ERA-NET SIINN
Safe **I**mplementation of **I**nnovative
Nanoscience and **N**anotechnology

Updated Deliverable D1.2 (M36)
Best Practices

Identification of best practices and endorsed measures about precautionary measures and actions and activities (commercial and consumer users of nanoproducts, medical, academic and research users, industrial users)

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Speranta Tanasescu (UEFISCDI, Romania)

Reviewed by Vladimir Maly (PtJ, Germany)

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1. Introduction

Nanotechnology is a system of innovative methods for controlling and manipulating matter at the nanoscale level with the potential to produce new manufactured materials, structures, and devices. Manufactured nanomaterials (MNMs) are generally considered to include a class or subset of these materials with at least one dimension of approximately 1 to 100 nanometers (*for definitions see the document D1.1 Glossary, chapters 1 and 2*). They are usually produced by bottom-up processes, such as physical and chemical vapor deposition, liquid phase synthesis, and self-assembly [Yokel, 2011; Bergamaschi E, 2009; Cao G, 2004] and are designed with very specific properties related to shape, size, surface properties and chemistry (*D1.1 Glossary, chapter 3*). Their properties promise to yield great societal benefits in all sectors. However, the same properties that are commercially and scientifically exploitable also may be the basis for adverse health effects. At these scales, materials exhibit unique properties beyond those expected at the chemical or bulk level that affect their physical, chemical, and biological behavior. Often, the behavior of NMs may depend more on surface area than particle composition itself. Relative surface area is one of the principal factors that enhance its reactivity. At the same time, there are also research reports in which this relationship between size, surface area and toxicity is not straightforward or even reverse. Therefore, it is not always possible to predict effects on the basis of size or surface area alone (Warheit, 2006; Tanasescu, 2006). Other characteristics like the association between structure and functionality, as well as energetic parameters could provide a useful handle for beginning to explore occupational health risk. Even though the full health effects of exposures to MNMs (*D1.1 Glossary, chapter 4)* are not fully understood at this time - much of the current information on the health effects of nanoparticles being limited to animal studies - the results of existing studies provide some basis for preliminary estimates of areas of concerns.

2. Potential health concerns and uncertainties

Exposure to MNMs, from occupational to consumer settings, may occur through inhalation, dermal contact, ingestion or injection (*D1.1 Glossary, chapter 4*), depending on how personnel use and handle them. Concerns with safety regarding the use of MNMs and nanotechnology have been arisen primary from the recognition of several unique attributes of nanoparticles:

- Increased toxicity of ultrafine particles or nanoparticles as compared to larger particles of similar composition. The biological behaviour of nanoparticles is determined not only by the chemical composition, including coatings on the surface, but also by the corresponding shifts in chemical and physical properties, associated to the increase in surface to volume ratio [Krug, 2011; Oberdörster et al., 2004, 2005; Tran et al., 1999; Duffin et al., 2002, 2007; Maynard and Kuempel 2005; Donaldson et al. 2006; Tanasescu et al. 2006].
- A greater proportion of inhaled nanoparticles will deposit in the respiratory tract as compared to larger particles. Particles may be deeply respired into the lungs; may pass through the blood-brain barrier; or translocate between organs [Yokel, 2011; ICRP 1994; Kim and Jaques 2004; Metner 2011].
- Nanoparticles can cross cell membranes and interact with sub cellular structures where they have been shown to cause oxidative damage and impair function of cells in culture. [Landsiedel 2010; Oberdörster, 2010, Möller et al., 2005; Geiser et al. 2005].

- Nanoparticles may be capable of penetrating healthy intact skin and translocating to other organ systems following penetration. [Oberdörster et al. 2010, 2004; Geiser et al. 2005; Borm P. 2006]
- Catalytic effects and fire or explosion are other hazards to consider. [Pritchard 2004].
- In addition to concerns about toxicity of nanoparticles that are inhaled, ingested, or absorbed through dermal exposure during initial contact, nanoparticle waste may present a hazard in the environment [Gerritzen *et al.* 2006].

The widespread use of nanoparticles in research and development for manufacturing and biomedical purposes has outpaced research of safety issues. Despite numerous discussions, workshops, reviews and reports about responsible development of nanotechnology, information describing health and environmental risk of engineered nanoparticles or nanomaterials is severely lacking and thus insufficient for completing rigorous risk assessment on their use. However, given the uncertainty as to the level of risk, one should follow the path of precaution to minimize possible adverse outcomes.

3. The precautionary principle

If a preliminary scientific evaluation emphasizes that there are reasonable grounds for concern that a particular activity might lead to damaging effects on the environment, or on human, animal or plant health, the precautionary principle is triggered [Hansen SF, 2007; Maynard 2007; Groso, 2010; Kessler, 2011]. While this principle has primarily been used internationally around environmental health issues [Rio Declaration Principle 15. Conference on Environment and Development; Rio de Janeiro 1992], other groups are adopting this philosophy to protect the health of workers. In 1996, the American Public Health Association passed a resolution entitled, “The Precautionary Principle and Chemical Exposure Standards for the Workplace”. This resolution recognized the need for implementing the precautionary approach, where chemicals are considered potentially dangerous, until the extent of its toxicity is sufficiently known, and the establishment of strict, preventive chemical exposure limits. In February 2000, the European Commission published a Commission Communication on the precautionary principle (EU Resolution on the Precautionary Principle, 2000) providing a general framework for its use in EU policy [Andorno, 2004]. The precautionary principle is recognized today as a basic principle of environmental, health protection and consumer protection law in many jurisdictions, including the EU and many other states. Together with the related requirement for impact assessments on new technologies, the precautionary principle goes beyond the conventional approach to averting danger by demanding that risks of new technologies should be avoided or at least minimized. Instead of asking the basic risk-assessment question - "How much harm is allowable?" - the precautionary approach asks, "How little harm is possible?" [Peter Montague, 2008]. Faced with reasonable suspicion of harm, the precautionary approach urges a full evaluation of available alternatives for the purpose of preventing or minimizing harm [Kessler, 2011].

Within this context, the precautionary principle is directly applicable to emerging nanotechnologies. Currently, a broad range of processes have been influenced by nanotechnology which will pose likely higher exposure potential to workforces in the nanotechnology occupational settings than consumers of final products. Considering inadequate information, until the results from research studies can fully elucidate the characteristics of MNMs that may potentially pose a health risk, precautionary measures are warranted [British Standard Institute (BSI), “Nanotechnologies – Part 2: Guide to safe handling and disposal of manufactured

nanomaterials," PD 6699-2:2007, UK, 2007; E 2535 – "Standard Guide for Handling Unbound Engineered Nanoscale Particles in Occupational Settings," ASTM, USA, 2007]. Minimizing the risks from known and unknown health, safety and environment hazards of handling, use and disposal of nanoparticles in nanotechnology workplaces (research laboratories and industrial firms) is considered as a priority [Code of Conduct for responsible nanosciences and nanotechnologies research, C(2008)424; Communication Regulatory Aspects of Nanomaterials, COM(2008)366].

The document "**Responsible Production and Use of Nanomaterials**" – Cefic, 17th January 2012 brings together best practice on the concrete application of Responsible Care to the development and use of nanomaterials. It focuses on the six Core Principles of the Responsible Care Global Charter – and, using concrete examples from member companies and federations, describes ways in which each of these principles can be applied to nanomaterials.

The 6 Core Principles of the Responsible Care Global Charter defined here are:

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

Public and private institutions as well as industries have the duty to adopt preventive and protective measures proportionate to the risk intensity and the desired level of protection. Currently, agencies charged with providing safety guidelines, promote the incorporation of cautionary measures in research, with a view toward minimizing or eliminating exposures to NPs.

To fulfill this main objective, a lot of Guidelines [Annex I] has been issued to address the potential health, safety and environment hazards of MNMs and available good practices for mitigating the risks. These guidelines are intended to help the decision makers to:

– develop site-specific controls that will protect workers and the environment,
– offer reasonable guidance for managing the uncertainty associated with MNMs whose hazards have not been determined and reducing to an acceptable level the risk of worker injury, worker ill-health and negative environmental impacts and
– promote consistency in policy and procedures between the nanotechnology workplaces.

Among the 30 industrialized countries of the Organizations for economic co-operation and development (OECD), that United States, England, Germany, France, European commission, Canada and Australia have developed good practices documents in the safety of MNMs field [Annex I - ref. 47]. Following the review of the literature, the present document

attempts to address briefly the good practices which could be suitable and effective in reducing the risks in the areas where exposures to manufactured nanoparticles will occur, that is in the workplace. They are addressed to employers, workers, and researchers engaged in the production, and use of MNMs. Some recommendations in the name of precautionary principle regarding the exposure of consumers to MNMs are also included.

