparticles which should be more widely applicable.

SANOWORK (Safe nano worker exposure scenarios). Anna Costa (ISTEC-CNR, Italy)

The project objectives are to, develop and Integrate ‘Design Options’ based Risk Remediation Strategies within manufacturing processing lines, to evaluate such strategies by assessing the properties of nanomaterials (ZrO2, TiO2 and Ag, CNTs, PA and TiO2), by analysing risk and by estimating cost/benefit, before and after their introduction. A sound balance between exposure and health hazards data, before and after the introduction of risk remediation strategies, will allow evaluating the effectiveness of existing and proposed exposure reduction strategies.

NANOMICEX (New approaches for Worker Protection and Exposure Risk Management). Carlos Fito (ITENE, Spain)

The NANOMICEX project, stems from the need of ensuring the safety of workers dealing with the production or handling of engineered nanoparticles employed in the pigment/ink industry, in other words, the need of providing the workers with integrated, cost effective and appropriate strategies to control the exposure to engineered nanoparticles. This project will conduct a life

cycle assessment combined with risk assessment studying the health and environmental impact of nanoparticle-based inks and pigments at all the stages of their life cycle.

SCAFFOLD (Strategies, methods and tools for occupational risks management of manufactured nanomaterials in the construction industry). Jesús López de Ipiña (TECNALIA, Spain)

This project is focussed on providing practical, robust, easy-to-use and cost effective solutions to the European construction industry, regarding current uncertainties about occupational exposure to manufactured nanomaterials (TiO_2, SiO_2, Cellulose Nanofibres, Carbon nanofibres and Nanoclays).

Discussion Panel (Challenges in Risk assessment of ENM)

The need for faster progress in exposure measurement and monitoring was recognised.

Session 6. End of life related issues for nanoproducts

(Chair: Maria Blázquez)

In the last session, speakers presented some issues related with the end of life of the nanoproducts, i.e. the concerns of nanoproducts in the whole life cycle.

Summary of Presentations

Environmental exposure of nanomaterials and their by-products through their life cycle. Jerome Rose (CNRS, France)

Nanomaterials are expected to be a key in innovation breakthroughs and to lead to many new applications by 2020. However, during the different stages of the life cycle of ENMs (extraction, nanomaterial production, nano-enabled product fabrication, usage and end of life), releases might occur, both in accidental normal use conditions while currently there are few data on the associated exposure side, a key aspect for the risk assessment.

Exposure routes will much differ depending on the product of interest, in fact, Jerome Rose introduced several examples of exposure routes from four different nanoproducts that are actually on the market on in pre-commercialization status. Methodologies and experimental issues concerning durability characterisation using accelerated aging protocols have been addressed: testing approaches involve the use of climatic chambers simulating different ageing conditions. The first example referred to Silica based nanocomposites, items of research of NEPHH FP7 founded collaborative project. A second example is a commercial product consisting on self-cleaning cement incorporating NanoTIO2 for which several tests are being performed as it is the case of NF EN 12457 Test (amongst other). Thirdly, a NanoCeO2 based composite in outdoor paint has been evaluated mainly in terms of coating maintenance under ageing conditions. Finally, the eco-toxicological profile of NanoTiO2 formulations used in sunscreens (NanoTiO2 Nanocomposite) has been evaluated in contrast to bare TiO2.

Post engineered nanomaterials lifespan: nanowastes classification, legislative development/implementation challenges, and proactive approaches. Ndeke Musee (CSIR NRE, South Africa). Attendance Excused.

This presentation was not given due to impossibility for the speaker to attend. However, a short introduction to the most relevant ideas of his presentation is hereby provided: The nanotechnology-driven economic growth underpinned by dramatic increase of consumer nanoproducts and industrial applications has an associated generation of nanowastes, i.e. waste streams containing environmental contaminants with nanoscale dimensions known as

engineered nanomaterials. Nanowaste generation has generated serious concerns from diverse groups such as: environmental regulatory agencies, scientist, government officials, and etc.

Efforts of Musee's group include the generation of the first systematic nanowastes classification, examining the potential impact of the proposed classification potential to the waste management paradigm, highlighting the unique challenges nanowastes posse to the waste management systems and providing practical steps in addressing some if the highlighted challenges as means of mapping the solution space in promoting safe and responsible nanowastes management.

State of the Science for Understanding MWCNT Release from Polymer Products: The NanoRelease Project. Richard Canady (ILSI, USA)

The presentation initiated from the observation that there is a paucity of information about the exposure side of the risk assessment equation from real-world uses of nanomaterials. Current attempts to characterise nanoparticle exposure are yet insufficient, because a realistic risk assessment requires consideration of real life scenarios and the release of nanoparticles during actual uses. So far mostly qualitative assessments of release from consumer products are available.

