Working Safely with Nanomaterials in Research & Development

Second Edition

May 2016

Developed by

The UK NanoSafety Group

(UKNSG)

Contents

Acknowledgements

This guidance has been produced from the contributions of those listed below who constitute the UK NanoSafety Group. It provides help to research establishments and academia on how to comply with their occupational health and safety legal obligations; it also provides additional information to help make improvements to health and safety systems when working with nanomaterials. It should be noted that the guidance may go further than the minimum you need to do to comply with the law. The HSE welcomes this guidance and will continue to work with partners to ensure that the health and safety risks to employees in the nanotechnologies industry are properly controlled.

This document and the information contained within are provided for informational purposes. It is not intended to substitute for the statutory requirements for workplace health and safety management. The information in this document is provided "as is" and without warranties of any kind. The UK NanoSafety Group (UKNSG) assumes no responsibility or liability arising from the use of this document. Mention of any company or product does not constitute endorsement by the UKNSG. All Web addresses referenced in this document were accessible as of the publication date.

UK NanoSafety Group Contributors

Higher Education and Research Councils

- University of Southampton - David Kinnison (Chair)
- University of Bristol - Stuart Bellamy
- University of Cambridge - John Hulme
- Medical Research Council - Arthur Mitchell
- University of Glasgow - Paul Veitch (retd)
- University of Strathclyde - June Freeland (retd)

Institute of Occupational Medicine (IOM)

- Steve Hankin
- Craig Poland
- Rob Aitken

Health & Safety Laboratory (HSL)

- Delphine Bard
- Rosemary Gibson
- John Saunders

Health & Safety Executive (HSE)

- James Wheeler

The UK NanoSafety Group wishes to acknowledge the following sources of funding and assistance in developing this guidance document.

Funding and Support

USHA - Universities Safety and Health Association

IOSH - Institution of Occupational Safety and Health

Support

ISTR - Institute of Safety in Technology and Research

UCSF - University Chemical Safety Forum

BOHS - British Occupational Hygiene Society

Forward by Judith Hackett CBE

As an engineer myself, I take a good deal of interest in the exciting technological developments taking place today.

The many challenges which face our own and future generations on this planet require the very best of scientific and technological innovation to provide solutions in healthcare, medicine, energy, climate change, transport to name but a few. Whilst we may recognise that the way we live our lives today is unsustainable, the future is about innovation in new products and new materials. Nanomaterials have the potential to provide solutions in many fields.

As a regulator, HSE sees its role as enabling business to innovate, develop and grow whilst ensuring that health and safety issues are identified and addressed as part of that introduction process. We all recognise that there are huge potential benefits offered by nanomaterials but understanding and managing the risks they may pose is vital to enabling them to be developed to their full potential.

Partnership working brings together key players from all sides to ensure that health and safety issues are jointly owned and solutions identified. The UK NanoSafety Group brings together key experts in the field of nanotechnology and helps to establish links with others who have interests in this area to address those issues and enable the technology to move forward. I wish the UK NanoSafety Group continued success.

Judith Hackitt CBE
Former Chair of the Health and Safety Executive

Preface to the Second Edition

This second edition of the guidance provides updates to account for changes in legislation, recent studies in the literature, and best practice since 2012. In particular, specific sections have been revised to account for the full implementation of Global Harmonised System (GHS) which came into force on 1 June 2015 through the CLP regulations.

The document explains the approaches that are presently being used to select effective control measures for the management of nanomaterials, more specifically control banding tools presently in use as listed in Table 1. Significant changes can be found in the following sections: 'Hazard Banding', 'Exposure Control', 'Toxicology', and 'Monitoring'.

Scope of Guidance

1 This Guidance Note draws attention to the possible health hazards which could result from exposure to particulate nanomaterials. It gives advice on the precautions that may be needed to prevent or adequately control exposure as required by the Control of Substances Hazardous to Health Regulations (COSHH) 2002 (as amended).

2 The aim of this document is to give guidance on factors relating to establishing a safe workplace and good safety practice when working with particulate nanomaterials. The document is applicable to a wide range of nanomaterials.

3 This guidance is aimed at employers, managers, health and safety advisors, and users of particulate nanomaterials in research and development. It should be read in conjunction with the Approved Code of Practice on COSHH, together with the other literature referred to below and in the Appendices.

4 The document has been produced taking account of the safety information currently available and is presented in the format of guidance and recommendations to support implementation of suitable protocols and control measures by employers and employee by advocating a precautionary strategy to minimise potential exposure. It is intended that the document will be reviewed and updated on a periodic basis to keep abreast of the evolving nature of the content.

5 This document is applicable to a broad set of nanomaterials that include nano-objects such as nanoparticles, nanofibres, nanotubes, nanowires, as well as aggregates and agglomerates of these materials.