We have to specify that EHS risk assessment (including toxicology testing) is not the objective of the *D1.2 Best practices*. Besides, general principles and practices for working safely with MNMs mentioned in this document are different from the methods of measurements of the specific MNMs properties previously described in the *WP1 Report on "Definition of criteria to examine environment, health and safety (EHS) relevant information"* and *D1.1 Glossary, chapter 3*. Particle sampling and measurement is extremely helpful in understanding exposure and risk in workplace scenarios [British Standard Institute (BSI), "Nanotechnologies – Part 2: Guide to safe handling and disposal of manufactured nanomaterials," PD 6699-2:2007, UK, 2007.8], but they may be more useful for evaluating the need for improvement of engineering controls and work practices. Several of the instruments and techniques like condensation particle counters (CPC), Electron microscopic analysis (SEM and TEM), Scanning or Stepped Mobility Particle Sizer (SMPS), Electrical Low Pressure Impactor (ELPI), Diffusion Charger and Tapered Element Oscillating Microbalance (TEOM) are readily available to measure or estimate directly or indirectly different metrics as mass, number and surface area of nanoparticles [Tiede, 2008; Methner, 2009; Groso, 2010; VCI & BAuA, "Guidance for handling and use of nanomaterials in the workplace," Germany, 2007]. However, any attempt to perform a risk assessment must involve a multifaceted approach incorporating many of the sampling techniques mentioned above, all relevant characteristics of nanoparticle exposure being measured. Searching for the knowledge gaps in the field, the SIINN project concluded that here still a lot of effort should be done before having reliable measurement techniques delivering all relevant data for establishing the risks, particularly in the workplace. At the same time, there are currently no exposure limits specific to MNMs or any national or international consensus standards on measurement techniques for MNMs in the workplace [Methner, 2010]. All this led to the development of practical, clear and simple procedure for nano - safety and health management, which is a general approach based on the state of the nanomaterial in question. The procedure presented as "Best practices" proposes pragmatic mitigation measures for limiting exposures as much as considered reasonable. The proposed methodology and protective measures are provisional in nature pending the availability of more reliable scientific data.

4. Safety Guidelines for handling and working with NMs

One of the first areas where exposures to manufactured nanoparticles will occur is in the workplace (Organizations involved may fall into multiple categories: • Research and Development of NMs; • Inventory companies; • Manufacturer of NMs, such as manufacture of metal oxides, carbon nanotubes, fullerenes or others;• Manufacturer of materials such as paints, plastics, textiles, and ceramics; • Manufacturer of consumer products such as cosmetics and appliances; • Electronics/Information Technology mostly referred to producers of electronic components;• Chemicals;• Coatings; • The developing nanotechnology measurements and standards, manufacturing technologies, environmental remediation and various applications). The quantities of NPs handled in a research/laboratory setting may be smaller compared to an industrial setting; however, unknown, as a whole, are still prevalent

in regards to the occupational safety and health risks of NPs [Nanotechnology safety and health program, NIH, 2012).

Occupational exposure to MNMs can occur:

- during manufacture
- through incorporation in other materials, e.g. polymer composites, medical applications and electronics
- by generating nanoparticles in non-enclosed systems
- during research into their properties and uses
- cleaning of dust collection systems used to capture nanoparticles
- as a result of incorrect disposal
- as a result of accidental spillage

4.1 Basic principles

NPs or NMs will likely be in one of three forms: a powder, in suspension, or in a solid matrix. The form of the NPs or NMs will play a large role in the exposure potential. Certain basic principles will contribute to minimizing your risk.

- Nanomaterials in dry powder form pose the most risk for inhalation exposure and must be handled with care to minimize the generation of airborne dust and to minimize dermal contact. There is also an increasing body of evidence to suggest that CNTs and other nanomaterials with a long, thin and straight shape (referred to as high aspect ratio nanomaterials or HARN) may be particularly hazardous.
- Nanomaterials suspended in a liquid present less risk for inhalation exposure than nanomaterials in dry powder form, but may present more risk from skin contact. Skin uptake of nanomaterials as dry powders and in solvents is poorly understood at this time. It is likely that skin uptake of nanoparticles may be enhanced significantly in compromised skin and/or in the presence of solvents!
- Nanomaterials incorporated into a solid matrix present the least risk for inhalation exposure due to their limited mobility. Although poorly understood at this time, there is circumstantial evidence to caution that certain nanomaterials incorporated into bulk solids may still pose some risk through skin contact, especially nanomaterials with immunological properties, which have some solubility in sebaceous fluids.

4.2 Recommendations for Exposure Control

Controls must be assessed on a case by case basis dependent upon the nanomaterial, quantity, sample matrix, and steps of the process. Among the most effective means to prevent occupational injuries and illnesses are anticipating potential occupational safety and health hazards early in the development of the technology or process and incorporating safe practices into all design, implementation, and operation phases. **Prevention through Design (PtD)** is a management tool for protecting workers from potentially unsafe work conditions. It emphasizes the importance of employee health and safety through the design, construction, manufacture, use, maintenance, and ultimate disposal or reuse of tools, equipment, machinery, substances, work processes, and work premises [NIOSH 2010]. PtD addresses occupational safety and health needs by eliminating hazards and minimizing risks

to workers throughout the life cycle of the process (Figure 2) [Schulte et al. 2008b]. Many nanotechnology research laboratories recognize PtD as a cost-effective means to enhance occupational safety and health and have incorporated PtD management practices within their facilities [Murashov and Howard 2009].

Prevention through Design strategies follow the standard hierarchy of controlling workplace hazards, which includes (1) hazard minimization, eliminating, substituting, or modifying the nanomaterials; (2) engineering the process to minimize or eliminate exposure to the nanomaterials; (3) implementing administrative controls that limit the quantity or duration of exposure to the nanomaterials; and (4) providing for use of PPE.

4.2.1. Hazard Minimization, Elimination, and Substitution

Hazard control starts with determining ways to substitute, minimize, or eliminate the more hazardous materials or processes where possible. Some examples include:

- Minimizing the scale of an experiment.
- Eliminating hazardous materials used in a process.
- Substituting process chemicals for less hazardous ones.
- Using processes or techniques that produce lower airborne concentrations and minimize skin contact.

For nanomaterial researchers, it is often not feasible to eliminate or substitute the nanomaterial. It may be possible, however, to change some aspects of the process in a way that reduces release of the NM. A liquid or solid sample matrix may be used with some NMs. For example, working with NMs suspended in a liquid is a significant improvement over working with them in dry powder form, because the potential for airborne release is reduced in most laboratory processes. However, physical agitation of the liquid (e.g., sonication) may aerosolize small droplets containing the nanomaterial [Johnson et al. 2010]. A liquid matrix such as an organic solvent may enhance in this case dermal absorption.

Opportunities for eliminating the use of hazardous materials or substituting for less hazardous forms do exist in other aspects of NMs production. Engineered nanoparticle research often requires the use of solvents and other potentially hazardous chemicals. Researchers should always attempt to identify and use chemical processes that utilize nontoxic or less-toxic alternatives whenever possible, in order to minimize worker exposures and environmental releases when the process is scaled up to full production. This control strategy, substituting a less toxic material in production processes, has been the focus of much research during the past 20 years.

It is also possible to substitute a less “energetic” operating condition, and thereby modify a process to make it inherently safer. An example of process modification was demonstrated in a laboratory producing CNTs by chemical vapor deposition. Optimizing the furnace reaction temperature maximized the production of CNTs while minimizing the release of CNTs in the furnace exhaust [Tsai et al. 2009].

4.2.2 Isolation and Engineering Controls

Isolation includes the physical isolation of a process or piece of equipment either by locating it in an area separate from the worker or by placing it within an enclosure that will contain the MNMs released. Engineering controls include any physical change to the process or

workplace that reduces contaminant emissions and subsequent employee exposure. Several factors will influence the selection of exposure controls for MNMs, including quantity of nanomaterial handled or produced, physical form, and task duration. As each one of these variables increases, exposure risk becomes greater, as does the need for more efficient exposure control measures (NIOSH 2009). Operations involving easily dispersed dry MNMs deserve more attention and more stringent controls (e.g., enclosure) than those where the MNMs are suspended in a liquid matrix or imbedded in a solid. Liquid nanoparticle suspensions rarely pose a danger of inhalation exposure during routine operations, but they may represent a significant hazard when aerosolized or in unexpected situations such as a spill. MNMs incorporated into bulk solids may pose some risk if the solid matrix is cut, sawed, drilled, sanded, or handled in any way that creates a dust or releases the nanomaterial.

Containment refers to the physical isolation of a process or a piece of equipment to prevent the release of the hazardous material into the workplace. An example of process isolation would be the location of a twin-screw extruder used to make CNT composites in a room separated from the rest of the research facility. An example in chemistry labs is the use of specially designed separate storage cabinets for flammables, acids, and bases. Another example of containment would be a glovebox, which is a sealed container with attached gloves that allows the researcher to carry out process or tasks while being physically separated from the hazard.

