VERSION [1]

JANUARY 1, 2017

Sustainable Nanotechnologies Project

RISK MANAGEMENT OF NANOMATERIALS

Guidelines for the Safe Manufacture and Use of Nanomaterials

Ceyda Oksel[1], Neil Hunt[2], Terry Wilkins[1] and Xue Z. Wang[1]

[1] University of Leeds, Leeds, UK

[2]The REACH Centre, Lancaster, UK

This project is funded by the EU 7th Framework Programme, contract no. 604305

ABSTRACT

Nanotechnology is an emerging field of science and engineering that has already been applied to a variety of industrial fields. Given the ever increasing use of engineered nanomaterials (ENMs) in industry, it is essential to properly assess all potential risks that may occur as a result of exposure to ENMs. It is generally agreed that the distinctive characteristics of ENMs that have made them superior to bulk materials for particular applications might also have a substantial impact on the level of risk they pose. However, the complexity and large variety of ENMs presents a challenge for the existing general and product-specific regulation. In order to facilitate sustainable manufacturing of ENMs, it is desirable to develop transparent and comprehensive tools and best practice guidelines for risk assessment and management.

While the risk management of ENMs receives significant attention, there is still a limited understanding of how to select optimal risk management measures (RMMs) for controlling and mitigating the risks associated with exposure to ENMs. Clearly, there exists the need to expand current risk management practices to ensure safe production, handling and use of ENMs. Moreover, the performance of the existing RMMs should be re-evaluated for ENMs since control options that are proven to be effective for preventing or limiting risks associated with traditional particles might give unsatisfactory results in the case of nano-scale particles.

This guidance document brings together evidence on the suitability of traditional controls to minimize potential health and environmental risks resulting from exposure to ENMs. The aim is to advance our understanding of the risk management approaches relevant for ENMs, and ultimately to support the selection of the most suitable RMMs when handling ENMs. To that end, evaluative evidence collected from the review of relevant literature, published guidelines, technical reports, and survey of nanotechnology institutions are summarised to understand the level of protection offered by each control measure and used to make recommendations on safe handling of nanomaterials.

Table of Contents

1. Introduction

Ongoing globalization of nanosciences and recent developments in nanotechnology have raised new challenges in the safety and regulatory domains. Despite recent collaborative research efforts to tackle safety issues linked to engineered nanomaterials (ENMs), a consensus on how to properly regulate environmental and health risks of ENMs has not been reached yet.

In order to facilitate sustainable manufacturing of ENMs, it is desirable to develop transparent and comprehensible tools for risk assessment and management. Most researchers agree that, although we do not need an entirely new risk management paradigm to manage ENM risks, there is a need to expand existing practices to better address nano-related issues and ensure safe production, handling and use of ENMs. However, the limited knowledge on nano-EHS (environment, health and safety) issues points to important gaps in research on the environmental and health risks associated with nanotechnology.

Currently, the main concern in the field of nanosafety is not only the identified hazardous effects of some ENMs (e.g. carcinogenicity of rigid acicular particles) but also the uncertainty around identifying the risks of newly manufactured materials and how to manage them. Once the potential risks are identified by means of hazard and exposure assessment, the next step is the implementation of suitable risk reduction measures for those risks that are outside the range of tolerable limits.

Safe handling and control of exposure at workplaces are critical for managing the hazardous properties of the nanoscale substance. The purpose of this guide is to compile existing information on risk management of ENMs and provide recommendations for safe handling and manufacture of ENMs.

→ The main goal of this guideline is to support the appropriate selection of effective and economical risk control option when dealing with nanomaterials and provide general safety strategies for handling nanomaterials at work places.

1.1. Background

Nanomaterials can demonstrate novel properties that are not seen with other substances. These unique properties have led to the rapid growth in the number of ENMs being exploited commercially. Given the ever increasing use of ENMs in industry, the potential exposure of workers, consumers and the environment is also rising. Therefore, it is essential to understand all possible risks that may occur as a result of exposure to ENMs and ameliorate any risks to health or the environment posed by the presence of ENMs.

The risk assessment process involves identification of potential hazards and evaluation of occupational, consumer and environmental exposure to hazardous substances, while risk management primarily focuses on the selection and implementation of effective measures to control risks. It is generally agreed that traditional risk management frameworks and tools do not cover all the issues associated with manufacturing, handling and using ENMs and hence, need to evolve to become more sensitive to nano-specific issues [1]. Although a revised risk management methodology for nano-scale objects has not been universally agreed yet, there are a number of technical reports and guidelines published by (inter)national organisations [2-6] and standard setting bodies [7-10] that provide guidance on risk management issues and control measures relating to ENMs. Additionally, numerous control-banding tools have been proposed [11-14], that associate predefined hazard and exposure levels with risk management measures and link hazard with physical characteristics in a qualitative or semi-quantitative way.

→ Quantitative risk assessment approaches, considered as the gold standard for risk assessment, are still in need of further development in both assessing ENM toxicity and characterising occupational exposure to ENMs.

Essentially, there are two ways of reducing the risk arising from ENMs:

1. Hazard control through modification of ENM properties while maintaining their original features and functionality.

2. Exposure control reducing the release of ENM from industrial processes or consumer products or limiting the exposure of workers and consumers to ENM by means of administrative measures and behavioral guidelines.

As with traditional risk management approach, once all potential hazards and exposure are identified, assessed and thoroughly evaluated, risk reduction strategies should be considered in a systematic and prioritizing approach (e.g. hazard control hierarchy [15]). For many situations, a combination of risk management options included in the hazard control hierarchy might be implemented. The critical point here is to explore all alternative risk control solutions and implement more effective controls (e.g. higher in the hierarchy) before considering less-effective options.

1.2. Nanomaterial Toxicity and Testing

Nanoforms of substances are not an entirely new phenomenon because several natural ENMs, such as clays (bentonite), have existed in the environment for millennia. Studies of materials displaying nanoscale dimensions were conducted in polymer science many years prior to the birth of nanotechnology as a specific scientific field [16]. Living organisms are assumed to have adapted to naturally occurring NMs in their ecosystem but it is feared that manufactured ones may introduce a new set of adverse effects [17]. Due to the small size and high surface area to volume ratio, some ENMs have the ability to easily enter into the body, accumulate in tissues, and potentially cause harm [18]. Their ability to enter into the body does not necessarily mean that they can readily cause harm but calls for a careful analysis of what health hazards they may pose there. In recent years, some types of ENMs have been shown to be hazardous to human health. For example, it has been reported that carbon nanotubes (CNTs) are capable of inducing reactive oxygen species (ROS) [19] and pulmonary effects [20]. Toxicological studies have also shown that nanosized titanium dioxide (TiO_2) particles have the potential to induce cytotoxic [21, 22], genotoxic [23, 24], and inflammatory [25, 26] effects.

→ Not every ENM presents new challenges to risk governance. Moreover, not all ENMs are hazardous. Priority should be given to ENMs that are (1) shown to exhibit nano-structure dependant toxicity and (2) capable of entering the human body through different routes such as inhalation, ingestion, dermal penetration and injection. Another thing that would cause concern is wide spread use and exposure.

Another important example of an ENM that raises toxicological concerns because of its widespread use in consumer products is nanosilver. Although nanosilver was initially perceived to show little hazard to human health, recent studies [27-30] have provided strong evidence of toxicity associated with exposure to nanosilver. More detailed information about the potential adverse effects of various ENMs has been provided by several researchers [21, 31-37].

A toxicological endpoint is the measure of a particular toxic effect of a substance on human health or the environment via a given route of exposure. The toxicity of compounds can be evaluated by conducting in vivo, in vitro, and in silico studies. For classical human health hazard assessment, several toxicological endpoints are relevant, e.g. acute and chronic dermal, oral or inhalation toxicity as well as skin, eye and respiratory corrosion/irritation. Although in vitro assays offer numerous advantages such as speed, reproducibility and control of test conditions, there is also a well-recognised need in nanoscience community to compare and validate in vitro findings with in vivo observations.

The REACH (Registration, Evaluation, Authorization and Restriction of CHemicals) regulation aimed at ensuring the safe production, use and import of substances entered into force in June 2007. Although there are no specific regulations of ENMs in the EU, REACH legislation requires assessment of ENMs within the registration of the bulk form of a substance.

The involvement of computational specialists in nano-safety research has become more prominent since REACH regulation promoted the use of in silico techniques, such as quantitative structure-activity relationship (QSAR) and read-across, for the purpose of risk assessment. However, the use of recently developed nano-QSAR models still require support from classical laboratory methods to be accepted by the regulatory authorities and the end-users.

The confidence in in silico predictions can be only gained through the validation of computational models with "real-life" results. Other key issues need to be considered in order to improve the regulatory acceptance of in silico models:

- the uncertainties in the constructed models and the model's applicability domain should be clearly and transparently reported.
- In addition to the extracted knowledge and the derived computational models, the model builder should also attempt to provide some probabilistic reasoning to justify the results obtained.
- the modeler/reporter should use intelligible language, instead of complex technical terms, considering the background of end-users (i.e experimentalists, industrial partners or regulating authorities), who should have a clear understanding of the model and its applicability in order to avoid misuse of it [38].

The road to regulatory acceptance of different testing (in vivo and in vitro) and non-testing (in silico) methods is shown in Figure 1.1. The implementation and future success of in silico models directly rely on the level of acceptance it gets from potential users and regulators. In order to increase the credibility of computational methods in nanotoxicology, it should be proven that the outcome of in silico models are (at least) as reliable as existing in vivo or validated in vitro tests. Given the complexity and heterogeneity of ENM classes, it is very likely that the regulatory acceptance of in silico models will be on a case by case basis.

→ As the field of nanotoxicology is still in its infancy, the use of predictive approaches in the risk assessment of ENMs is correspondingly recent.