6 The term 'particulate nanomaterials' used in this document applies to these entities either in their original form or incorporated into materials or preparations from which they could be released.

Terms and Definitions

7 The terms and definitions used in this document are based on internationally accepted definitions wherever possible, specifically those defined by the European Commission (EC) and the International Standards Organisation (ISO). For the purposes of this document the following terms and definitions apply:

Nanomaterial: as defined by the European Commission (EC, 2011): a natural, incidental or manufactured material containing particles (nanomaterials), in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness, the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50%." By derogation, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials.

Particle: a minute piece of matter with defined physical boundaries;

Agglomerate: a collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components;

Aggregate: a particle comprising strongly bound or fused particles.

Nanofibre: nano-object with two similar external dimensions in the nanoscale and the third dimension being significantly larger [ISO/TS 27687, def. 4.3].

Nano-object: material with one, two or three external dimensions in the nanoscale [ISO/TS 27687, def.2.2].

Nanoparticle: nano-object with all three dimensions in the nanoscale [ISO/TS 27687, def. 4.1].

Nanoplate: nano-object with one external dimension in the nanoscale and the two other external dimensions significantly larger [ISO/TS 27687, def. 4.2].

Nanoscale: size range from approximately 1 nm to 100 nm [ISO/TS 27687, def. 2.1].

Nanotube: hollow nanofibre [ISO/TS 27687, def. 4.4].

Particulate nanomaterial(s): nanomaterials that consist of nano-objects such as nanoparticles, nanofibres, nanotubes, nanowires, as well as aggregates and agglomerates of these materials either in their original form or incorporated in materials or preparations, from which they could be released.

Introduction

8 There are three major properties of nanoparticles that make them unique and give them the properties leading to their increased use across a wide spectrum of fields for a large variety of uses. These are that in the “free state” nanoparticles are highly mobile and reactive, secondly they have an enormous specific surface area in relation to their physical size and finally they may exhibit what is termed quantum effects. It is the combination of these properties that provide exciting opportunities to nano-based technologies to improve efficiency, sustainability and speed to already existing manufacturing and industrial processes. This has led to their use in sunscreen products, as potential vehicles for tissue specific drug delivery and increasingly their use by the clothing industry to provide properties to fabrics such as microbe killing silver where odour from a variety of sources is reduced or prevented, materials can also be made water-proof or stain resistant or used as anti-static agents. It is also these properties that have led to the widely accepted view that there is a crucial need for further information and knowledge concerning the implications of manufactured particulate nanomaterials on both human health and their effect on the global environment as a whole. Risk assessment requires a detailed examination of the properties of the nanoparticle or particles that are being used and may include some or all of the following:

- particle size
- surface area
- stability
- surface properties
- solubility
- chemical reactivity

Some, or perhaps all, of these properties may not be known, however, comparisons with well-known existing hazards may help inform the risk assessment. Existing hazards used in this way could include those from airborne fine particles and also fibres. Wider use of nanomaterials may also lead to increases in environmental exposure (Kumar, 2014). Kumar *et al*. studied the behaviour of nanoceria in different physiological conditions demonstrating that the shape and reactive properties vary enormously according to the molecular composition. Little is presently known about how specific nanomaterials may behave in air, water or soil. Thus the nanomaterials may be concentrated in particular "hot spots", either by clumping together with minerals or by interaction with organic matter. Similar to other pollutants, they may pass from organism to organism, and perhaps move up food chains. Concerns regarding potential risks to the environment, manipulation, use and disposal of these materials have been voiced over the past few years (Kühnel, 2014). Other reports, including those from the Royal Commission on Environmental Pollution (RCEP, 2008), the UK's Health & Safety Executive (see reports available at www.hse.gov.uk/nanotechnology/research.htm and the UK's Department for Environment, Food & Rural Affairs (see reports available at http://randd.defra.gov.uk/ have further depicted the concerns and have gone someway to helping to address them. However, the increasing volumes of particulate nanomaterials that are being produced and introduced into commerce have resulted in an urgent need to address exposure and risk assessment data gaps.

9 This document has been developed in collaboration between the UK NanoSafety Group and the Health and Safety Executive. It is recognised that the field of nanotechnology is rapidly expanding and transcends the traditional academic discipline boundaries and incorporates a wide range of products, production processes and uses. The document is primarily concerned with the use, storage and disposal of particulate nanomaterials. It does not deal with incidental release of nanomaterials such as those from diesel exhaust and welding fumes.

Legal Duty

COSHH (http://www.hse.gov.uk/coshh/index.htm)

10 The synthesis/manufacture and use of nanomaterials is regulated under the Control of Substances Hazardous to Health (COSHH) Regulations 2002 (as amended).