Ventilation. It is important that any workplace involving NMs have sufficient general exhaust ventilation (GEV); GEV is typically provided by the building's heating, ventilation, and air conditioning (HVAC) system. They should have nonrecirculating ventilation systems (preferably, 100% exhaust air), and lab pressurization should be negative to the hallway. Recommended ventilation rates for general laboratory use range from 4 to 12 air changes per hour, if GEV systems are used as the primary means of exposure control [OSHA 1990]. Additionally, the air supply and air exhaust should be carefully located so that supplied air passes through the area that is being controlled. The exhaust should be as close as possible to the source of contamination, and the workers should be positioned between the air supply and the source. Exhausted air should be discharged away from windows, other air intakes, or other means of re-entry [ACGIH 2007]. **HEPA-filtration** is recommended for passing the exhaust air [OECD Series on the Safety of Manufactured Nanomaterials No. 28, 2010].

Care must be taken to prevent the migration of MNMs into adjacent rooms or areas through the building's HVAC system, because of area pressurizations and directional airflows, or as a result of equipment and personnel moving from one area to another.

4.2.3 Administrative Controls and Work Practices

Administrative controls contribute to worker exposure reduction, but they do not always reduce the airborne concentration of the contaminant in the workplace. They often include limiting exposure by reducing the time the employee is handling the material, specifying good housekeeping and other good work practices, training employees, and implementing proper labeling and storage of materials. Administrative controls in some research laboratories may include maintaining clean room conditions [Schulte et al. 2008].

Some administrative controls that should be considered include:

- Providing known information to workers and students on the hazardous properties of the nanomaterial precursors or products;
- Education of workers and students on the safe handling of nanomaterials;

- Restricting access to areas by using signs or placards to identify areas of nanoparticle research;
- Transport dry nanomaterials in closed containers;
- Handle nanoparticles in suspension on disposable bench covers;
- Always perform nanoparticle aerosol generating activities in a fume hood, externally ducted biological safety cabinet, or glove box; and
- Clean the nanomaterial work area daily at a minimum with vacuum cleaners equipped with **HEPA filters** or wet wiping method for any operation involving powdered NPs.

Training is an important component of the administrative control:

- Ensure that employees/researchers/students have both general safety training and lab-specific training relevant to the MNMs and associated hazardous chemicals used in the process/experiment. Some specific Laboratory Chemical Safety Toolkit for guidance on training (SU Toolkit) could be used (http://chemtoolkit.stanford.edu/ChemSafetyTraining)
- Lab-specific training can include a review of this safety fact sheet, the relevant Material Safety Data Sheets (if available), and the lab's Standard Operating Procedure for the experiment.
- It is necessary to inform and involve the employees in the risk assessment process. They should know the significant findings of the risk assessment; the precautions they should take to protect themselves and their fellow employees; the results of any monitoring of exposure, especially if these exceed any workplace exposure limit (WEL); the collective results of any health surveillance. Without the informed and competent participation of employees, any measures identified as necessary in the risk assessment are unlikely to be fully effective.

Work Practices

- ***Selection of Nanomaterials:***
  - Whenever possible, handle nanomaterials in solutions or attached to substrates to minimize airborne release.
  - Consult the Material Safety Data Sheet (MSDS), if available, or other appropriate references prior to using a chemical or nanomaterial with which you are unfamiliar. Note: Information contained in some MSDSs may not be fully accurate and/or may be more relevant to the properties of the bulk material rather than the nano-size particles.
- ***Safety Equipment:***
  - Know the location and proper use of emergency equipment, such as safety showers, fire extinguishers, and fire alarms.
- ***Hygiene:***
  - Do not consume or store food and beverages, or apply cosmetics where chemicals or NMs are used or stored since this practice increases the likelihood of exposure by ingestion.
  - Do not use mouth suction for pipetting or siphoning.
  - Wash hands frequently to minimize potential chemical or nanoparticle exposure through ingestion and dermal contact.

- Remove gloves when leaving the laboratory, so as not to contaminate doorknobs, or when handling common use objects such as phones, multiuser computers, etc.

- ***Labeling and Signage:***
  - Store in a well-sealed container, preferable one that can be opened with minimal agitation of the contents.
  - Label all chemical containers with the identity of the contents (avoid abbreviations/ acronyms); include term “nano” in descriptor (e.g., “nanozinc oxide particles” rather than just “zinc oxide.” Hazard warning and chemical concentration information should also be included, if known.
  - Use cautious judgment when leaving operations unattended: i) Post signs to communicate appropriate warnings and precautions, ii) Anticipate potential equipment and facility failures, and iii) Provide appropriate containment for accidental release of hazardous chemicals.
- ***Cleaning:***
  - Wet wipe and or HEPA-vacuum work surfaces regularly.
- ***Transporting:***
  - Use sealed, double-contained container when transporting NMs inside or outside of the building.
- ***Buddy System:***
  - Communicate with others in the building when working alone in the laboratory; let them know when you arrive and leave. Avoid working alone in the laboratory when performing high-risk operations.

4.2.4 Clothing and Personal Protective Equipment

Personal protective equipment (PPE) should be required when engineering and/or administrative controls are not feasible or effective in reducing exposures to acceptable levels and wherever it is necessary because of hazards. Protective equipment must be used and maintained in a sanitary and reliable condition [OSHA 2008]. Based on the uncertainty of the health risk of nanomaterials, it may be prudent to wear appropriate PPE on a precautionary basis. PPE can include respirators, gloves, clothing, face shields, safety glasses, and other garments designed to protect the wearer.

There are limited referenced guidelines for appropriate PPE (e.g. gloves, clothing) for protection from nanoparticles.

PPE is typically tested at certain particle size ranges. For example, protective clothing 5 (PC5) exhibited a penetration of about 17% at 100 nm whereas protective clothing 2 (PC2) was found to have a penetration of about 80% at 500 nm (Safe Work Australia 2009). The size of the nanoparticle may be a factor in determining appropriate PPE. Accordingly, this should be tested at 300 nm, because particles in this size range have been found to be the most penetrating ones.

Research is ongoing into the appropriate selection of labcoat material as it related to NP penetration.

Standard laboratory PPE (e.g. lab coat, gloves, etc.) should be utilized when working with NPs.

Gloves

Personnel should wear polymer gloves (e.g. nitrile) when handling NMs. Wearing two layers of gloves may be a best practice until more is known on nanoparticle penetration through glove materials and skin. Reference the following for general guidelines on glove type selection in reference to the chemical or material being used:

> Appendix D of the *NIH Chemical Hygiene Plan*:
> http://www.ors.od.nih.gov/sr/dohs/LabServices/Pages/default.aspx
>
> PPE selection guide (link from OSHA website):
> http://www.osha.gov/Publications/osha3151.pdf

Respirators

Personnel should utilize appropriate engineering controls in lieu of respirator use. Respirators may be considered for use for certain job task/procedures where engineering controls are not feasible.

Research into the effectiveness of respirators used for protection from nanoparticles is ongoing and incomplete. Some studies indicate that respirators, including N-95 respirators, may provide some protection. The particle size of the nanoparticle should be evaluated in determining the appropriate respirator (penetrating particle size of the respirator).

Respirators, if used, should be in accordance with the Respiratory Protection Program (RPP)
http://www.ors.od.nih.gov/sr/dohs/HealthAndSafety/IH/Pages/ih_respiratory.aspx

The results show that the NIOSH and CE respirators generally limit penetration of ENMs to concentrations below their ranked efficiency level, which is based on 300 nm particles (Yokel, 2011).

Dust Masks (and Surgical Masks)

Dust masks (and surgical masks) should not be used for protection from nanoparticles.

Eye protection

Safety glasses are mandatory when manipulating nanoparticles, whether in powdered form or in solution (Guide for the Safe Handling of Nanotechnology-based Products, 2009).

For increased protection, safety goggles with a full seal around eyes should be worn for certain applications (e.g., those involving significant exposure to aerosols). Some universities recommend that a face shield be worn.

(Canadian Centre for Occupational Health and Safety
www.ccohs.ca/oshanswers/prevention/ppe/glasses.html)

Prevention of injection

Exposure by accidental injection (skin puncture) is also a potential route of exposure, especially when working with animals or needles. To prevent this, wear gloves and lab coats, and apply the standard practices for working with sharps. Use of safer sharps is strongly recommended. (Guidelines for Nanomaterials, WFUSM General Guidelines for Handling and Working Safely with Nanomaterials, 2009; Nanotechnology:

Guidelines for Safe Research Practices, Fact Sheet Environment, Health and Safety Information for the Berkeley Campus No. 73)

Prevention of ingestion

As with any particulate, ingestion can occur if good hygiene practices are not followed. Once ingested, some types of nanoparticles might be absorbed and transported within the body by the circulatory system. To prevent ingestion, eating and drinking are not allowed in laboratories.

4.3. Standard Operating Procedures:

- Prepare a Standard Operating Procedure (SOP) for operations involving NMs. The SOP should be tailored to be specific to the proposed experimental procedure.
- Consider the hazards of the precursor materials in evaluating the process.
- Special consideration should be given to the high reactivity of some nanopowders with regard to potential fire and explosion [Pritchard 2004].