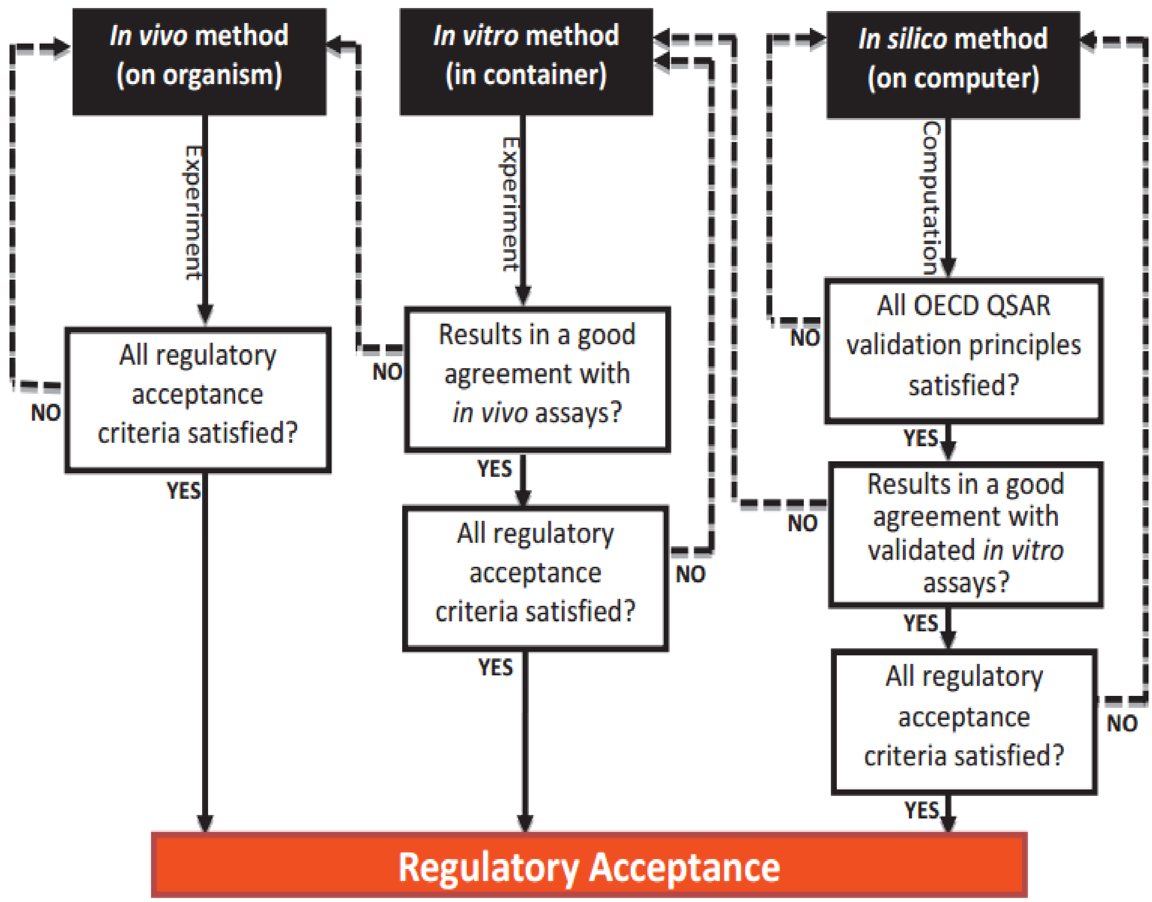

Figure 1.1: The road to regulatory acceptance of toxicity assessment methods

1.3. Risk Assessment of Engineered Nanomaterials

Risk and hazard are often used interchangeably but they are distinct terms. Hazard is the possibility of something causing a harm impact while risk refers to the probability of the impact occurring. Risk assessment is as an action to identify, assess and prioritise potential risks that are most likely to occur as a result of a given exposure to a particular substance. It involves identification of potential hazards and evaluation of occupational, consumer and environmental exposure to hazardous substances.

Hazard ***Risk (Hazard x Exposure)***

A hazard is any source of potential damage (e.g. a poisonous drink) while the risk is the chance that an individual can experience a hazardous effect if exposed to a hazard (e.g. ingestion).

The likelihood of an adverse effect to occur is assessed through four main steps: hazard identification, dose-response assessment, exposure assessment and risk characterization. A complete risk assessment process consists of multiple steps with the aim of answering following questions as accurate as possible:

- What harmful effects may be caused to human body and the environment from a toxic substance?
- What quantitative correlations exists between the dose of a toxicant and the likelihood of adverse effect in an exposed population?
- What exposures are experienced or anticipated under different conditions?
- What is the severity, frequency and probability of adverse effects in exposed populations?

→ The immediate goal in regulatory risk assessment of ENMs is to ensure the safety in their intended applications and full lifecycle along value creation chains.

The risk assessment process starts with the identification of the potential hazards associated with the exposure to a hazardous chemical; e.g. any human health or environmental problems that a chemical can cause. The second step is to determine the maximum tolerable or acceptable dose above which signs of adverse effects begin to occur. Generally, the higher the dose, the greater the likelihood of harmful effects to occur. For most substances, the safe levels are determined based on a threshold dose below which exposure poses no risks (the exceptions being carcinogens and mutagens where a dose that would result in an acceptable risk). The third step (i.e., exposure assessment) focuses on the identification of the exposed population and the determination of the exposure routes, amount, duration and pattern. In the risk characterisation phase, the data obtained from the previous steps of risk assessment are integrated to determine the probability of an adverse human health and/or environmental effects occurring as a result of exposure to a hazardous substance. It is also important to include uncertainty associated with the risk estimates in this phase.

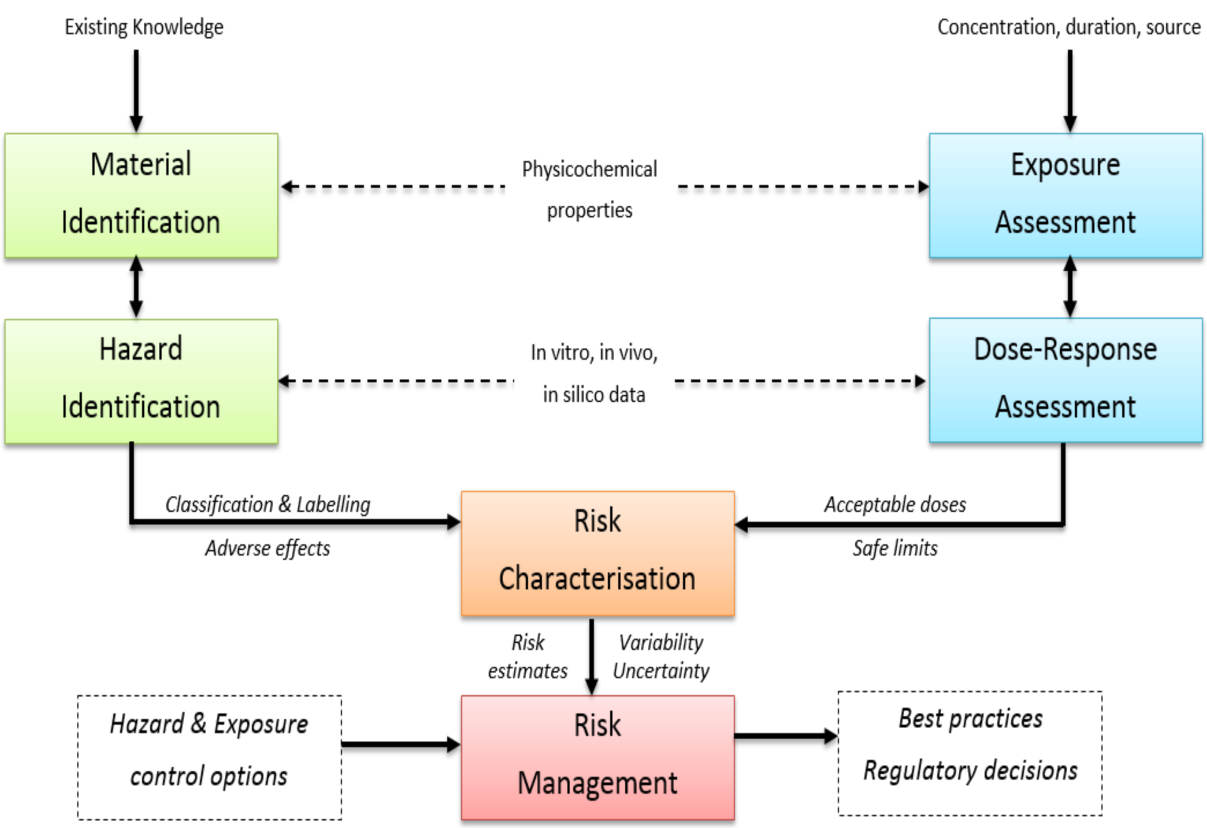

Figure 1.2: Risk assessment and management process

1.4. Risk Management of Engineered Nanomaterials

Considering the expansion of nano-industry and consequently the increasing rate of exposure to ENMs, effective risk management strategies to ensure and maintain a significant level of protection for consumers and the environment are essential. It has been discussed in many of the published guidelines that risk management measures should follow the standard hierarchy of control strategies in order to eliminate hazard or reduce exposure [2, 3, 7, 39]. The traditional hierarchy of controls given in Figure 1.3 describes the order that should be followed when choosing between viable control options for controlling risks in an effective manner.

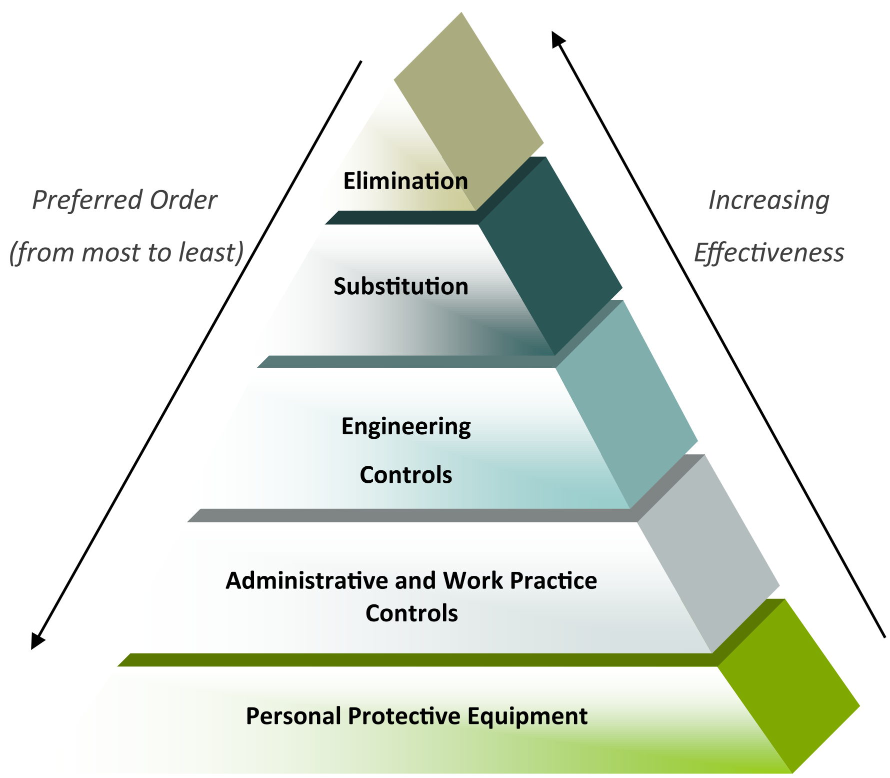

Figure 1.3: The traditional hierarchy of risk reduction measures

According to the traditional hierarchy of control, the most effective hazard control strategy is the elimination of all hazards within a process (e.g. by replacing the process). If the complete elimination of hazard at source is not practical, risk should be minimised by substituting the process or compound with a less hazardous (i.e. safer) alternative. The third most effective risk management strategy is the use of engineering controls, which require physical change to the workplace.