Experts have already identified epoxy, polycarbonate, polyurethane, polyamide, polyethylene as most prevalent plastic matrices in commercial applications of MWCNT (Multi Wall Carbon NanoTube). The release-relevance of these ENMs under known use and projected real life cycle scenarios is being explored in the frame of NanoRelease project, focused on MWCNT in consumer products, so that the methods selected for development can have the greatest impact on improving understanding of potential risk-relevant releases. This assessment is being carried out the frame of an international collaboration with relevant stakeholders from industry, science and administrations.

Evaluation of these methods has revealed that standard or generally usable quantitative detection and characterization methods do not exist for ENMs release measuring from consumer products.

Evaluating Nanoparticle Generation during Shredding of Nanocomposites for Recycling. Peter Raynor (University of Minnesota, USA)

The use of nanocomposite parts in new vehicles has raised concerns among US automobile manufacturers about potential releases of engineered nanoparticles as the parts are shredded during EOL recycling. In this United States Council for Automotive Research (USCAR) supported study, test plaques of polypropylene resin reinforced with montmorillonite, polypropylene reinforced with talc, and plain, unreinforced polypropylene were manufactured to

be subsequently shredded by a small-scale granulator inside a filtered and ventilated enclosure n order to more precisely evaluate the release potential of ENMs embedded into plastic matrices.

The findings suggest that recycling of nanoclay-reinforced plastics does not have a strong potential to generate more airborne nanoparticles than recycling of conventional plastics, nor does it have a strong potential to generate unique airborne nanoparticles of the composite nanomaterial.

LCA case studies of nanotechnology-based applications in the project NanoSustain. Michael Steinfeldt (University of Bremen, Germany)

Life Cycle Assessment is the most extensively developed and standardized methodology for assessing environmental and potential impacts throughout a product life from raw material acquisition through production, use and recycling and/or disposal, being its main steps: the definition of the goal and scope of the investigation, inventory analysis, impact assessment and interpretation.

However, the LCA method has some deficiencies that NanoSustains seeks to address such as, the actually existing gap of material and energy flow data in the different stages of the life cycle, the fact that there is no nanospecific emission data along the life cycle, the absence of nanospecific environmental impact categories (PM10 potential, Ecotox and Humantox potential are not relevant) and that neither the technical risks nor the potency of applications are generally considered.

Discussion Panel (Challenges in nanoproducts end of life)

The main discussion was related to the material flows during the life cycle of ENMs including potential release taking place in different real life scenarios (both in normal and accidental conditions).

The need to generate new emission data associated to the different life cycle stages of nanoproducts in order to cover the actually existing gap was highlighted and is actually being pursued by several projects (e.g. NanoSustain). This assessment would contribute to the optimization of the actual LCA modelling tools.

Additional mechanisms causing release were also suggested to Richard Canady, namely ageing and incineration. Logically, release mechanisms to be addressed are to be selected depending on their associated release potential (incineration possibly being a relevant scenario in terms of associated release). Moreover, planned efforts in terms of standardization and possibility of transferring the outcomes of NanoRelease to international organizations such as ISO were confirmed.

Questions addressed to Peter C. Raynor reveal the current need of standardized methodologies at international level for the simulation of the release of ENMs from different consumer products, since the assessment he performed was carried out by means of internally developed protocols on the basis of the state of the art equipment when the experiments were conducted. Possibly, until this standardization is carried out, the most logical approach is work on as many approaches as possible so that there is a wide and sound basis of information that can be retrospectively evaluated in case of need in future stages.

ANNEX

Final Agenda

DAY 1 (Thursday 3rd May)

Arrival & Registration

Official Opening & Welcome

Session 1. Four different projects: Four different ways to approach nanosafety

HINAMOX

Sergio Moya (CIC biomaGUNE, Donostia-San Sebastián, Spain)

NANOPOLYTOX

Socorro Vázquez-Campos (LEITAT, Barcelona, Spain)

NEPHH

María Blázquez (EKOTEK, Bilbao, Spain)

ENPRA

Lang Tran (IOM, Edinburgh, UK)

Poster Session

Session 2. Regulatory testing of ENM and an international perspective
CHAIR: Juan Riego Sintes

Which nano-EHS strategy for Europe?