5. Guidance on Developing a Control Scheme (Control Banding)

In the absence of occupational exposure limits and definitive knowledge of toxicity, **control banding** is a qualitative strategy for classifying and handling chemicals and hazards associated with chemical exposures in the workplace. Control banding has its origins in the pharmaceutical industry (Naumann et al. 1996) and it is based on the appropriate control technology recommended to a chemical that falls within a given hazardous group (based on risk phrases from safety data sheets and handling). Early references on the concept include a manual published by the Association of the British Pharmaceutical Industry (Guest et al., 1997) and the paper by Naumann et al.(Naumann et al. 1996). More general concepts of control banding emerged in the early 1990s, as the European system for classification and labeling was being developed, and occupational health experts began to examine the alignment between the classification, the exposure limit, and data on exposure and control systems (Annex I - ref. 54). As the principle of control banding was applied to dangerous chemicals, chemical mixtures, and fumes, the premise was that the greater the potential for harm, the greater the degree of control needed to manage the situation and make the risk "acceptable." Control banding has the potential to be a useful concept for workplaces that handle NMs (Maynard et al., 2007, Schulte et al., 2008).

As the principle of control banding was applied to dangerous chemicals, chemical mixtures, and fumes, the premise was that the greater the potential for harm, the greater the degree of control needed to manage the situation and make the risk "acceptable." (Schulte, 2008; Annex I – ref. 2; 11; 37; 49). Although there are various approaches, four main control bands have been described for exposure to chemicals by inhalation:

Band 1: Use good industrial hygiene practice and general ventilation.

Band 2: Use an engineering control, typically local exhaust ventilation.

Band 3: Enclose the process.

Band 4: Seek expert advice.

There are several control banding tools developed for use with NMs exposures [Paik et al. 2008; Zalk et al. 2009; *GoodNanoGuide* 2009; European perspectives and contributions to

the global development strategy 2010 - 2015 of the WHO / ILO ITG Control Banding, BAuA Perspectives of Control Banding, June 21 - 22, 2011, Safe Work Australia 2012]. About 50 different Control Guidance Sheets are appreciated as standardized working practices and evaluated in field studies by means of workplace monitoring. The *GoodNanoGuide* (www.goodnanoguide.org) is an Internet-based platform for the exchange of ideas on handling nanomaterials, and it recommends a simplified approach to control banding of nanomaterials (Figure 1). With this approach, NMs are grouped into three hazard groups: (A) known to be inert, (B) understand reactivity and function, or (C) unknown properties. The exposure duration is described as Short (<4 hours/day, 2 days/week), Medium (4–6 hours/day, 3–5 days/week) or Long (>6 hours/day, 3–5 days/week). The potential for exposure is described through the state of the NM: bound (nanoparticles in a solid matrix), potential release (nanoparticles in friable matrix), or free/unbound (nanoparticles unbound, not aggregated). These elements are used to determine the recommended control band.

Another tool, the CB Nanotool, bases the control band for a particular task on the overall risk level (RL), which is determined by a “severity” score and a “probability” score (Figure 2). The severity score is determined by the sum of points assigned to the following factors: surface chemistry, particle shape, particle diameter, solubility, carcinogenicity, reproductive toxicity, mutagenicity, dermal toxicity, and hazard potential of the nanomaterial and the macro-parent material. The overall probability score is based on the following elements: estimated amount of nanomaterial used during the task, dustiness or mistiness, number of employees with similar exposures, frequency of operation, and duration of operation [Paik et al. 2008]. The CB Nanotool is being used at the Lawrence Livermore National Laboratory (LLNL) and can be downloaded at http://controlbanding.net/Home.html.

The Australian Control Banding tool is specific to carbon nanotubes [Safe Work Australia 2012]. The exposure potential is based on the amounts and types of activities, and determines the control band.

Exposure Duration	Bound Materials	Potential Release	Free / Unbound
Hazard Group A (Known to be inert)			
Shout	1	1	2
Medium	1	1	2
Long	1	2	2
Hazard Group B (Understand reactivity/function)			
Short	1	2	2
Medium	1	2	3
Long	1	3	3
Hazard Group C (Unknown Properties)			
Short	2	2	3
Medium	2	3	4
Long	2	4	4

Band 1: Use good industrial hygiene practice and general ventilation.
Band 2: Use an engineering control, typically local exhaust ventilation.
Band 3: Enclose the process.
Band 4: Seek expert advice.

Figure 1. GoodNanoGuide control banding matrix [Annex I – ref. 2]

Severity \ Probability	Extremely Unlikely (0–25)	Less Likely (20–50)	Likely (51–75)	Probable (76–100)
Very High (76–100)	RL 3	RL 3	RL 4	RL 4
High (51–75)	RL 2	RL 2	RL 3	RL 4
Medium (26–50)	RL 1	RL 1	RL 2	RL 3
Low (0–25)	RL 1	RL 1	RL 1	RL 2

Control bands:

RL 1: General ventilation
RL 2: Fume hoods or local exhaust ventilation
RL 3: Containment
RL 4: Seek specialist advice

Figure 2. Risk level matrix for the CB Nanotool [Annex I – ref.2]

Limitations of Control Banding

Control banding is not without limitations and still requires professional knowledge and experience to verify that the control measures specified have been properly installed, maintained, and used. Controls should be validated prior to use by either using substance specific industrial hygiene methods or performing surrogate monitoring.

One limitation of the CB Nanotool and other control banding tools for NMs is that there are very few toxicological data on which to recommend control levels, other than the highest two levels, and to evaluate the validity of the tool. As health hazard studies continue to expand, and the understanding of the toxicity of NMs improves, the severity scores may be adjusted to reflect the new knowledge and thereby affect the severity score to elicit a more defined control band [Zalk et al. 2009].

The ability to apply a control banding approach, as well as more extensive exposure assessment and risk management, will require some type of science-based classification scheme for engineered nanoparticles. This is likely to involve an evaluation of the nanoparticle hazard, including consideration of the physicochemical properties influencing toxicity and the ability of the material to become airborne or present an exposure hazard by other routes [Schulte 2008].

6. Management of MNMs

6.1 General

MNMs must be managed as a hazardous material. The following label should be placed on all containers containing engineered nanomaterials:

CAUTION
Nanomaterials Sample
Consisting of (Technical Description Here)
Contact: (POC)
at (Contact number)
in Case of Container Breakage.

6.2 Management of Nanomaterial-containing Waste Streams

The NM-bearing waste streams considered here are:

- Pure NMs (e.g., carbon nanotubes)
- Items contaminated with NMs (e.g., wipes/PPE)
- Liquid matrices containing NMs (e.g., hydrochloric acid containing carbon nanotubes)
- Solid matrices with NMs that are friable or have a nanostructure loosely attached to the surface such that they can reasonably be expected to break free or leach out when in contact with air or water, or when subjected to reasonably foreseeable mechanical forces. The guidance does not apply to NMs embedded in a solid matrix that can not reasonably be expected to break free or leach out when they contact air or water.

The following guidance notes are used for the **Waste Streams management:**

- Do not put NM waste in the regular trash or dump it down the drain.
- All NM waste, as defined above, should be collected in labeled, enclosed hazardous waste containers. The label should include a description of the waste and the words "*contains nanomaterials*".
- Collect paper, wipes, PPE and other items with loose contamination in a plastic bag or other sealable container and store it in a fume hood until it is full, then double-bag it, label it, and dispose of it according to these procedures.
- NM hazardous waste containers shall be collected and disposed of as hazardous waste following the standard procedures of your university.

6.3 Management of Nanomaterial Spills

Procedures should be developed to protect employees from exposure to NMs during the cleanup of spills and spill-contaminated surfaces. Inhalation and dermal exposures will likely present the greatest risks. The potential for inhalation exposure during cleanup will be influenced by the likelihood of NMs becoming airborne, with powder form presenting a greater inhalation potential than NMs in solution, and liquids in turn presenting a greater potential risk than encapsulated NMs.

Until relevant health and workplace exposure information is available, it is prudent to base strategies for dealing with spills and contaminated surfaces on the use of current good practices such as dust control and suppression. Standard approaches for cleaning powder spills can be used for cleaning surfaces contaminated with dry powder nanomaterials. These include access control, using HEPA-filtered vacuum cleaners, wiping up dry powders with damp cloths, or wetting the powder before wiping. Liquid spills containing nanomaterials can typically be cleaned by applying absorbent materials/liquid traps. If vacuum cleaning is employed, HEPA-filtered vacuums should be used, and care should be taken that HEPA filters are installed properly and that vacuum bags are changed according to the manufacturer's recommendations. Dry sweeping or air hoses should not be used to clean work areas. As in the case of any material spills or cleaning of contaminated surfaces, the handling and disposal should follow all applicable state, federal, and local regulations.

Equipment to contain and clean a NM spill should be readily available in or near each laboratory working with such materials. A NM spill kit for a laboratory environment may contain the following:

- Barricade tape.
- Nitrile or other chemically impervious gloves.
- Elastomeric respirator with appropriate filters.
- Adsorbent material.
- Wipes.
- Sealable plastic bags.
- Walk-off mat (e.g., Tacki-Mat®).
- HEPA-filtered vacuum.
- Spray bottle with deionized water or other appropriate liquid.