→ Ideally, risk control options should be implemented in the hierarchical order:
  - → Elimination/reduction of the hazard by design
  - → Application of engineering controls at the source
  - → Implementation of administrative controls and other protective measures

The remaining control measures, namely administrative controls that are designed to enforce operational procedures to minimise release to a working area and PPE aiming to protect an individual person from risks to health and safety, are least effective when used on their own because they rely on human behaviour and supervision. Ideally, these measures should be used in conjunction with more effective control measures if control of risk at source is very impractical. Given the uncertain risks around ENMs, the administrative controls affecting worker behaviour often play a greater role in their risk management. The Control of Substances Hazardous to Health (COSHH) regulation, which requires employers to properly control the occupational exposure to all chemicals used in the workplace, concentrates on preventing or reducing exposure to hazardous substances by controlling equipment, procedures and worker behavior, demonstrating the clear importance given to management controls (e.g. supervision and training to reduce exposure) in the COSHH regulation.

2. Existing Risk Assessment and Management Methods for Engineered Nanomaterials

Most researchers agree that, although we do not need an entirely new risk management paradigm to manage ENM risks, there is a need to expand existing practices to better address nano-related issues and ensure safe production, handling and use of ENMs [40, 41]. Although the existing risk management approaches may be applied to ENMs, the ability of ENMs to transform from one nanoform to another over time or in different environments makes the process much more complex because this can result in changes to exposure, hazard and risk.

At present, the main limitations in the field of ENM risk management are:

- the insufficiency of the hazard/exposure research data that can be used to validate existing risk management approaches
- the difficulties in translating these measures into modified practices
- the lack of systematic approaches for collecting and managing the information needed.

In this section, the existing tools, scoring systems and strategic approaches for minimising risks of exposure to ENMs are briefly described.

→ After careful assessment of the risks that may arise as a result of exposure to ENMs, the next step is to ensure that such risks are adequately controlled and reduced to the lowest practicable level by taking prevention measures.

2.1. Risk Prioritisation and Management Tools

Risk assessment and management tools used to mitigate risk and manage exposure can be divided into three main categories: qualitative, semi-quantitative and quantitative. Qualitative or semi-quantitative tools are currently favourable for the control of potential risks associated with ENMs since there is still lack of knowledge or understanding in relation to the safety assessment of nano-scale materials [42].

→ The existing risk management approaches need to be modified to encompass the unique hazardous behaviour and exposure pathways associated with nanoscale substances.

A control banding approach is a potential solution to assess and manage workplace risks where there is limited information, particularly relating to safety procedures and workplace exposure limits. It combines risk assessment and management to simplify risk complexity in the scarcity of input data [43]. To date, a number of control banding tools such as CB Nanotool [11], ANSES Nano [12, 13], NanoSafer [14] and Swiss precautionary matrix [44] have been developed to protect the health of workers handling ENMs. The basic nano-tools for risk management and prioritisation are given in Table 2.1. More detailed reviews of the existing tools for risk management and prioritisation of ENMs can be found elsewhere [45, 46].

Table 2.1: Risk prioritisation and management tools for ENMs

Tool	**Description**
CB Nanotool [11]	A control banding tool for assessing risks associated with ENM operations and selecting effective engineering controls
Stoffenmanager Nano [47]	A generic online tool for ranking potential human health risks as well as risk management measures applicable to ENMs
ANSES Nano [12, 13]	A control banding tool for managing the potential risks of ENMs
Swiss precautionary matrix [44, 48]	A risk prioritisation tool for safe handling of synthetic NMs
NanoSafer [14]	A semi-quantitative risk prioritisation tool for managing ENMs in the workplace
NanoRiskCat [49]	A conceptual decision support tool for risk categorisation and ranking of ENMs
A low-cost/evidence-based tool [50]	A low-cost/evidence-based for assessing and managing the risks associated with exposure to Carbon Nanofiber

2.2. Strategic approaches and practical guidelines

A number of risk management strategies proposed for use with ENMs are summarised in Table 2.2, including risk management approaches, methods and models.

Table 2.2: Existing risk management strategies for ENMs

Ref.	Description
[41]	— It provided a detailed overview on making use of current hazard data and risk assessment techniques for the development of efficient risk management guidelines for nanomaterials (NMs). — The authors proposed an integrated approach for risk management of ENMs including research and tools, risk characterisation, risk management and workplace actions.
[51]	— This paper provided an overview on the application of risk management approaches for NMs. — The authors concluded that risk management process for NMs should be an internal part of an enterprise-wide risk management system, including both risk control and a medical surveillance program that assesses the frequency of potential side effects among groups of employees (potentially) exposed to NMs. They also suggested that the medical surveillance can be used to estimate the effectiveness of risk management program.
[52]	— This extensive review drawn together finding from a broad range of research on risk assessment and management of ENMs and outlines some good workplace practices. — The authors investigated the elements of occupational health protection and hierarchy of exposure control, including primary prevention (e.g. elimination, substitution, engineering controls, environmental monitoring, administrative controls and PPE), secondary prevention (e.g. medical examination of workers) and tertiary prevention (e.g. diagnosis, therapy and rehabilitation), for NMs.
[53]	— The researchers proposed a 10-step qualitative risk management model for nanotechnology projects: the basic knowledge of the work; a thorough risk assessment; identifying nanoparticles; identifying hazardous nanoparticles; obtaining latest information; evaluating exposure routes; identifying risks; performing actions; documenting the whole process; and reviewing the risk management.
[54, 55]	— The investigators constructed a risk management strategy to protect employees working with NMs based on the precautionary risk management and reported the results of case studies with NMs. — Overall, they developed four risk management approaches: technology control (removing potential hazards from raw materials, manufacturing processes, mechanical equipment and factory facilities and other operating environments, changing operating pattern, confining production process systems), engineering control (adopting additional protective methods such as preventing and limiting sources of risk, using local ventilation and high efficiency particulate filters), personal protective equipment (breathing

	apparatuses, gloves or protective clothing), and working environment monitoring (exposure monitoring and special health examinations).
[56, 57]	— These papers outlined latest efforts and outcomes in regard to risk assessment and management of NMs. — The authors highlighted the importance of integrating risk and life cycle analyses to guide engineering design using multi-criteria decision analysis.
[58]	— The researchers introduced a methodology for nano-safety and health management. — The procedure they developed employs a schematic decision tree to classify risks into three hazard classes with each class being provided with a list of required risk mitigation measures (technical, organisational and personal).
[59]	— This paper provided an overview of eco-toxicological effects and risk management of NMs. — The authors noted that a NM risk assessment framework should include three main steps: (1) Emission and exposure pathway, nanoparticle characteristics and exposure metric, (2) Effects and impacts on both ecosystem and human health, (3) Risk assessment (risk characterisation and risk levels).
[60]	— The authors proposed a new risk assessment approach based on the "control banding" approach comprising five occupational hazard bands (1-5). — The methodology they proposed considers exposure based on seven parameters including the main properties of the NMs, their emission potential, the condition of use and exposure characterisation parameters such as duration and frequency.

Kuempel, Geraci [41] suggested an integrated procedure for risk management of ENMs including research and tools (toxicology & epidemiology, exposure and risk analysis), risk characterisation (weight of evidence, severity & likelihood, variability & uncertainty), risk management (occupational safety & health guidance, exposure limits, communication) and workplace actions (engineering controls & PPE, exposure monitoring, worker training, medical monitoring). Schulte, Geraci [51] proposed that risk management process for NMs should be a part of an enterprise-wide risk management system, including both risk control and a medical surveillance program assessing the frequency of adverse effects among groups of workers exposed to NMs. Goudarzi, Babamahmoodi [53] proposed a 10-step qualitative risk management model for detecting significant risks in a systematic approach and providing decisions and suitable actions to reduce the exposure and hazard to an acceptable level. Ling, Lin [54] developed a risk management strategy based on the precautionary risk management, which is a modified version of Luther's method [55]. The risk management strategies were constructed according to the different levels of precautionary risk management, which includes the measures relating to technology control, engineering control, personal protective equipment, and monitoring of the working environment for each level.

Fadel, Steevens [57] highlighted that the use of multi-criteria decision analysis (MCDA) for risk management purposes and the integration of risk and life cycle analysis using MCDA can be helpful to support the next generation of sustainable nano-enabled product designs and effective management of ENM risks. In the European project SCAFFOLD, the structure, content and operation modes of the Risk Management Toolkit [48] were developed to facilitate the implementation of "nano-management" in construction companies with the consideration of 5 types of nanomaterials (TiO2, SiO2, carbon nanofibres, cellulose nanofibers and nanoclays), 6 construction applications (Depollutant mortars, self-compacting concretes, coatings, self-cleaning coatings, fire resistant panels and insulation materials) and 26 exposure scenarios, including lab, pilot and industrial scales. The proposed risk management model included the following main tools: Risk management to open checklist for diagnostic, implementation or audit; Risk assessment to evaluate the identified risks; Planning to schedule the implementation of control measures specified in the evaluation tool; Key performance indicators to define, customise, calculate and visualise the indicators; Documents and templates to provide a list of templates with procedures, instructions, registers and manuals. Groso, Petri-Fink [58] developed a practical, user-friendly hazard classification system for the safety and health management of nanomaterials. The process starts using a schematic decision tree that allows classifying the nano laboratory into three hazard classes similar to a control banding approach (from Nano 3 - highest hazard to Nano 1 - lowest hazard). For each hazard level, they provide a list of required risk mitigation measures (technical, organisational and personal) such as protective measures, technical measures, organisational measures, personal measures and cleaning management. Yokel and MacPhail [52] reviewed the exposures, hazards and risk prevention measures of ENMs, in particular, the occupational exposure assessment and the approaches to minimise exposure and health hazards including engineering controls such as fume hoods and personal protective equipment, and the efficiencies of the control measures. The recommendations to minimise exposure and hazards were largely based on common sense, knowledge by analogy to ultrafine material toxicity, and general safety and health regulations, due to the lack of available information and/or unverified research findings.

Chen, Yadghar [59] reviewed the eco-toxicological effects of ENM and the existing regulations that can be related to ENMs. They concluded that the variety of ENMs and their properties make the identification and characterisation of ENMs a challenging task, so an improvement in sensitivity and selectivity of analytical methods to detect and quantify ENMs in the environment was essential. They proposed a risk assessment framework as a practical alternative for the environmental assessment and effective management of ENMs. Based on the occupational hazard band (OHB) method, a new approach to assess the risks inherent in the implementation of powders was developed [60], which considers exposure based on seven parameters which take into account the characteristics of the materials used, their emission potential, the conditions of use, as well as classic parameters of exposure characterisation like duration and frequency. The result of the reflection is then positioned on a hazard versus exposure matrix from which 4 levels of priority of action are defined, as in the classical OHB method used to manage pure chemical risk.