Georgios Katalagarianakis (EC, Brussels)

EU regulatory perspectives on Nanomaterials safety testing and assessment

Henrik Laursen (DG ENV, Brussels)

OECD's Sponsorship Programme for the Testing of Manufactured Nanomaterials

Tom van Teunenbroek on behalf of Mar González (OECD, France)

Research for Regulatory needs

Tom van Teunenbroek (MINIENM, The Netherlands)

Present developments in nanosafety research and regulatory in Brazil: A nanomedicine perspective
Paulo César de Morais (University of Brasilia, Brazil)

Nanosafety, nanomedicine research in China: Experiences from the participation in EU programs
Zhengwei Mao (Zhejiang University, China)

Discussion Panel (Regulatory issues of NM in EU)

Poster Session

Session 3. Challenges in nanosafety research: New materials and technologies
CHAIR: Sergio Moya

Tailoring Morphology and Surface Chemistry in Gold Nanoparticles

Luis Liz-Marzán (University of Vigo)

Assessment of the biodistribution pattern of labelled metal oxide NPs and inflammatory response after single-dose exposure using Positron Emission Tomography

Jordi Llop (CIC biomaGUNE, Donostia-San Sebastián, Spain)

Methodologies for proper dosis quantification of NPs at cellular level

Irina Estrela-Lopis (University of Leipzig, Germany)

Polymer nanocomposites: NM-matrix compatibility issues in industrial production processes

Loredana Mercante (LATI, Italy)

Discussion Panel (New perspectives for ENM)

Poster Session

Session 4. Nanomaterial interactions with living systems
CHAIR: Socorro Vázquez-Campos

Methodology challenges in safety assessment of nanomaterials. Implications for their environmental impact and for their use in nanomedicine

Marcello G. Cacace (National Council of Research, Italy)

Safety assessment of novel polymer-silicon composites - from LCA perspective

Huijun Zhu (Cranfield University, UK)

Nanostructures and immune system

África González (University of Vigo, Spain)

Effect of nanoparticle surface functionalization and accelerated ageing on in vitro toxicity

Gemma Janer (LEITAT, Spain)

In vitro models of dose-response to ENP

Vicki Stone (Heriot Watt University, Edinburgh, UK)

The use of toxicogenomics on characterization of risk associated with nanomaterials

Sabina Halapannavar (Health Canada, Canada)

Discussion Panel (Challenges in Hazard Evaluation of ENM)

Closure of Day 1.

DAY 2 (Friday 4th May)

Session 5. Exposure and Risk assessment of ENM
CHAIR: Lang Tran

In vivo dose-response model for ENP

Håkan Wallin (NRCWE, Denmark)

Industry Needs and Research Activities

David Carlander (NIA, Belgium)

Engineered nanomaterials: from source to dose and the role of measurement devices and measurement strategies

Derk Brouwer (TNO, The Netherlands)

Mapping environmental risk across Europe from nanoparticles used in consumer products

Richard J. Williams (Centre for Ecology and Hydrology, UK)

Risk Management (New Projects)

SANOWORK

Anna Costa (ISTEC-CNR, Italy)

New Approaches for Worker Protection and Exposure Risk Management - NANOMICEX project

Carlos Fito (ITENE, Spain)

SCAFFOLD: Strategies, methods and tools for occupational risks management of manufactured nanomaterials (MNMs) in the construction industry

Jesús M. López de Ipiña (TECNALIA-USI, Spain)

Discussion Panel (Challenges in Risk assessment of ENM)

Poster Session

Session 6. End of life related issues for nanoproducts
CHAIR: María Blázquez

Environmental exposure of nanomaterials and their by-products through their life cycle

Jerome Rose (CNRS, France)

Post engineered nanomaterials lifespan: nanowastes classification, legislative development/implementation challenges, and proactive approaches

Ndeke Musee (CSIR NRE, South Africa) CANCELLED

State of the Science for Understanding MWCNT Release from Polymer Products: The NanoRelease Project

Richard Canady (ILSI Research Foundation, USA)

Evaluating Nanoparticle Generation during Shredding of Nanocomposites for Recycling

Peter Raynor (University of Minnesota, USA)

LCA case studies of nanotechnology-based applications in the project NanoSustain

Michael Steinfeldt (University of Bremen, Germany)

Discussion Panel (Challenges in nanoproducts end of life)

Closure of the Symposium

Attendance Lists

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Vicki Stone	Heriot Watt University
Lang Tran	IOM
Tom van Teunenbroek	MINIENM
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Huijun Zhu	Cranfield University

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Abstract

This document represents a summary of the presentations and discussions of the Symposium on “Safety Issues and Regulatory Challenges of Nanomaterials” organized by four European FP7 Projects (HINAMOX, NANOPOLYTOX, NEPHH, ENPRA) and the Joint Research Centre, held in San Sebastián (Spain) on the 3rd and 4th May 2012.

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Key policy areas include: environment and climate change; energy and transport; agriculture and food security; health and consumer protection; information society and digital agenda; safety and security including nuclear; all supported through a cross-cutting and multi-disciplinary approach.

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