6.4 Fire and Explosion

Because of their size, NPs may pose a greater fire and explosion risk than those same particles that are larger in size. A general guideline in the fire hazard of airborne particles: As the particle size decreases, and those particles are dispersed into the atmosphere, the fire hazard can increase.

Personnel working with NPs shall identify from the manufacturer or distributor whether or not the nanoparticle or material is flammable and/or combustible.

Both carbon-containing and metal dusts can explode if they are aerosolized at a high enough concentration and if oxygen and an ignition source are present. Because the surface-to-volume ratio increases as a particle becomes smaller, NPs may be more prone to explosion than an equivalent mass concentration of larger particles. In general, the potential and severity of NMs explosions increase proportionally to the quantity of combustible NMs being used. Thus, bench-scale research should present fewer explosion risks than work in pilot plants or full-scale manufacturing facilities. Nonetheless, all researchers should avoid creating large, highly concentrated aerosols of combustible NMs.

7. Medical Surveillance

The need of medical surveillance for employees involved in working with NPs is still emergent [*Nanotechnology Safety and Health Program*, National Institutes of Health Office of Research Services, Division of Occupational Health and Safety, Technical Assistance Branch, 2012].

Occupational health surveillance involves the ongoing systematic collection, analysis, and dissemination of exposure and health data on groups of workers for the purpose of preventing illness and injury [NIOSH 2009]. Occupational health surveillance, which includes hazard and medical surveillance, is an essential component of an effective occupational safety and health program [Harber et al. 2003; Baker and Matte 2005; NIOSH 2006; Wagner and Fine 2008]. NIOSH continues to recommend occupational health surveillance as an important part of an effective risk management program for nanomaterial workers.

Medical screening in the workplace focuses on the early detection of health outcomes for individual workers and may involve an occupational history, medical examination, and application of specific medical tests to detect the presence of toxicants or early pathologic changes before the worker would normally seek clinical care for symptomatic presentations. Medical screening and resulting interventions represent secondary prevention and should not replace primary prevention efforts to minimize employee exposures to NMs. Medical surveillance involves the ongoing evaluation of the health status of a group of workers through the collection and aggregate analysis of health data for the purpose of preventing disease and evaluating the effectiveness of intervention programs.

Specific guidance for workers exposed to Carbon Nanotubes or Nanofibers is described in the NIOSH *Current Intelligence Bulletin: Occupational Exposure to Carbon Nanotubes or Nanofibers* [NIOSH 2010]. NIOSH has developed interim guidance relevant to medical screening (one component of an occupational health surveillance program) for nanotechnology workers (see NIOSH *Current Intelligence Bulletin: Interim Guidance on Medical Screening of Workers Potentially Exposed to Engineered Nanoparticles* [http://www.cdc.gov/niosh/docs/2009-116]).

If medical screening recommendations exist for chemical or bulk materials of which nanomaterials are composed, they would apply to nanomaterials as well. A basic medical surveillance program should contain the following elements [Trout and Schulte 2010]:

- An initial medical evaluation performed by a qualified health professional and other examinations or medical tests deemed necessary by the health professional.
- Periodic evaluations including symptoms surveys, physical exams, or specific medical tests based on data gathered in the initial evaluation.
- Post-incident evaluations.
- Employee training.
- Periodic analysis of the medical screening data to identify trends or patterns.

8. Exposure of consumers to manufactured nanomaterials

In March 2010, the French Agency for Environmental and Occupational Health Safety - **Afsset**) published results of a collective expert appraisal assessing the risks associated with NMs for the general population and the environment.

- This expert appraisal has identified several hundred widely used products containing NMs, present in our daily life: textiles, cosmetics, foodstuffs, sports equipment, building materials, etc. New studies suggest the possibility of health and environmental risks from certain products.
- Given this uncertainty, Afsset recommends taking immediate action in the name of the **precautionary principle:**
  - Making the traceability of nanomaterials compulsory. This will be done by compulsory declaration by the manufacturing companies.
  - Implementing clear labelling that states whether the products contain NMs and informs about the possibility of release upon use.
  - Going as far as prohibiting certain uses of NMs for which the usefulness is low in comparison to the potential hazards.
  - Harmonising French and European regulatory frameworks in order to bring best practices into general use: declaration, authorisation, substitution. In particular, revising REACH is essential in order to take specific account of MNMs whatever their tonnage.
- It has also made recommendations to develop a new health risk assessment method that is suitable for the specific characteristics of NMs.

In order to do this, Afsset has tested standard risk assessment methods on 4 characteristic and common products: antibacterial socks (silver nanoparticles), self-cleaning cement and sun protection lotion (titanium dioxide nanoparticles), and food silica in a nanometric form. These 4 products represent human exposure pathways (skin, inhalation, ingestion) and the possibility of environmental dispersion. This work has shown the urgent need to further knowledge on exposure and potential hazards of NMs. Today, only 2% of studies published on NMs are about their risks to health and the environment.

The first step must be to standardise nanomaterial characteristics. Research priorities should focus on toxicology, ecotoxicology and the measurement of exposure. Finally, Afsset expects to give itself the task of defining, with its working group, a simplified risk assessment tool. This is a risk evaluation matrix that will allow products to be categorised into several risk scales.

Faced with this considerable project, networking between European and international organisations is necessary in order to share the work. It began with the OECD, which coordinates risk assessment studies, and ISO, which works on the implementation of new standards.

As for Afsset, it is coordinating a European project called "nanogenotox" that aims to identify the toxicity to genes and DNA of 14 NMs. 18 organisations from 13 countries are involved. This new report follows the expert appraisal of October 2008 on "occupational health and safety" in the face of risks from NMs. It had suggested the application of regulations for dangerous chemical substances, such as containment in production sites. The Agency underlines that consumer exposure to MNMs and the environmental dispersion resulting from their consumption, prove "*to be extremely complex to evaluate, both qualitatively and quantitatively*", particularly because of the low traceability of NMs in products intended for consumption. As for studies on risks to health and environment, they represent only 2% of published studies on NMs**,** and are often affected by many biases (absent or incomplete characterization of nanomaterials, studies conducted on synthetic molecules not deriving from finished products, studies on far higher doses than actual exposure, etc.).

Furthermore, the SCCP (Guidance on the Safety Assessment of Nanomaterials in Cosmetics, SCCS, June 2012) has published an opinion on the safety of NMs specifically in cosmetic products. These reports and other reviews have concluded that the existing risk assessment paradigm, in use for conventional chemicals, should in principle be applicable to MNMs. However, it has also been pointed out that the current testing methods may need certain adaptations to take account of the special features of NPs (Rocks et al. 2008, SCENIHR 2009, OECD 2009, SCCP 2007).

On April 2012, the US Food and Drug Administration (FDA) proposed two new draft guidelines (for industry) for the evaluation and use of NMs in food and cosmetics (Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, April 2012; Guidance for Industry: Safety of Nanomaterials in Cosmetic Products). The agency said in a Consumer Update that this is the continuation of a "dialogue" that started in June 2011, when they issued a draft of the first guideline on the subject, one that helps industry decide whether an FDA-regulated product involves the use of nanotechnology, by considering for instance the size and properties of the materials. The FDA began looking into nanotechnology in 2006, when it set up the Nanotechnology Task Force to identify ways to evaluate the potential effects of the technology on health. In 2007, the task force recommended the agency issue guidelines to industry, and start addressing the potential risks and benefits of FDA-regulated products that use the technology, such as drugs, medical devices, cosmetics, food

substances, and packaging. According to the new Guidance, in the specific instance of nanotechnology, a food substance manufactured for the purpose of creating very small particle sizes with new functional properties likely would not be covered by an existing GRAS (Substances Generally Recognized as Safe) determination for a related food substance manufactured without using nanotechnology. A determination that a particular use of a substance is GRAS (unless established by common use prior to 1958) requires *both* technical evidence of safety *and* a basis to conclude that this technical evidence of safety is generally known and accepted (i.e., general recognition of safety). At present, for nanotechnology applications in food substances, there are questions related to the technical evidence of safety as well as the general recognition of that safety, that are likely to be sufficient to warrant formal premarket review and approval, rather than to satisfy criteria for GRAS.

Meanwhile in Britain, the government is also looking into the safety of nanotechnology. In their 2010 report on nanotechnologies and food, a science and technology committee of the House of Lords of the British Parliament, said there were several features of NMs that raise potential health and safety concerns.