3. Risk Prevention Strategies for Engineered Nanomaterials

Most technical exposure control methods (e.g. glove boxes, dust suppression systems, fume cupboard, safety cabinet, good hygiene practices and personal protective equipment) can be applied to ENMs, since these measures rely on the bulk properties of nanoscale materials not on their nano-specific properties (Table 3.1). However, their performance in controlling ENM exposure should be separately evaluated from their effectiveness towards other forms since control measures that are proven to be effective for controlling exposure to traditional particles might give unsatisfactory results in the case of nano-scale particles [61].

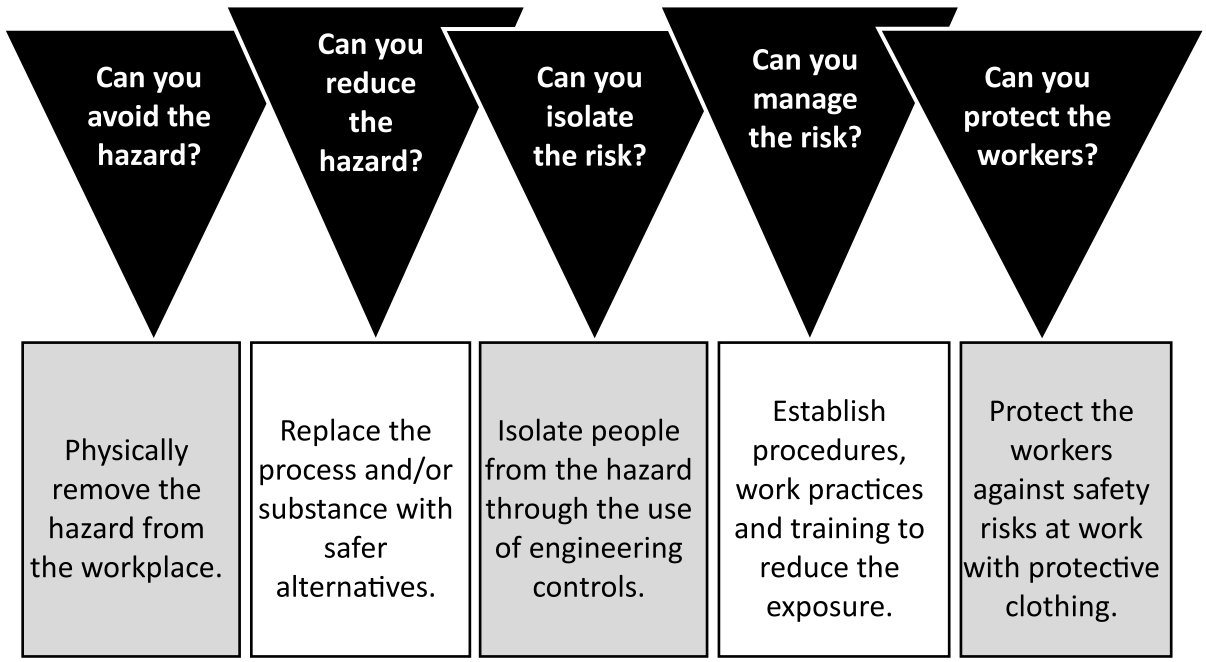

Figure 1.4: Risk management strategies in an order of priority

In the SUN RMM questionnaire, we asked respondents to score four risk management categories (intrinsic safety measures such as elimination and substitution, engineering controls, organisational measures and personal protective equipment) in terms of their relevance to their firms' activities in risk reduction process. The relevance was measured on a scale of 1 to 4, with 4 being most relevant and 1 being least relevant, for reducing potential risks that are associated with ENMs. In this context, relevance could be considered as a subjective parameter, which was estimated from the questionnaire survey of 36 nanotechnology organisations. The overall score for each method was a mean average of the scores given by individual respondents. The respondents selected the personal protective equipment (2.99/4) and the engineering measures (2.9/4) to be the most relevant control strategies for ENMs followed by organisational measures (2.77/4). Despite their high efficiency, survey respondents ranked substitution and elimination (e.g. physical manipulation of raw materials into forms that reduce hazard or exposure such as change of physical state and coating) as the least relevant control methods (2.54/4). This finding was consistent with previous core surveys in that the most common risk reduction strategies were observed to be based on isolating people from hazard through engineered measures or PPE, rather than eliminating hazard at source. It needs to be noted here that the use of PPE for risk reduction purpose should be used as a last resort after implementing other controls according to COSHH.

Table 3.1: The proposed classification system for technological alternatives and risk management measures of ENMs

Product/Substance Controls	
Substitution of hazardous material	Surface modification
Limiting concentration of hazardous ingredient	Embedding in matrix
Change of physical form and solubility	Packaging
Change in physicochemical properties	Granulation, controlled aggregation, purification
Process and Waste Controls	
Change of env. conditions (e.g. humidity)	Reduction/cleaning of air emissions
Automation	Reduction/cleaning of general waste
Suppression systems- wetting at point of release	Disposal of general waste
Suppression systems- Knockdown suppression	Reduction/cleaning of nano-specific waste
Use of mechanical transportation	Disposal of nano-specific waste
Containment of operator (e.g. cabin with filtered air for operator)	
Engineering (enclosure, isolation and ventilation) Controls	
Physical containment (e.g. covers, sealing heads)	Glove bags and glove boxes
Chemical fume hoods	Enclosed (isolated) operations
Biosafety cabinets	Sealed operations
Local exhaust ventilation systems (e.g. with enclosing, capturing or receiving hoods)	
Mechanical room ventilation	Dilution (general exhaust) ventilation
Natural ventilation	Laminar flow booths & benches

Good Work Practices and Administrative Controls	
Cleaning and maintenance of process equipment	Management systems
Vacuum cleaner with an air filter (e.g. HEPA)	Operating practice
Spill containment measures	Supervision
Workplace housekeeping	Monitoring
Personal hygiene facilities	Health surveillance
Restricted or prohibited process areas	Worker training

Personal Protective Equipment Controls	
Body protection	Face / Eye protection
Hand protection	Foot protection
Respiratory protection	

3.1. Substance-related Controls

The most effective hazard control method is the elimination of all hazards at the source (e.g. by replacing the process or use of a non-hazardous substance). If the complete elimination of hazard within the process is not technically or economically viable, risk should be minimised by substituting the compound with a safer alternative or modifying the product form to make it less hazardous. One aspect of ENMs that is exciting is that changing the hazard by manipulating the substance is possible, whereas with bulk materials, the hazard can be viewed as intrinsic to the substance so the risk is can only be controlled by limiting exposure.

→ Despite the efficiency and sustainability of intrinsic safety measures, their current use in reducing ENM risks is limited due to the unknown effects of manipulating nano-characteristics on the desired functionality.

Although control measures related to the modification of ENMs have high efficiency in the occupational risk control hierarchy, they are not widely employed because there is currently a high degree of uncertainty regarding the impact of manipulating nano-characteristics on the technical performance of final product. However, the ability to remove the source of risk through safety-by-design approaches (e.g. use of a nano-form encapsulated in micro/macro form that reduce human and environmental exposure while preserving nanoscale reactivity) is one of the most effective risk management strategy and deserves further investigation [62-65].

- Substitution should be considered as a primary control option for ENMs with high level of toxicity concern (e.g. carcinogenic or mutagenic ENMs).
- Low-dust ENMs and low-dust processing methods should be preferred wherever possible.
- Use of ENMs encapsulated in micro/macro form or strongly adhered to a substrate should be preferred over the forms that may become airborne.
- Coating the surface of metal-based ENMs with appropriate organic substances has great potential to reduce hazardous effects.

3.2. Engineering Controls

Engineering controls include different type and design of control measures that isolate or remove a hazard from the workplace. In principle, most of the conventional engineering controls are applicable to ENMs. However, in practice, there is a clear need to re-evaluate their performance when dealing with ENMs since control options that are proven to be effective for reducing risks associated with traditional particles might give unsatisfactory results in the case of nano-scale particles.

Between 2006 and 2011, NIOSH conducted site visits to 46 U.S. companies that produced and/or used ENMs and collected information on the most frequently used engineering controls, housekeeping methods and PPE types [66]. Their assessment showed that the most frequently employed engineering controls for reducing occupational exposures to ENMs were local exhaust ventilation (59%) and chemical fume hoods (54%) followed by ventilated enclosures (50%), enclosed production (48%) and glove boxes (22%). Similarly, it was noted in NIOSH's guidance document [3] that the most common control measures used for ENMs are fume hoods, local exhaust ventilation systems, filtered vacuum cleaners, walk-in ventilated enclosures and isolation techniques such as negative pressure rooms or boxes.

→ Currently, the most frequently employed engineering control measures for reducing exposure to ENMs are local exhaust ventilation and chemical fume

In 2007, Conti et al. carried out an international survey among 83 nanotechnology companies and research laboratories to find out (nano-specific) health and safety programs and risk control measures implemented by these organisations to ensure safe working practices and environmental protection [67]. The results demonstrated that the most common type of engineering control measure was fume hoods (66%) followed by some kind of exhaust filtration (49%). Schmid, Danuser [68] conducted a survey between 1626 Swiss Companies investigating the quantity of nanoparticles and current protection measures that are in place. Performing manipulation within a closed process was identified to be the most common protection method in liquid applications while PPE was observed to be the most prominent safety measure followed by local exhaust ventilation in case of powder applications.

Similarly, in 2010, NEPHH project conducted a survey on occupational health and safety procedures that are in place in nano-manufacturing sector with the aim of collecting information on engineering controls, PPE and waste management [69]. They reported that the majority of their respondents (66%) use fume hoods, followed by laminar flow clean bench (34%), glove boxes (29.8%), biological safe cabinet (27.7%), cleanrooms (23.4%), glove bag (21.3%), closed piping system (21.3%), pressure differentials (19.1%), separate HVAC (8.5%) and chemical box (2.1%) to reduce worker exposure to ENMs [69]. It should be noted that although these engineering measures significantly reduced the risk for workers, they did not eliminate it.

The ENM was still existing so the risk was moved to other stages such as handling and disposal of the filters.

→ When there is no information on the efficiency of control measures specific to ENMs, the default efficiencies can probably be used for initial assessment purposes, although it should not be considered exhaustive.

Studies quantitatively examining the efficiency of different control measures for ENMs are summarised in Table 3.2 and the data collected from the reviewed projects are given in Tables 3.3.