11 COSHH places a duty on employers to carry out a risk assessment for work which is liable to expose employees to hazardous substances. Embodying the principles of proportionality and risk assessment, COSHH enables employers to make a valid decision about the measures necessary to prevent or adequately control the exposure of their employees. Employers must understand the risks and make sure the risks are kept as low as is reasonably practicable.

DSEAR (http://www.hse.gov.uk/fireandexplosion/dsear.htm)

12 The chemical and physical properties of some particulate nanomaterials mean that they can give rise to a risk of fire and explosion, depending on how they are handled or used. If this is the case, the principal legislation applying to their control in the workplace are the Dangerous Substances and Explosive Atmospheres Regulations 2002 (DSEAR).

13 DSEAR requires that the risks from dangerous substances are assessed and eliminated or reduced so far as is reasonably practicable. The principle of risk assessment applies under these regulations.

REACH (http://hse.gov.uk/reach/)

14 REACH is a European Union Regulation concerning the Registration, Evaluation, Authorisation and restriction of Chemicals. It came into force on 1 June 2007 and replaces a number of European Directives and Regulations with a single system.

15 REACH will operate alongside COSHH and is designed to ensure that better information on the hazards of chemicals and how to use them safely will be passed down the supply chain by chemical manufacturers and importers through improved safety data sheets.

16 Further information can be found on HSE's website: www.hse.gov.uk/reach/ and on the European Chemical Agency's website: www.echa.europa.eu/home_en.asp.

CLP (http://www.hse.gov.uk/chemical-classification/legal/clp-regulation.htm)

17 The Classification, Labelling and Packaging of Substances and Mixtures –- the CLP Regulations – came into force in all EU member states, including the UK, on 20 January 2009, and replaces the Chemicals (Hazard Information and Packaging for Supply) Regulations 2009 – CHIP – with effect from 1 June 2015.

Exposure Risk and Hazardous Properties of Nanomaterials

18 Exposure to some particulate nanomaterials may occur by inhalation, ingestion, and/or skin penetration, with any resultant adverse effects depending upon the size, dose and reactivity of the particles. The exposure potential can be expected to be related to the structure and physical form of the nanomaterial; particles encapsulated in a matrix or strongly adhered to a substrate will have a lower exposure potential than that from 'free' aerosolised particulate nanomaterials, or those powders exhibiting high dustiness.

19 Some particulate nanomaterials may have inherent hazardous properties and may be classified as carcinogens or mutagens. They may also have other hazardous properties such as toxic, harmful etc, as classified in the Classification, Labelling and Packaging of Substances and Mixtures – the CLP Regulations. It is generally agreed that the current knowledge regarding the toxicity of particulate nanomaterials is incomplete and current safety data sheets may not adequately contain all the required safety information. Hence, at present it is essential that a precautionary approach be used when uncertainties are encountered during exposure risk assessment.

20 Fire and explosions from dust clouds of organic, inorganic and metallic substances are well known. The potentially higher surface area and reactivity of particulate nanomaterial powders means that this safety hazard should be seriously considered and addressed in risk assessments.

Risk Management Principles

21 It is important to emphasise that existing legislation in the form of the COSHH regulations applicable in the UK, or their equivalent elsewhere, will always apply to workplace activity involving particulate nanomaterials. The guidance and recommendations given in this document closely mirror the eight principles of good practice associated with the COSHH risk assessment process.

22 Nanomaterials are not necessarily intrinsically hazardous *per se* but there is a need to take specific considerations into account during their risk assessment. Therefore, one purpose of the aforementioned definition is to provide clear and unambiguous criteria to identify materials for which any nanomaterial-specific considerations should apply. The process of risk assessment is the most suitable and systematic means to determine which hazard and exposure controls (i.e. risk management measures) are required.

23 In general, the potential risks to health from particulate nanomaterials can be reduced by safe handling and control of exposure. Whilst no single piece of guidance can provide a definitive, step-by-step approach to safe handling of all nanomaterials in all circumstances, there are a number of general and specific best practice guides that can be used in most applications.

24 The general approach for safe handling and control of particulate nanomaterials is similar to that for other types of chemical substances and seeks to:

- identify the hazards and assess the risks;
- identify who or what would be affected;
- decide what precautions are needed;
- prevent or adequately control exposure;
- ensure that control measures are used and maintained;
- monitor the exposure;
- carry out appropriate health surveillance;
- prepare plans and procedures to deal with accidents, incidents and emergencies;
- ensure employees are properly informed, trained and supervised.