9. Needs and Challenges for addressing the recommended practices

- Labeling - There are no requirements to list nanoparticle content for the end user either on the label or on the Material Safety Data Sheets (MSDS)
    a. MSDSs are only required to list known hazards. There is no requirement to identify nanomaterials.
    b. Before a label would help, awareness needs to be raised in consumers so they can understand the information on nanoparticles in general as well as the specific ones added to the product.
    c. No official nomenclature currently exists for NMs. This is misleading to the extent that the nanoscale form of a substance is subsumed under its macroscale form. This has implications for example when substances are included in positive lists or products are labelled with the substances they contain.
- Given the fact that the health impacts of a NM can change based on its chemical environment, it is not clear who is responsible for developing toxicity information (for instance in the case of cosmetics: the cosmetics company or the nanoparticle manufacturer?)
- End of lifecycle analysis is not often included in product development especially for consumer. When and how will longer term lifecycle issues be addressed?
- There is little consensus even on how to destroy some NPs – incineration is basically how they are made so it cannot be relied on to degrade them and the metals remain regardless.
- Management of substances hazardous to waters:
    a. It should be ensured that NMs are separately classified according to the various water hazard classes. Classifying NMs in this way will trigger the application of appropriate requirements for industrial facilities. If a NM cannot be classified with certainty, any facilities manufacturing or processing it must come under the strictest requirements.

b. The use of the product involves environmental exposure (surface waters, etc.) and washing it into wastewater plants. Any claimed disposal method that doesn't take this into account will make the message incomplete or inconsistent.

c. What are the environmental fate, potential bioaccumulation, and effects on water treatment plants?

- Unknowns include: bioavailability in the waste stream under various conditions, its affect on a treatment plant, and particles' behavior. How might this issue relate to the current hot topic of drugs in wastewater?
- Testing requirements: Key factors with regard to testing requirements are the solubility of NMs, their distribution in biota and the environment, and chronic toxicity. Data on these aspects should be presented and the test design tailored to the special characteristics of NMs.
- The lack of good toxicological information for the vast number of NPs with any number of different functional groups attached, each of which may contribute to different health outcomes. Should there be a difference in handling functionalized CNTs and does this require different guidelines for each?
- The lack of good measurement information. We don't know which parameters are most important in terms of possible biological effects. There are also issues in terms of the cost of advanced monitoring equipment, which would make it difficult for smaller employers to self-monitor.
- There is a need to consider the human factor. Even with training, engineering controls, and personal protective equipment, how do you ensure that employees will actually work in an appropriate manner?
- Can the nanoparticles captured in HEPA filters be released?
- How will the waste handler actually treat the waste?
- Medical monitoring: is baseline testing and periodic retesting for lung capacity a help or a potential liability? Is it necessary? If desired, what should the metrics be?
- Regulating the manufacture and use of MNMs in industrial facilities. NMs are already produced in industrial facilities, in some cases in large quantities. However there are no statistics on the numbers of such facilities involved. Requirements for plant construction and operation are decisive to the safety of the environment and of the population in the surrounding area. The manufacture and use of NMs in industrial facilities should therefore be subject to official monitoring where necessary.
- According to GAARN (Group Assessing Already Registered Nanomaterials) [GAARN 2013] special attention should be given to endpoints for which no classification is derived based on hazard data (e.g. mutagenicity, soil and sediment ecotoxicity), but where available data show such hazardous effects. Moreover, it is important not to overlook a potential hazard because of (technical) difficulties encountered (e.g. when applying or adapting the current standardised test guidelines for NMs as well as other forms or when implementing sample preparation considerations in OECD TGs). When registering NMs and bulk substances under the same technical dossier, specific exposure scenarios for NMs (or other forms) should be included in the registration dossiers

if these differ from the ones for the bulk materials. It is important that the exposure scenarios describe:

- how the substance is produced;
- its life-cycle uses; and
- how the manufacturer or importer controls the exposure for humans and the environment.

- Minimising environmental releases of synthetic MNMs. Substances can never fully be prevented from entering the environment. To ensure the best possible level of environmental protection despite this, prohibitions and quality standards are supplemented with emission limits that are generally based on currently available knowledge. Too little is so far known both about the release of NMs and about their behaviour in the environment.
- How can small companies afford to do monitoring and measurement of NPs?
- There are no worker exposure limits (Recommended Exposure Limits, Permissible Exposure Limits or Threshold Limit Values) specific to NPs.
- Incomplete information on protective measures to some MNMs. It is a challenge the evaluating the effectiveness of current personal protective equipment and safety devices, such respirators, filters and ventilation systems, to see if they are sufficient for protection from NM exposure. There is a need for an interdisciplinary approach (fundamental material studies, instrumentation, risk evaluation, implementation of standards and protocols) to tackle the complex problem of understanding the environmental and health impacts of NMs.
- Need for rethinking hazards. Previously, “less is better,” has been guidance for reducing exposure. Now, although the total mass quantity of material is reduced, the hazard may be greater.

References

Andorno R: The Precautionary Principle: A New Legal Standard for a Technological Age. J Int Biotechnol Law 2004, 1:11-19.

ASTM E2456-06, “Standard Terminology Relating to Nanotechnology.

Baker EL, Matte TP, Occupational health surveillance. In: Rosenstock L, Cullen E, Brodkin R (eds). Textbook of clinical occupational and environmental medicine, Philadelphia, PA: Elsevier Saunders Company, 2005, http://www.osha.gov/SLTC/medicalsurveillance/surveillance.html

Bergamaschi E: Occupational exposure to nanomaterials: present knowledge and future development. Nanotoxicology, 3:194-201, 2009.

Borm, P., Klaessig, F.C., Landry, T.D., Moudgil, B., Pauluhn, J., Thomas, K., Trottier, R., and Wood, S. (2006). Research strategies for safety evaluation of nanomaterials, Part V: role of dissolution in biological fate and effects of nanoscale particles. *Toxicol. Sci.*, 90, 23–32.

Cao G: Nanostructures & nanomaterials. Synthesis, properties & applications London: Imperial College Press; 2004.

Donaldson K, Aitken R, Tran L, Stone V, Duffin R, Forrest G, Alexander A., Carbon Nanotubes: a Review of Their Properties in Relation to Pulmonary Toxicology and Workplace Safety. Toxicol Sci. 92(1): 5-22, 2006.

Duffin R, Tran L, Brown D, Stone V, Donaldson K., Proinflammogenic effects of low-toxicity and metal nanoparticles in vivo and in vitro: highlighting the role of particle surface area and surface reactivity. Inhal Toxicol *19*(10):849–856, 2007.

Duffin R, Tran CL, Clouter A, Brown DM, MacNee W, Stone V, Donaldson K, The importance of surface area and specific reactivity in the acute pulmonary inflammatory response to particles. Ann Occup Hyg *46*:242–245, 2002.

GAARN, The third meeting of the Group Assessing Already Registered Nanomaterials (GAARN) from Helsinki, 30 September 2013.

Geiser M, Rothen-Rutishauser B, Kapp N, Schurch S, Kreyling W, Schulz H, Semmler M, Im Hof V, Heyder J, Gehr P, Ultrafine particles cross cellular membranes by nonphagocytic mechanisms in lungs and in cultured cells. Environ Health Perspectives 113(11):1555-1560, 2005.

Gerritzen, G., Huang. L, Killpack, K., Mircheva, M., Conti, J., Magali, D., Harthorn, B.H., Appelbaum, R.P. and Patricia Holden. A Report to ICON: “Review of Safety Practices in the Nanotechnology Industry.” University of California, Santa Barbara, 2006.

Groso A., A. Petri-Fink**,** A. Magrez**,** M. Riediker and T. Meyer: Management of nanomaterials safety in research environment. Particle and Fibre Toxicology, 7:40, 2010.

Guest I, Newton D. Industrial hygiene in the pharmaceutical industry. In Stave GM, Joines R, eds. Occupational Medicine State of the Art Reviews, Vol. 12, No. 1. Philadelphia: Hanley & Belfus; 81–94, 1997.

Hansen SF, BH Larsen, SI Olsen, A. Baun, Categorization framework to aid hazard identification of nanomaterials. Nanotoxicology 1(3):243–250; 2007.

Harber P, Conlon C, McCunney RJ, Occupational medical surveillance. In: McCunney RJ, (ed). A practical approach to occupational and environmental medicine. Philadelphia, PA: Lippincott, Williams, and Wilkins. 2003.

Helland A, Wick P, Koehler A, Schmid K, Som C, Reviewing the Environmental and Human Health Knowledge Base of Carbon Nanotubes. Environ Health Perspectives 115(8):1125-1131, 2007.

ICRP [1994]. Human respiratory tract model for radiological protection. Oxford, England: Pergamon, Elsevier Science Ltd., International Commission on Radiological Protection Publication No. 66, 1994.

Johnson DR, Methner MM, Kennedy AJ, Steevens JA, Potential for occupational exposure to engineered carbon-based nanomaterials in environmental laboratory studies. Environ Health Perspect 118(1):49–54, 2010.

Kessler R., Engineered nanoparticles in consumer products: understanding a new ingredient. Environ Health Perspect 119:A120–A125, 2011.

Kim CS, Jaques PA, Analysis of total respiratory deposition of inhaled ultrafine particles in adult subjects at various breathing patterns. Aerosol Sci Technol 38:525-540, 2004.

Krug H.F., Wick P., Angew.Chem.Int. Ed., 50: 1260, 2011.

Landsiedel R., Ma-Hock L., Kroll A., Hahn D., Schnekenburger J., Wiench K., and Wohlleben W., Adv. Mater, 22: 2601, 2010.