Table 3.2: Studies (quantitatively) evaluating the efficiency of engineering controls for ENMs

Measure	ENM Type	Efficiency	Ref
Process change (harvest wait time)	CNTs and/or graphene	99.6 and 100% reduction in conc.	[70]
Process change (isolation valves)	CNTs and/or graphene	99.9% reduction in con.	[70]
Process ventilation (exhaust fan)	CNTs and/or graphene	82.6% reduction in worker's breathing zone (BZ)	[70]
Exhaust ventilation system-with enclosure	CNTs	93-96% filtration efficiency on average	[71]
Biological safety cabinet	CNTs	36% reduction in con. in WBZ and 40% reduction outside the hood	[72]
Canopy hood	CNTs	15-20% increase in conc.	[72]
Custom fume hoods and biological safety cabinet	Epoxy/CNT nanocomposites	Process/Background conc. in BZ Ratios; None: 5.9, Custom hood: 24.4, BSC:0.66	[73]
Fume hood (fan ON and OFF)	Titanium tetraisopropoxide	Particle number con. reduced from 150 000 to ~6 300 particles/cm3	[74]

Cabin air filter- high fan speed	Diesel engine exhaust	55% and 48.9% reduction in exposure based on particle number and surface area concentration	[75]
Cabin air filter- medium fan speed	Diesel engine exhaust	65.6% and 60.6% reduction in exposure based on particle number and surface area concentration	[75]
Personal protective clothing (cotton, polyester and Tyvek)	Nanoalumina	Mass of NP deposit (C:3364, P:2463, T:2121 µg/swatch) Mass of NP release (C:1674, P:1312, T:877 µg/swatch)	[76]
Ventilated feeder enclosure	Nanoalumina	Particle number con. reduced from 6060 to 360 particles/cm3	[77]
Ventilated full enclosure	Nanoalumina	Particle number con. reduced from 360 to -520 particles/cm3	[77]
Ventilated feeder enclosure	Nanoclay	Particle number con. reduced from 97 380 to -20 particles/cm3	[77]
Ventilated full enclosure	Nanoclay	Particle number con. reduced from -20 to340 particles/cm3	[77]
Unventilation full enclosure	Nanoclay	Particle number con. reduced from -20 to 0 particles/cm3	[77]
Sealed and unsealed respiratory protection device	Nanoscale NaCl aerosol	When RPD is sealed, the protection factor is 100- 1000 000 greater than the protection factor in an unsealed fit.	[78]
Local exhaust ventilation with a custom-filtered flange	Nanometal oxides	92% reduction in emission and 100% reduction in particle concentration.	[79]
Local exhaust ventilation	Nanometal oxides	88-96% reduction in concentration.	[80]
Thermo-denuder	CNT-containing polystyrene	99.9% reduction in the number of released NP	[81]

Table 3.3: Scores for reducing exposure through protective measures [82]. Generally, a score of 1 is considered to be the default value that leads to a certain concentration. Values >1 indicate situations with increased exposure and values <1 situations with reduced exposure)

RMM	Score	RMM	Score
General Ventilation		**Localised Controls**	
No general ventilation, room size<100m3	10	No control measure	1
Mechanical and/or natural ventilation, room size <100m3	3	Limiting emission (e.g. wetting a powder, spraying of water)	0.3
Spraying booth, room size <100m3	0.1	Local exhaust ventilation (LEV)	0.3
No general ventilation, room size=100-1000m3	3	Containment of the source without LEV	0.3
Mechanical and/or natural ventilation, room size100-1000m3	1	Containment of the source with LEV (e.g. fume cupboard)	0.03
Spraying booth, room size100-1000m3	0.3	Glove boxes/bags	0.001
No general ventilation, room size>1000m3	1		
Mechanical and/or natural ventilation, room size>1000m3	1		
Spraying booth, room size>1000m3	1		

In general, ENMs can be divided into three categories based on their potential for airborne release: no potential for airborne release (e.g. ENMs that are bound in matrix), moderate potential for airborne release (e.g. ENMs in liquid suspensions) and very high potential for airborne release (e.g. ENMs in powder form). The type of exposure is also important when choosing between different control options. For example, most of engineering controls are adequate to control exposure by inhalations while control of dermal exposure is usually done by containment procedures and/or protective gloves.

- When there is no/low potential for airborne release (e.g. ENMs bound in solid matrix), advance engineering controls are not needed.
- When there is moderate potential for airborne release (e.g. ENMs in liquid suspensions), performing the work in fume hood, biological safety cabinet, or removing the airborne emissions through local exhaust ventilation is usually sufficient.
- When there is high risk for airborne exposure (e.g. ENMs in powder form or pellets), the work should be performed in an enclosed system such as glove box or glove bags.

More specific recommendations to choose optimal engineering controls when handling ENMs are provided below:

1. When the intrinsic safety measures (e.g. elimination and substitution) are not viable, the second best option for safe handling of ENMs is to implement engineering control measures.
2. The choice of engineering controls at workplaces should be made based on the state of the nanomaterial (e.g. physical form and properties), the level of concern about a particular hazard (e.g. low, medium, high), the exposure potential (e.g. low, medium, high) and the primary routes to exposure (e.g. inhalation, dermal absorption and ingestion).
3. The most desirable engineering control for ENM processes is isolation of emission sources to prevent worker exposure to ENMs by means of placing a barrier between the worker and hazard.
4. Working with dry ENMs requires very careful attention. Ideally, they should be handled in a glove box, fume hood, biological safety cabinet or a vented filtered enclosure.
5. ENMs that are encapsulated in a solid or bound in a matrix have low potential for local exposure since they cannot be dispersed into the environment.

6. When there is significant airborne risk, emissions should be captured and removed as close to the source as possible through use of local exhaust ventilation or fume hoods.
7. The combination of isolation and ventilation should be employed if an increase in exposure control efficiency is needed.

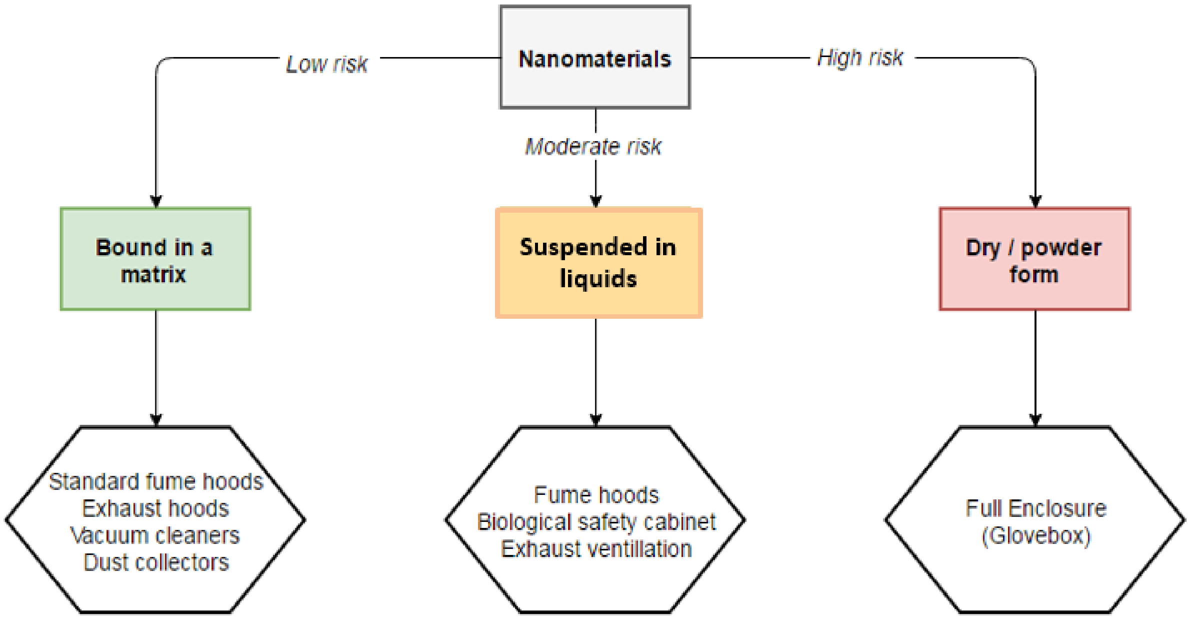

Figure 3.1: The selection of engineering controls based on the level of airborne release potential

→ Among 36 SUN survey respondents, only 5 of them provided quantitative data on the effectiveness of control measures. Moreover, provided answers are incomplete and mostly conflicting, suggesting that more research is needed with respect to the efficiencies of risk control measures for clarification. Overall, all type of ventilation methods except dilution ventilation and controls such as embedding in matrix were observed to have high efficiency (>80%) while surface modification approaches and automation were observed to have very low efficiency (<50%) for ENMs. The main difficulty here is defining which nano-form the efficiency applies to.

3.3. Administrative Controls

→ Currently, the most frequently employed housekeeping methods are wet wiping and HEPA vacuum when dealing with ENMs.

Administrative controls are designed to enforce operational procedures to minimise release of exposure to a working area. They involve multiple organizational measures and good housekeeping practices including cleaning and maintenance of process equipment, vacuum cleaner with an air filter, spill containment measures, workplace housekeeping, management systems, monitoring, supervision, training operating practice, personal hygiene facilities, restricted or prohibited process areas, limited workers' exposures (shorter work times) and worker training. It should also be noted that the housekeeping methods such as HEPA vacuum cleaner and wet wipes are useful for spill clear up but the risk from the ENM can be viewed as being moved in space and time to the point where the split clean-up residues have to be disposed (e.g. emptying vacuum or drying of wet wipes).

- When handling dry ENMs, all surfaces that are potentially contaminated with ENMs should be cleaned using a HEPA vacuum cleaner with verified filtration effectiveness.
- Containers holding ENMs should be kept closed as much as possible.
- Cleaning of contaminated surfaces and equipment should be carried out using wet wiping while cleaning with compressed air should be avoided.
- Special care must be taken with regard to handling and disposal of filters/cloths.
- Specialised training should be given to workers on the safest way of handling ENMs and particular hazardous properties of handled ENMs.
- Effectiveness of the implemented risk reduction measures should be monitored and reviewed on a regular basis.

Administrative controls are employed to minimise the duration and quantity of exposure at the workplace following appropriate hygiene measures and suitable working procedures for the safe handling, storage and transport of ENMs within the workplace.

According to the COSHH control hierarchy, engineering and management controls are generally preferred over PPE, when feasible. However, in the case of moderate/high exposure potential, management controls are usually not sufficient when used alone and hence, should be used in conjunction with engineering controls for ensuring safety.

3.4. Personal Protective Equipment

Personal protective equipment (PPE) refers to a large group of products designed to protect wearer's body from specific health and safety risk. PPE is the least effective category in the hierarchy of risk management control options and hence, should be used as a last resort prevention measure and always in conjunction with more effective control measures. Currently, there are no universally agreed guidelines for appropriate selection of personal clothing for protection against ENMs. When there are no nano-specific PPE recommendations, workers active with/near ENMs should apply a conservative approach and wear the most efficient PPE available.

- Disposable, preferably non-woven and impermeable gloves should be worn.
- Disposable Tyvek-type protective clothing is advised to be worn in case when the arm or other body parts are at risk of being exposed to dry or liquid ENMs.
- As in all other lab facilities and production, safety googles are mandatory for workers dealing with ENMs.
- No respiratory protection is required if the work is performed in a fully enclosed systems. If not, depending on the operation, the use of (at least) FFP3 respiratory-grade masks is advised (e.g. during spill or leak clean up).