Maynard AD, B. Ku, M. Emery, M. Stolzenburg and P. McMurry, Measuring particle size-dependent physicochemical structure in airborne single walled carbon nanotube agglomerates. J Nanoparticle Res 9(1):85–92; 2007.

Maynard AM, Kuempel ED, Airborne nanostructured particles and occupational health. J Nanoparticle Research 7(6):587-614, 2005.

M. Methner, L. Hodson & C. Geraci, Journal of Occupational and Environmental Hygiene, 7(3): 127, 2009.

M. Methner, L. Hodson, A. Dames & C. Geraci, Journal of Occupational and Environmental Hygiene, 7(3): 163, 2010.

Moller W, Brown DM, Kreyling WG, Stone V. Ultrafine particles cause cytoskeletal dysfunctions in macrophages: role of intracellular calcium. Part Fibre Toxicol. 2:7, 2005.

Montague Peter, Kessler R., Environmental Research Foundation, [Printer-friendly version] January 21, 2008.

Montague Peter, The precautionary principle in the real world, 2011. Engineered nanoparticles in consumer products: understanding a new ingredient. Environ Health Perspect 119:A120–A125.

Murashov V, Howard J, Essential features for proactive risk management. Nat Nanotechnology 4(8):467–470, 2009.

Naumann, BD, EV Sargent, BS Starkman, WJ Fraser, GT Becker and DL Kirk: Performance-based exposure control limits for pharmaceutical active ingredients. Am. Ind. Hyg Assoc. J. 57:33-42, 1996.

Oberdörster G, Sharp Z, Atudorei V, Elder A, Gelein R, Kreyling W, Cox C, Translocation of inhaled ultrafine particles to the brain. Inhal Toxicol *16*(6–7):437–445, 2004

Oberdörster G, Oberdörster E, Oberdörster J, Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect. *113*(7):823–839, 2005

Oberdörster, G., Concepts of Nanotoxicology, NANOAGRI Conference 2010, Cairo, Egypt.

OSHA [1990].29 CFR 1910.1450 Occupational exposure to hazardous chemicals in laboratories [www.osha.gov]. Washington, DC: Occupational Safety and Health Administration. Date accessed: July 20, 2011.

OSHA [2008]. 29 CFR 1910.132. General requirements: personal protective equipment. Washington, DC: Occupational Safety and Health Administration. Date accessed: December 15, 2011.

Paik SY, Zalk DM, Swuste P, Application of a pilot control banding tool for risk level assessment and control of nanoparticle exposures. Ann Occup Hyg *52*(6):419–428, 2008.

Pritchard DK, Literature review—explosion hazards associated with nanopowders. United Kingdom: Health and Safety Laboratory, HSL/2004/12, 2004.

Schulte P, Geraci C, Zumwalde R, Hoover M, Kuempel E. Occupational risk management of engineered nanoparticles. J Occup Environ Hyg *5*(4):239–249, 2008a.

Schulte P, Rinehart R, Okun A, Geraci C, Heidel D. National Prevention through Design Initiative. J Safety Research *39*:115–121, 2008b.

Tanasescu S., C. Marinescu, Size effects controlling the toxicity and energetics of nanostructured oxide materials, in Convergence of micro-nano-biotechnologies, series in Micro and Nanoengineering, Ed. Romanian Academy 9, 59-76, 2006.

Tiede, K., Boxall, A.B.A., Tear, S.P., Lewis, J., David, H. and Hassellov M., "Detection and Characterization of Engineered Nanoparticles in Food and the Environment", Food Additives and Contaminants, vol. 25, no. 7, pp. 795-821, 2008.

Tran CL, Cullen RT, Buchanan D, Jones AD, Miller BG, Searl A, Davis JMG, Donaldson K, Investigation and prediction of pulmonary responses to dust. Part II. In: Investigations into the pulmonary effects of low toxicity dusts. Contract Research Report 216/1999 Suffolk, UK: Health and Safety Executive, 1999.

Trout-DB; Schulte-PA, Medical surveillance, exposure registries, and epidemiologic research for workers exposed to nanomaterials, Toxicology; 269(2-3):128-135, 2010

Tsai S-J, Ada E, Isaacs J, Ellenbecker M, Airborne nanoparticle exposures associated with the manual handling of nanoalumina and nanosilver in fume hoods. J Nanopart Res 11(1):147–161, 2009a.

Tsai S-J, Hofmann M, Hallock M, Ada E, Kong J, Ellenbecker M, Characterization and evaluation of nanoparticle release during the synthesis of single-walled and multiwalled carbon nanotubes by chemical vapor deposition. Environ Sci Technol 43(15):6017–6023, 2009b.

Wagner GR, Fine LJ, Surveillance and health screening in occupational health. In: Maxcy-Rosenau-Last Public Health and Preventive Medicine. RB Wallace (ed.) 15th ed.

New York: McGraw-Hill Medical Publishing, pp 759–793, 2008.

Warheit DB, Webb TR, Sayes CM *et al.*, Toxicol Sci 91:227–36, 2006.

Yokel and MacPhail Journal of Occupational Medicine and Toxicology 2011, 6:7 http://www.occup-med.com/content/6/1/7

Zalk D, Paik S, Swuste P, Evaluating the control banding nanotool: a qualitative risk assessment method for controlling nanoparticle exposures. J Nanopart Res *11*(7):1685–1704, 2009.

Annex I. Guidelines and procedures

1. Responsible Production and Use of Nanomaterials: Implementing Responsible Care, 2nd Edition, CEFIC January 2012.
2. General Safe Practices for Working with Engineered Nanomaterials in Research Laboratories, NIOSH, May 2012.
3. Safe handling and use of carbon nanotubes. Commonwealth Scientific and Industrial Research Organisation (CSIRO) and Safe Work Australia. ISBN 978–0–642–33351–3, Safe Work Australia, 2012.
4. Guidance for Industry. Safety of Nanomaterials in Cosmetic Products (Draft), FDA, April 2012.
5. Guidance on the Safety Assessment of Nanomaterials in Cosmetics, SCCS, June 2012.
6. Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, April 2012.
7. Best practices, Standards, and Guidelines to using engineered nanomaterials, Nanotoolkit, Working Safely with Engineered Nanomaterials in Academic Research Settings, California, April 2012.
8. Best Practices in Cancer Nanotechnology: Perspective from NCI Nanotechnology Alliance, Clin Cancer Res.;18(12):3229-3241, 2012 June 15.
9. Nanotechnology Stewardship Guiding Principles, Bayer Company, "Code of Good Practice" Zamboni WC, Torchilin V, Patri AK, Hrkach J, Stern S, Lee R, Nel A, Panaro NJ, Grodzinski P., March 2012.
10. Nanotechnology: Guidelines for Safe Research Practices, U.S. National Nanotechnology Initiative NNI, 2012, http://blink.ucsd.edu/safety/research-lab/nanotechnology.html
11. European perspectives and contributions to the global development strategy 2010 - 2015 of the WHO / ILO ITG Control Banding, BAuA Perspectives of Control Banding, June 21 - 22, 2011.
12. Guidance for safe handling of nanomaterials, Dhawan A, Shanker R, Das M, Gupta KC, J Biomed Nanotechnol. 2011 Feb;7(1):218-24.
13. Precautionary Strategies for managing Nanomaterials, German Advisory Council on the Environment (SRU), 2011.
14. BSU Nanomaterial Laboratory Safety, October 2011.
15. Éléments de faisabilité pour un dispositif de surveillance épidémiologique des travailleurs exposés aux nanomatériaux intentionnellement produits. Saint-Maurice: Institut de veille sanitaire; Boutou-Kempf O. 69 p., 2011.
    Downloadable from: http://www.invs.sante.fr/pmb/invs/%28id%29/PMB_9341
16. Current Intelligence Bulletin 63: Occupational Exposure to Titanium Dioxide, DHHS (NIOSH) Publication No. 2011–160, April 2011.
17. Nanotechnology and Environmental, Health, and Safety: Issues for Consideration, John F. Sargent Jr., Congressional Research Service, 7-5700, 2011, http://www.fas.org/sgp/crs/misc/RL34614.pdf
18. Nanoproducts: France recommends the precautionary principle (French Agency for Environmental and Occupational Health Safety (Afsset) 2010.
19. Nanoparticle Safety and Health Guidelines, Purdue Univ. 2010.
20. Review of nanomaterial and nanoproduct regulation working group 3 of the Nanokommission, Sept. 2010.