In general, clothing made of materials that do not retain dust and have low particle contamination and release ability are recommended for use with ENMs. Gloves, aprons, and Tyvek suits are currently the most frequently used PPE for the reduction of dermal exposure [83]. In the case of high uncertainty, chemically and physically impermeable protective clothing should be preferred as it provides a further increased higher level of chemical protection [84]. However, a special care must be taken when removing and disposing the protective gloves and clothing to avoid re-release of the ENMs.

Table 3.4: The experimental penetration factor (e.g. the ratio between the number concentration of particles inside and outside the protective device) of PPE [85]

ENPs	PPE	PF_{Av} %	ENPs	PPE	PF_{Av} %
ZnO	Aut. Mask	7.40	Fe2O3	Latex Gloves	0.040±06
ZnO	Half Mask 1	8.50	Fe2O3	Nitrile Gloves	0.03±0.07
ZnO	Half Mask 2	12.00	Fe2O3	Lab coat	2.0±0.5
Fe2O3	Aut. Mask	5.52	ZnO	Latex Gloves	0.00±0.09
Fe2O3	Half Mask 1	6.58	ZnO	Nitrile Gloves	0.00±0.1
Fe2O3	Half Mask 2	8.55	ZnO	Lab coat	0.8±0.2
TiO2	Aut. Mask	6.24	Al2O3	Latex Gloves	0.35±0.19
TiO2	Half Mask 1	5.88	Al2O3	Nitrile Gloves	1.2±0.8
TiO2	Half Mask 2	6.51	Al2O3	Lab coat	5.0±1.4
Al2O3	Aut. Mask	6.50	TiO2	Latex Gloves	0.04±0.03
Al2O3	Half Mask 1	9.99	TiO2	Nitrile Gloves	0.0±0.4
Al2O3	Half Mask 2	6.26	TiO2	Lab coat	8.5±1.9
CoAl2O3	Aut. Mask	7.80	CoAl2O3	Latex Gloves	0.0±0.4

CoAl2O3	Half Mask 1	7.16	CoAl2O3	Nitrile Gloves	0.0±0.4
CoAl2O3	Half Mask 2	7.87	CoAl2O3	Lab coat	12±4

Table 3.5: Scores for modifying respiratory and dermal exposure through protective measures [82]. Generally, a score of 1 is considered to be the default value that leads to a certain concentration. Values >1 indicate situations with increased exposure and values <1 situations with reduced exposure

Respiratory PPE		**Gloves**	
No PPE	1	No gloves	1
FFP2 filtering half masks	0.4	Woven clothing	0.3
FFP3 filtering half masks	0.2	Gloves-Non-woven permeable, not connected well to clothing or arms	0.3
P2 replaceable filter Half Mask	0.4	Gloves-Non-woven permeable connected well to clothing or arms	0.1
P3 replaceable filter Half Mask	0.2	Gloves-Non-woven impermeable, not connected well to clothing or arms	0.03
A1P2 combined half mask	0.2	Gloves-Non-woven impermeable connected well to clothing or arms	0.09
A1P3 combined half mask	0.1	**Protective Clothing**	
Full-Face masks with P3 filters	0.1	No clothing	1
A powered filtered device incorporating a TH1 hood	0.2	Woven clothing	0.09
A powered filtered device incorporating a TH2 hood	0.1	Non-woven permeable	0.03
A powered filtered device incorporating a TH3 hood	0.05	Non-woven impermeable	0.009

4. Cost of Risk Control Measures

Achieving environmental and worker protection at low cost is an integral feature of several risk management principles (e.g. European Commission's Precautionary Principle [86], UK Health and Safety Executive's "As Low as Reasonably Practicable" principle [87]) and regulations (e.g. Socioeconomic Analysis [88]). Although cost is not a direct factor in REACH, economic viability to the company is a factor when assessing alternatives within Authorisation. Therefore, this section is of particular use to downstream users trying to compare and implement alternative control measures. Given the significant uncertainties around ENM risk and ambiguous risk perception of stakeholders, evaluation of costs is even more critical to support a rational risk management approach. Helland et al. (2008) report that small firms identified cost as the biggest barrier to occupational risk management[89]. Fleury et al (2011) pinpoint difficulties in implementing risk management for nanocomposites based on acceptable risk thresholds and propose risk management and cost evaluation based on the ALARP principle [90].

Key methodologies used to assess the balance between environmental protection and the personal or societal costs to achieve it include cost-benefit analysis (comparison of net benefits and net costs of an action for manufacturer or society) and cost efficiency analysis (assessing which action maximises the level of risk reduction per unit cost). The cost-benefit balance for all RMMs can be difficult to calculate because the cost is a tangible quantity whereas the benefit depends on the potential cost of an adverse effect that is not certain to occur. To illustrate how efficiency and cost criteria can be integrated, emerging findings (Fig. 3.1) from the questionnaire on respondents ranking on cost (on a scale from 1 to 4) are compared with the occupational risk control hierarchy for efficiency (Fig. 1.3). As can be seen from Fig. 3.1, automated control and process control are observed to be costly risk management solutions. However, despite their relatively high investment and implementation costs, they significantly reduce the likelihood of different types of risks. Survey respondents rank PPE for hand, face/eyes, feet and body as the least expensive RMMs. In most cases, the respondents did not specify whether their responses were related to one piece of PPE for single or repeated use. Although PPE is a low-cost intervention, it is the least effective category in the occupational risk control hierarchy and would not be useful in situations where significant risk reduction is required. It should also be noted that the effectiveness of PPE in real-life conditions may only be acceptable if they are used appropriately (e.g. proper fitting of face masks, shaving of beards before use of fitted face masks). Organisational and work practice control measures are rated by the respondents among the more expensive RMMs but are penultimate in the occupational control hierarchy. On the other hand, most of the engineering controls (except operator containment) are higher than PPEs in cost (e.g. large up-front cost), but more preferred according to the occupational risk hierarchy, suggesting that engineering controls could have the optimum tradeoff between efficiency and cost for medium to high-risk scenarios.

Elimination (e.g. limiting concentration of hazardous material) and substitution (e.g. change of physical state, change in physicochemical properties) have the highest ranking in the occupational risk control hierarchy but also ranked among the most expensive RMMs, suggesting that they will be used in high-risk scenarios. By developing quantitative estimates of efficiency and cost for ENMs, RMMs can be clearly compared to find the alternative that makes the most optimum trade-off between these factors toward the achievement of risk thresholds. Specifically, once the sufficient amount of quantitative data is available, it would be possible to find an optimum set of financially efficient RMMs using efficiency-cost ratio as an indicator.

The cost of risk management is also expected to have an inverse relationship with insurance premia for nanomanufacturing. Insurance sector representatives attending the first SUN Stakeholders' Workshop in Utrecht in 2014 expressed a willingness to offer discretionary insurance premium discounts if industry demonstrated an understanding of risk, regulation and Standard Operating Procedures. Therefore, along with supporting industry in implementing RMMs that will prevent adverse effects on human beings and the environment, finding an optimum set of financially efficient RMMs will also enable industry to reduce insurance costs for nanomanufacturing.

> Although the initial cost of employing engineering controls is higher than administrative controls and PPE, it leads to cost savings over time from lower operating costs and higher effectiveness in risk mitigation.

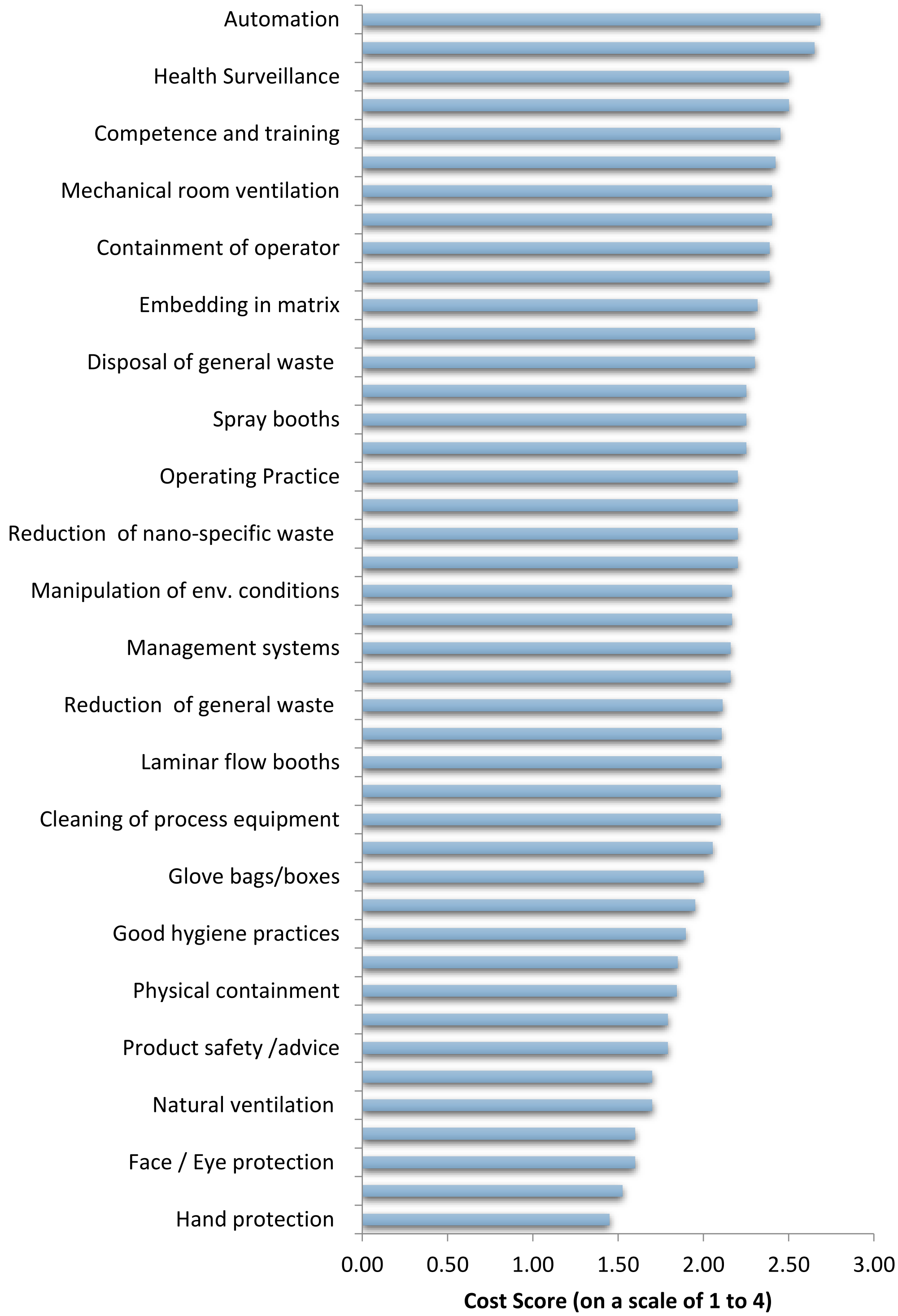

Figure 4.1: Relative cost of risk management measures on a scale of 1 (lowest) to 4 (highest).