21. OECD, Preliminary Guidance Notes on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials, No. 24, 2010, ENV/JM/MONO(2010)25.
22. OECD, Series on the Safety of Manufactured Nanomaterials No. 28, December 2010, Compilation and Comparison of Guidelines Related to Exposure to Nanomaterials in Laboratories, ENV/JM/MONO(2010)47
23. Lab Safety Guidelines for Handling Nanomaterials, Stanford University, 2010.
24. Nanoparticle Handling Guidelines, OUHSC Committee Approvals, 2009.
25. 'Best Practices' for Handling Nanomaterials in the Workplace, 2009, UCSB.
26. Best Practices Guide to Synthetic Nanoparticle Risk Management, Claude Ostiguy et Brigitte Roberge, REPORT R-599, 2009.
27. Best Practices for Working Safely with Nanoparticles in Laboratories, Turi, Michael J. Ellenbecker, January 2009.
28. Guidelines for safe handling, use and disposal of nanoparticles, Gh. Amoabediny, A. Naderi, J. Malakootikhah, MK. Koohi , SA. Mortazavi, M. Naderi and H. Rashedi, Journal of Physics: Conference Series 170, 012037, 2009.
29. IRSST Studies and Research Projects: Best Practices Guide to Synthetic Nanoparticle Risk Management, Claude Ostiguy, Brigitte Roberge, Luc Ménard, Charles-Anica Endo, REPORT R-599, : ISBN: 978-2-89631-317-4, 2009.
30. Guidance for handling and use of nanomaterials at the workplace, Heinemann M, Schäfer HG., Hum Exp Toxicol.;28 (6-7):407-11, 2009 June.
31. Interim Guidance for Medical Screening and Hazard Surveillance for Workers Potentially Exposed to Engineered Nanoparticles, *Current Intelligence Bulletin 60,* NIOSH 2009.
32. Safety Net # 132 – Nanotechnology: Guidelines for Safe Research Practices, UC Davis 2009.
33. A Good Practice Guide for Safe Work with Nanoparticles: The Quebec Approach, Journal of Physics: Conference Series 151, 2009, 012037**.**
34. General Principles and Practices for Working Safely with Engineered Nanomaterials, Standford Univ. 2009.
35. Comparison of Guidance on Selection of Skin Protective Equipment and Respirators for Use in the Workplace: Manufactured Nanomaterials, International Organization for Economic Cooperation and Development report, June 19, 2009.
36. Emission Assessment for Identification of Sources and Release of Airborne Manufactured Nanomaterials in the Workplace: Compilation of Existing Guidance, International Organization for Economic Cooperation and Development report, June 18, 2009.
37. Guide for the Safe Handling of Nanotechnology-based Products, Scientific and Technical Report #509, 16 + viii pages, Environment Canada, Science and Technology Branch, Aquatic Ecosystem Protection Research Division, 2009.
38. NIOSH [2009]. Approaches to Safe Nanotechnology. Managing the Health and Safety Concerns Associated with Engineered Nanomaterials. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. [www.cdc.gov/niosh/docs/2009-125/].
39. Guidance for Handling and Use of Nanomaterials at the Workplace, NANOSAFE 2008: International conference on safe production and use of nanomaterials iop publishing, journal of physics: conference series 170, 012037 DOI:10.1088/1742-6596/170/1/012037, 2009.

40. Guidance Manual for the Testing of Manufactured Nanomaterials: OECD Sponsorship Programme: First Revision, 2009.
41. Engineered Nanomaterials: Evidence on the Effectiveness of Workplace Controls to Prevent Exposure, Safe Work Australia, 2009.
42. “Chemical Hygiene Plan,” Massachusetts Institute of Technology (MIT), Department of Aeronautics & Astronautics, USA, January 2008.
43. Health and safety practices in the nanomaterials workplace: results from an international survey, Conti JA, Killpack K, Gerritzen G, Huang L, Mircheva M, Delmas M, Harthorn BH, Appelbaum RP, Holden PA., Environ Sci Technol. 2008 May 1;42(9):3155-62.
44. A survey of environmental and occupational work practices in the automotive refinishing industry of a developing country: Sonora, Mexico. Velázquez L, Bello D, Munguia N, Zavala A, Marin A, Moure-Eraso R., Int J Occup Environ Health. 2008 Apr-Jun; 4(2):104-11.
45. “Nanomaterial Safety Plan”, Stanford Linear Accelerator Center, 4 August 2008.
46. Guidance for a tiered Gathering of Hazard Information for the risk assessment of nano-materials, VCI, 2008.
47. Department of Energy Proposed Laboratory Safety Guidelines for Handling Nano-materials, Approach to Nanomaterial ES&H, Revision 3a, May 2008.
48. Working with Nanotechnology Materials and Processes, July 31, 2008.
49. Organisation for Economic Co-operation and Development (OECD), “Current Develop-ments/Activities on the Safety of Manufactured Nanomaterials,” OECD Environment, Health and Safety Publications Series on the Safety of Manufactured Nanomaterials, Berlin, Germany, 25-27 April 2007.
50. “Guidance on the Labeling of Manufactured Nanoparticles and Products Containing Manufactured Nanoparticles,” British Standard Institute (BSI), PAS 130, First published, UK, 2007.
51. VCI & BAuA, “Guidance for handling and use of nanomaterials in the workplace,” Ger-many, 2007.
52. “Nanotechnology and Nanoparticles- Safe Working Practices Information,” Virginia Commonwealth University, Office of Environmental Health and safety, 2007.
53. Current OHS Best Practices for the Australian Nanotechnology Industry, A Position Paper by the NanoSafe Australia Network, November 2007
54. Progress Toward Safe Nanotechnology in the Workplace, A Report from the NIOSH, Nanotechnology Research Center, DHHS (NIOSH) Publication No. 2007–123, 2007
55. Nanotechnology: Guidelines for Safe Research Practices, No.73, 2007, UC, Berkeley CA.
56. ACGIH [2007]. Industrial ventilation: A manual of recommended practice for design. 26th ed. Cincinnati, OH:American Congress of Governmental Industrial Hygienists.
57. “RCRA Regulation of Wastes from the Production, Use and Disposal of Nanomaterials,” American Bar Association, Section of Environment, Energy and Resources, USA, June 2006.
58. “Review of Safety Practices in the Nanotechnology Industry,” Phase One Report: Cur-rent Knowledge and Practices Regarding Environmental Health and Safety in the Nano-technology Workplace, the International Council on Nanotechnology (ICON), Gerritzen Gina, Li-Chin Huang, Keith Killpack, Maria Mircheva, Joseph Conti, 2006.
59. "A Review of Current Practices in the Nanotechnology Industry" Phase two report: sur-vey of current practices in the nanotechnology workplace, the International Council on

Nanotechnology (ICON), Gina Gerritzen, Li-Chin Huang, Keith Killpack, Maria Mircheva, Joseph Conti, 2006.

60. BAuA Guidance for Handling and Use of Nanomaterials at the Workplace, 2006.
61. NIOSH [2006]. Criteria for a recommended standard: occupational exposure to refractory ceramic fibers. Cincinnati, OH: Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2006–125.
62. Safe Handling of Nanotechnology, Andrew D. Maynard, Nature, Vol. 444/16, 2006.
63. Interim Guideline for Working Safety with Nanotechnology, Based on the Most Current NIOSH Information at 01-Sep-2005.
64. Approaches to Safe Nanotechnology: An Information Exchange with NIOSH, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, October 1, 2005. http://www.cdc.gov/niosh/topics/nanotech/pdfs/Approaches_to_Safe_Nanotechnology.pdf
65. Guidelines for Safe Handling of Nanoparticles in Laboratories, Draft, Revised 03/31/05
66. Good Current Practices for Managing Nanomaterials, Safety&Health Bulletin, Issue No 2005-06, Environment, Safety & Health, US Department of Energy, 2005.
67. GoodNanoGuide http://goodnanoguide.org
68. Risk management of carbon nanotubes. Health and Safety Executive, http://www.hse.gov.uk/pubns/web38.pdf
69. Health and Safety of Working with Nanomaterials at Brookhaven http://www.bnl.gov/cfn/newsletter/Sept07/workWithNanomat.asp
70. Nano Health & Safety Protocols and Good Practices http://www.nanoceo.net/nanorisks/OHS-Protocols-Best-Practices#Reviews
71. Nanomaterials Safety Implementation Plan, Ames Laboratory http://energy.gov/nepa/downloads/nanomaterials-safety-implementation-plan-ames-laboratory
72. Nanotechnology Consensus Workplace Safety, ORC Worldwide, Mercer http://www.orc-dc.com/?q=node/1962
73. Nanotechnology Safety, University of North Carolina at Chapel Hill http://ehs.unc.edu/
74. OTA Technology Guidance Document: Nanotechnology - Considerations for Safe Development OTA Technology Guidance Document http://nanotech.lawbc.com/uploads/file/00064286.PDF
75. Practical Safety Guidance for Academic Research Involving Engineered Nanomaterials, Larry Gibbs, Associate Vice Provost for EH&S, Stanford University.
76. Potential Risks of Nanomaterials and How to Safely Handle Materials of Uncertain Toxicity, By Marilyn F. Hallock, Pam Greenley, Lou DiBerardinis, Dan Kallin, Division of Chemical Health and Safety of the American Chemical Society Elsevier Inc., doi:10.1016/j.jchas.2008.04.001.
77. Laboratory Safety, Florida University http://www.safety.fsu.edu/lab-nano.html
78. General guidelines on reducing the risk for occupational exposure, NIH Chemical Hygiene Plan, http://www.ors.od.nih.gov/sr/dohs/LabServices/Pages/default.aspx
79. "Laboratory Safety Manual," Iowa State University, USA.