5. Concluding remarks

This document is intended to provide guidance on how to select adequate risk control measures for managing the risks associated with exposure to ENMs, according to the current state of knowledge on health and safety issues of ENMs. The ultimate aim here is to support employees/researchers working with ENMs in their design of suitable control measures to organise and maintain a safe workplace.

The findings show that isolating people from hazard through engineering measures (e.g. local exhaust ventilation, chemical fume hoods, glove boxes and biological safe cabinet) and reducing employee exposure to hazards through protective clothing (e.g. Gloves, aprons, and Tyvek suits) are more commonly used to reduce ENM risks, compared to eliminating hazard at source. It is also observed that despite the high efficiency and sustainability of risk prevention measures such as the elimination and substitution (e.g. modification of ENMs in a way that reduces the risks they pose) in the hierarchy of hazard control, their current use is not widespread due to the unknown effects of manipulating nano-characteristics on the desired functionality. Clearly, more quantitative research is needed with respect to the efficiency and cost of each RMM to fully understand and compare their suitability in preventing risks that may arise as a result of occupational or consumer exposure to ENMs.

Some of the key conclusions drawn for selecting the appropriate risk management measures when dealing with ENMs are as follows:

- Substance-related safety measures such as elimination or substitution should be considered as primary control options for ENMs, especially in the case of high level of toxicity concern (e.g. carcinogenic or mutagenic ENMs).
- The exposure risk is not only related to the quantity of ENMs being used but also their form of use e.g. ENMs forms that are or may become airborne represent a greater risk due to increased exposure potential.
- Safe-by-design approaches altering the biological activity by modifying toxicity-related properties have high efficiency in the occupational risk control hierarchy and can be applied to some ENMs. However, there is a profound need to ensure that while these

alterations in properties reduce the toxicity of ENMs, they do not affect the desired functionality and hence, commercial viability of the material.

- When intrinsic safety measures are not viable, the second best option for safe handling of ENMs is to implement engineering control measures.
- The selection of engineering controls at workplaces should be made based on the state of the nanomaterial (e.g. physical form and properties), the level of concern about a particular hazard (e.g. low, medium, high), the exposure potential (e.g. low, medium, high) and the primary routes to exposure (e.g. inhalation, dermal absorption and ingestion).
- According to the COSHH control hierarchy, engineering and administrative controls are generally preferred over PPE, when feasible. However, in the case of moderate/high exposure potential, management controls are usually not sufficient when used alone and hence, should be used in conjunction with engineering measures.
- When there is no nano-specific PPE recommendations, people working with/near ENMs should wear extensive PPE depending on the type of ENMs being exposed to. In general, personal clothing made of materials that do not retain dust and have low particle contamination and release ability is recommended for use with ENMs. In the case of high uncertainty, impermeable protective clothing should be preferred since it provides relatively higher level of chemical protection.

Most of the traditional hazard and/or exposure control options can be applied to ENMs since these measures rely on the bulk properties of nanoscale materials, not on their nano-specific properties. However, their efficiency in controlling ENM risks should be separately evaluated. When there is no information on the efficiency of control measures specific to ENMs, the default efficiencies may be used for initial assessment purposes although they should not be considered exhaustive. In the case of high uncertainty, the precautionary principle should be applied.

The limited knowledge on nanoEHS issues points to important gaps in research on the environmental and health risks associated with nanotechnology. Clearly, much research remains to be done on the risk management of ENMs, including identification and categorization of ENMs (e.g. classification of nano-enabled materials based on key parameters or biological interactions) data collection (e.g. scientific data pertinent to hazard and exposure), standardization (e.g. definitions, control limits, measurement methods and metrics etc.), safety-by-design research (e.g. integrating safety into design), development of new measurements (e.g. developing a combination of different analytical methods for determining nanomaterial mass concentration, particle concentration, morphological information etc.), and risk prediction/management tools (e.g. quantitative tools for the predictive risk assessment and management including databases and ontologies).

The existing challenges in risk management of ENMs are not only scientific but are also related to insufficient communication and integration between different scientific disciplines, which might lead to unnecessary overlapping of studies. More focused research, integrated processes, and more dialogue are required. In part, this is currently being addressed by a growing number of European projects and international efforts. For example, SUN is a collaborative EU project aiming at making best use of available knowledge on environmental and health risks of ENMs to develop a user-friendly, versatile software-based DSS for practical use by industries and regulators. It aims to contribute to the sustainability of nanotechnology by addressing health and safety issues of ENMs throughout their complete life cycle in close collaboration with research organisations, industry and regulating bodies. These projects will undoubtedly lead to many insights into the risk management issues involved in nanoscale production and products.

Bibliography

1. Marchant, G.E., D.J. Sylvester, and K.W. Abbott, *Risk management principles for nanotechnology.* Nanoethics, 2008. **2**(1): p. 43-60.
2. NIOSH, *General Safe Practices for Working with Engineered Nanomaterials in Research Laboratories.* DHHS (NIOSH), 2012. **147**: p. 2012-147.
3. NIOSH, *Current Strategies for Engineering Controls in Nanomaterial Production and Downstream Handling Processes*, 2013, Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH): Cincinnati, OH:U.S.
4. HSE, *Using nanomaterials at work: Including carbon nanotubes (CNTs) and other bio-persistent high aspect ratio nanomaterials (HARNs)*, H.a.S.E. HSG272, Editor 2013.
5. FNV, V.-N.a.C., *Guidance working safely with engineered nanomaterials and nanoproducts: a guide for employers and employees*, 2011. p. http://www.industox.nl/Guidance%20on%20safe%20handling%20nanomats&products.pdf.
6. OECD, *Compilation of nanomaterial exposure mitigation guidelines relating to laboratories.* 2010(Series on the Safety of Manufactured Nanomaterials No. 28).
7. EPA, *Approaches for assessing and controlling workplace releases and exposures to new and existing nanomaterials*, in *INTERNAL CEB INTERIM DRAFT*2012. p. http://www.epa.gov/oppt/exposure/pubs/cebnanodraft_05_12.pdf.
8. ISO, T., *12901-2:2014 Nanotechnologies -- Occupational risk management applied to engineered nanomaterials -- Part 2: Use of the control banding approach.* 2014.
9. ISO, T., *12901-1:2012 Nanotechnologies -- Occupational risk management applied to engineered nanomaterials -- Part 1: Principles and approaches.* 2012.
10. ISO, T., *12885:2008 Nanotechnology—health and safety practices in occupational settings relevant to nanotechnologies.* ISO, Geneva, 2008.
11. Zalk, D.M., S.Y. Paik, and P. Swuste, *Evaluating the control banding nanotool: a qualitative risk assessment method for controlling nanoparticle exposures.* Journal of Nanoparticle Research, 2009. **11**(7): p. 1685-1704.
12. Riediker, M., et al., *Development of a control banding tool for nanomaterials.* Journal of Nanomaterials, 2012. **2012**: p. 8.
13. ANSES, *Development of a specific control banding tool for nanomaterials*, 2010. p. https://www.anses.fr/sites/default/files/documents/AP2008sa0407RaEN.pdf.
14. Jensen, K.A., et al. *NanoSafer vs. 1.1-Nanomaterial risk assessment using first order modeling*. in *6th International Symposium on Nanotechnology, Occupational and Environmental Health*. 2013.
15. Manuele, F.A., *Risk assessment & hierarchies of control.* Professional Safety, 2005. **50**(5): p. 33.
16. Paul, D. and L. Robeson, *Polymer nanotechnology: nanocomposites.* Polymer, 2008. **49**(15): p. 3187-3204.

17. Sadik, O.A., *Anthropogenic nanoparticles in the environment.* Environmental Science: Processes & Impacts, 2013. **15**(1): p. 19-20.

18. Oberdorster, G., et al., *Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy.* Particle and Fibre Toxicology, 2005. **2**(1): p. 8.

19. Sharma, C.S., et al., *Single-walled carbon nanotubes induces oxidative stress in rat lung epithelial cells.* Journal of nanoscience and nanotechnology, 2007. **7**(7): p. 2466.

20. Shvedova, A.A., et al., *Unusual inflammatory and fibrogenic pulmonary responses to single walled carbon nanotubes in mice.* American Journal of Physiology-Lung Cellular and Molecular Physiology, 2005. **289(5)**: p. L698-L708.

21. Saquib, Q., et al., *Titanium dioxide nanoparticles induced cytotoxicity, oxidative stress and DNA damage in human amnion epithelial (WISH) cells.* Toxicology in vitro, 2012. **26**(2): p. 351-361.

22. Setyawati, M.I., et al., *Cytotoxic and genotoxic characterization of titanium dioxide, gadolinium oxide, and poly (lactic-co-glycolic acid) nanoparticles in human fibroblasts.* Journal of Biomedical Materials Research Part A, 2012. **101(3)**: p. 633-640.

23. Trouiller, B., et al., *Titanium dioxide nanoparticles induce DNA damage and genetic instability in vivo in mice.* Cancer Research, 2009. **69**(22): p. 8784-8789.

24. Shukla, R.K., et al., *ROS-mediated genotoxicity induced by titanium dioxide nanoparticles in human epidermal cells.* Toxicology In Vitro, 2011. **25**(1): p. 231-241.

25. Grassian, V.H., et al., *Inhalation exposure study of titanium dioxide nanoparticles with a primary particle size of 2 to 5 nm.* Environmental Health Perspectives, 2007. **115**(3): p. 397-402.

26. Han, S.G., B. Newsome, and B. Hennig, *Titanium dioxide nanoparticles increase inflammatory responses in vascular endothelial cells.* Toxicology, 2013. **306**: p. 1-8.

27. Hussain, S.M., et al., *The interaction of manganese nanoparticles with PC-12 cells induces dopamine depletion.* Toxicological Sciences, 2006. **92**(2): p. 456-463.

28. Kim, S., et al., *Oxidative stress-dependent toxicity of silver nanoparticles in human hepatoma cells.* Toxicology in vitro, 2009. **23**(6): p. 1076-1084.

29. Foldbjerg, R., D.A. Dang, and H. Autrup, *Cytotoxicity and genotoxicity of silver nanoparticles in the human lung cancer cell line, A549.* Archives of toxicology, 2011. **85**(7): p. 743-750.

30. Asare, N., et al., *Cytotoxic and genotoxic effects of silver nanoparticles in testicular cells.* Toxicology, 2012. **291**(1): p. 65-72.

31. Magrez, A., et al., *Cellular toxicity of carbon-based nanomaterials.* Nano letters, 2006. **6**(6): p. 1121-1125.

32. Jeng, H.A. and J. Swanson, *Toxicity of metal oxide nanoparticles in mammalian cells.* Journal of Environmental Science and Health Part A, 2006. **41**(12): p. 2699-2711.

33. Horie, M. and K. Fujita, *Toxicity of metal oxides nanoparticles.* Adv Mol Toxicol, 2011. **5**: p. 145-178.

34. Holgate, S.T., *Exposure, uptake, distribution and toxicity of nanomaterials in humans.* Journal of biomedical nanotechnology, 2010. **6**(1): p. 1-19.

35. Wani, M.Y., et al., *Nanotoxicity: dimensional and morphological concerns.* Advances in Physical Chemistry, 2011. **2011**: p. 450912.

36. Arora, S., J.M. Rajwade, and K.M. Paknikar, *Nanotoxicology and in vitro studies: The need of the hour.* Toxicology and applied pharmacology, 2012. **258**(2): p. 151-165.

37. Sharifi, S., et al., *Toxicity of nanomaterials.* Chemical Society Reviews, 2012. **41**(6): p. 2323-2343.

38. Oksel, C., et al., *(Q) SAR modelling of nanomaterial toxicity: A critical review.* Particuology, 2015. **21**: p. 1-19.

39. Eija-Riitta Hyytinen, V.V., Sanni Uuksulainen, Helene Stockmann-Juvala, Panu Oksa,Finnish Institute of Occupational Health (FIOH), *Guidance on health surveillance for workers in the construction industry*, in *Scaffold Report*2015.

40. Oksel, C., et al., *Evaluation of existing control measures in reducing health and safety risks of engineered nanomaterials.* Environmental Science: Nano, 2016. **3**(4): p. 869-882.

41. Kuempel, E.D., C.L. Geraci, and P.A. Schulte, *Risk Assessment and Risk Management of Nanomaterials in the Workplace: Translating Research to Practice.* Ann. Occup. Hyg., 2012. **56**(5): p. 491-505.

42. Boldrin, A., et al., *Environmental exposure assessment framework for nanoparticles in solid waste.* Journal of Nanoparticle Research, 2014. **16**(6): p. 1-19.

43. NIOSH, *Qualitative Risk Characterization and Management of Occupational Hazards: Control Banding (CB)*, in *Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health*2009.

44. Höck, J., et al., *Guidelines on the precautionary matrix for synthetic nanomaterials.* Federal Office for Public Health and Federal Office for the Environment, Bern, 2010.

45. Work, E.A.f.S.a.H.a., *E-fact 72: Tools for the management of nanomaterials in the workplace and prevention measures.* 2013.

46. Brouwer, D.H., *Control banding approaches for nanomaterials.* Annals of occupational hygiene, 2012. **56**(5): p. 506-514.

47. Van Duuren-Stuurman, B., et al., *Stoffenmanager nano version 1.0: a web-based tool for risk prioritization of airborne manufactured nano objects.* Annals of occupational hygiene, 2012: p. mer113.

48. de Ipiña, J.M.L., et al., eds. *Strategies, methods and tools for managing nanorisks in construction*. Journal of Physics: Conference Series. Vol. 617. 2015. 012035.

49. Hansen, S.F., K.A. Jensen, and A. Baun, *NanoRiskCat: a conceptual tool for categorization and communication of exposure potentials and hazards of nanomaterials in consumer products.* Journal of nanoparticle research, 2014. **16**(1): p. 1-25.

50. Genaidy, A., et al., *Risk analysis and protection measures in a carbon nanofiber manufacturing enterprise: An exploratory investigation.* Science of the total environment, 2009. **407**(22): p. 5825-5838.

51. Schulte, P.A., et al., *Overview of Risk Management for Engineered Nanomaterials.* Journal of Physics: Conference Series, 2013. **429**(012062).

52. Yokel, R.A. and R.C. MacPhail, *Engineered nanomaterials: exposures, hazards, and risk prevention.* J Occup. Med. Toxicol., 2011. **6**: p. 7.

53. Goudarzi, S., et al., *Nano technology risks: A 10-step risk management model in nanotechnology projects.* Hypothesis, 2013. **11**(1): p. e5.

54. Ling, M.-P., et al., *Risk management strategy to increase the safety of workers in the nanomaterials industry.* Journal of Hazardous Materials, 2012. **229-230**: p. 83-93.

55. Luther, W., *Technological analysis: industrialnapplication of nanomaterials - chances and risks*, 2004: Dusseldorf, Germany: VDI Technologiezentrum Report.

56. Eddy, D., et al., *An Integrated Approach to Information Modeling for the Sustainable Design of Products.* ASME J. Comput. Inf. Sci. Eng., 2014. **14**: p. 021011-13.

57. Fadel, T.R., et al., *The challenges of nanotechnology risk management.* Nanotoday, 2015. **10**: p. 6-10.

58. Groso, A., et al., *Management of nanomaterials safety in research environment.* Particle and Fibre Toxicology, 2010. **7**: p. 40.

59. Chen, Z., et al., *A review of environmental effects and management of nanomaterials.* Toxicological & Environmental Chemistry, 2011. **93**(6): p. 1227-1250.

60. GRIDELET, L., et al., *Proposal of a new risk assessment method for the handling of powders and nanomaterials.* Industrial Health, 2015. **53**: p. 56-68.

61. Jahnel, J., T. Fleischer, and S. Seitz. *Risk assessment of nanomaterials and nanoproducts–adaptation of traditional approaches*. in *Journal of Physics: Conference Series*. 2013. IOP Publishing.

62. Ortelli, S. and A.L. Costa, *Nanoencapsulation techniques as a "safer by (molecular) design" tool.* Nano-Structures & Nano-Objects, 2016.

63. Ortelli, S., et al., *Silica matrix encapsulation as a strategy to control ROS production while preserving photoreactivity in nano-TiO 2.* Environmental Science: Nano, 2016. **3**(3): p. 602-610.

64. Costa, A.L., N.A. Monteiro-Riviere, and C. Lang Tran, *A Rational Approach for the Safe Design of Nanomaterials.* Nanotoxicology: Progress toward Nanomedicine. CRC Press, Boca Raton, FL, 2014: p. 37-44.

65. Bergamaschi, E., et al., *Impact and effectiveness of risk mitigation strategies on the insurability of nanomaterial production: evidences from industrial case studies.* Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 2015. **7**(6): p. 839-855.

66. Schubauer-Berigan, M.K., et al., *Characterizing adoption of precautionary risk management guidance for nanomaterials, an emerging occupational hazard.* Journal of occupational and environmental hygiene, 2015. **12**(1): p. 69-75.

67. Conti, J.A., et al., *Health and safety practices in the nanomaterials workplace: results from an international survey.* Environmental science & technology, 2008. **42**(9): p. 3155-3162.

68. Schmid, K., B. Danuser, and M. Riediker, *Nanoparticle usage and protection measures in the manufacturing industry—a representative survey.* Journal of occupational and environmental hygiene, 2010. **7**(4): p. 224-232.

69. NEPHH. *Health and safety procedures for silicon*

based materials – survey's results 2010; Available from: file:///C:/Users/pm11co/Downloads/D1_2_Health_Safety_Procedures%20(2).pdf.

70. Heitbrink, W.A., L.-M. Lo, and K.H. Dunn, *Exposure Controls for Nanomaterials at Three Manufacturing Sites.* Journal of occupational and environmental hygiene, 2015. **12**(1): p. 16-28.

71. Lo, L.-M., et al., *Evaluation of engineering controls for manufacturing nanofiber sheets and yarns*, 2012, Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Report No. EPHB 356–11a.

72. Lo, L.-M., et al., *Evaluation of engineering controls in a manufacturing facility producing carbon nanotube-based products*, in *2012*2012, Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Report No. EPHB 356–13a

73. Cena, L.G. and T.M. Peters, *Characterization and control of airborne particles emitted during production of epoxy/carbon nanotube nanocomposites.* Journal of occupational and environmental hygiene, 2011. **8**(2): p. 86-92.

74. Sahu, M. and P. Biswas, *Size distributions of aerosols in an indoor environment with engineered nanoparticle synthesis reactors operating under different scenarios.* Journal of Nanoparticle Research, 2010. **12**(3): p. 1055-1064.

75. Wang, J. and D.Y. Pui. *Characterization, exposure measurement and control for nanoscale particles in workplaces and on the road*. in *Journal of Physics: Conference Series*. 2011. IOP Publishing.

76. Tsai, C.S.-J., *Contamination and Release of Nanomaterials Associated with the Use of Personal Protective Clothing.* Annals of Occupational Hygiene, 2015: p. meu111.

77. Tsai, C.S.-J., et al., *Exposure assessment and engineering control strategies for airborne nanoparticles: an application to emissions from nanocomposite compounding processes.* Journal of Nanoparticle Research, 2012. **14**(7): p. 1-14.

78. Brochot, C., et al., *Measurement of protection factor of respiratory protective devices toward nanoparticles.* annals of occupational Hygiene, 2012. **56**(5): p. 595-605.

79. Methner, M.M., *Effectiveness of a custom-fitted flange and local exhaust ventilation (LEV) system in controlling the release of nanoscale metal oxide particulates during reactor cleanout operations.* International journal of occupational and environmental health, 2010. **16**(4): p. 475-487.

80. Methner, M., *Engineering case reports. Effectiveness of local exhaust ventilation (LEV) in controlling engineered nanomaterial emissions during reactor cleanout operations.* Journal of occupational and environmental hygiene, 2008. **5**(6): p. D63-9.

81. Ogura, I., et al. *Potential release of carbon nanotubes from their composites during grinding*. in *Journal of Physics: Conference Series*. 2013. IOP Publishing.

82. Scaffold, *Customized control banding approach for potential exposure to manufactured nanomaterials (mnms) in the construction industry*, in *Scaffold Public Documents – SPD23*2015.

83. Geraci, C., et al., *Perspectives on the design of safer nanomaterials and manufacturing processes.* Journal of Nanoparticle Research, 2015. **17**(9): p. 1-13.

84. Thilagavathi, G., A. Raja, and T. Kannaian, *Nanotechnology and protective clothing for defence personnel.* Defence Science Journal, 2008. **58**(4): p. 451.

85. Fito, C. *Preventing exposure to common ENMs in the ink & paint sector: design and effectiveness testing of respiratory and dermal protective*

equipment (RPE/DPE). NanoMICEX Webminar 2015; Available from: file:///C:/Users/pm11co/Desktop/NanoMICEX_Webinar_Presentation_2015.pdf.

86. Communities, C.o.T.E., *Communication from the Commission on the precautionary principle*, in *COM (2000) 1 final*2000: Brussels, Belgium.

87. Report, H.a.S.E.E., *Reducing risks protecting people: HSE's decision-making process*, 2001, Her Majesty's Stationery Office.

88. ECHA. *Guidance on Information Requirements and Chemical Safety Assessment*. 2012; Available from: http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

89. Helland, A., H. Kastenholz, and M. Siegrist, *Precaution in Practice.* Journal of Industrial Ecology, 2008. **12**(3): p. 449-458.

90. Fleury, D., et al. *Nanoparticle risk management and cost evaluation: a general framework*. in *Journal of Physics: Conference Series*. 2011. IOP Publishing.