Nanomaterials' Characterisation

Background and challenges

25 Characterisation of nanoparticles plays an essential role in a variety of overlapping contexts ranging from fundamental and applied research, through process and product quality control and commercialisation to health and environmental protection. Fibre-like particles and platelets present distinct challenges for characterisation using many of today's routine measurement techniques which are often based on principles suited to *idealised* spherical particles. Moreover, not all particles with the same 'apparent' composition have the same potential to cause harm. As with other chemical substances, appreciation of the relationship between the wide range of physico-chemical characteristics of nanomaterials is important in understanding their toxicology. The implementation of reliable findings from experimental studies into regulatory frameworks with the objective of protecting human and environmental health is also subject to the limitations of inadequately characterised materials and the complexity of mixtures of particles in 'real world' exposures.

26 Nanomaterials may exhibit properties and behaviour that are very different from the bulk-scale materials (non-nanoscale form) of the same chemical identity. Knowledge of their size, shape and surface-related properties can be used to account for many of the observed differences. It is widely acknowledged that adequate characterisation of a nanomaterial is therefore necessary to accompany any toxicity study, particularly in cases where particulate

nanomaterials (for example, carbon nanotubes) can be produced by different processes yielding notionally the same material, but which exhibit quite different morphology and chemical properties.

27 It is important to recognise that no individual technique can provide an entirely holistic and meaningful characterisation of the sample. Multiple techniques are required to formulate as complete an understanding of the nanomaterial's properties as necessary. Different techniques will suit different sample forms (for example, aerosol, suspension etc.) and the optimum set of required techniques should be selected based on the specific nanomaterial type, form under investigation and purposes of the study.

28 A further important challenge is how representative the sample is of the material, which may be influenced by the surrounding environment and may change as a function of time.

Selection of properties and techniques for characterisation

29 It is important to recognise that complete characterisation of test materials is time consuming, expensive, complex and may never be fully achievable. The degree of characterisation required depends on the needs or objectives of the study, which can include informing a hazard exposure assessment and overall risk posed by a material. Characterisation information required to comply with applicable regulatory or notification requirements needing to be met must be identified and gathered. Recommended characterisation information is also evident in guidance on the preparation of safety datasheets. Beyond this, researchers in the field of nanosafety generally agree that information on a number of fundamental properties needs to be gathered, including but not necessarily limited to, composition, size and shape, state of dispersion, surface area, and surface chemistry.

30 A range of techniques have been adapted or developed for the characterisation of particulate nanomaterials, including microscopic, spectroscopic, spectrometric, and chromatographic methods. Whilst it is beyond the scope of this document to provide guidance on all properties and techniques, several reviews, publications and Standards are available that can provide appropriate details, as highlighted in the Further Reading. The selection of an appropriate technique depends on the type of material, the required characterisation and the resolution/quality of the data needed.

31 Taking the example of hazard assessment, there is consensus that thorough and accurate particle characterisation is an essential part of assessing the potential toxicity of particulate nanomaterials in biological systems. Information is required on the response to the material against a range of potentially relevant dose metrics, including mass, surface area, and number concentration. Appropriate characterisation of test materials is important to ensure that the results are reproducible (within and between laboratories), and also to provide the basis for understanding the properties of particulate nanomaterials that determine their biological effects. Some of the key parameters influencing the biological activity of particulate nanomaterials remain to be fully understood at this point in time. Any study however conducted with material that has not been characterised with respect to a property later found to be critical for toxicity will ultimately be of little value.

32 A rationale and dataset should be developed and documented that meets the characterisation requirements. It is recommended that best practices advocated in published Standards and guidance for nanoparticle characterisation should be adopted.

Toxicology

33 As a crucial and integral part of the risk assessment framework, the understanding of the hazard potential of a substance is important and this is established on the basis of a toxicological assessment. The role of toxicology in chemical risk assessment is multi-factorial but fundamentally is there to provide information on the impact a substance may have on the body and how or if this may manifest with differing exposures. This assessment of impact can provide information on:

- the specific target organs such as the lungs and likely health effects, for example dyspnoea due to respiratory inflammation;
- potency, for example are profound effects associated with low exposure or are relatively high exposures required to cause adverse health effects?
- the evidence base (preferably in conjunction with epidemiology data) for a robust health based exposure limit, or in the absence of this more prescriptive, process based limits such as DNELs (Derived No Effect Levels) under REACH in the EU or qualitative assessments such as hazard banding.

The quantity and quality of toxicological data available dictates the robustness and how informed a hazard assessment can be and this can vary markedly from well-established substances for which a great deal of information exists (for example, NaCl) to substances that are early in development (for example, graphene platelets) for which there is little data.

34 The level of information available influences the type of assessment that can be performed, such as the development and adoption of an Workplace Exposure Limit (WEL) or the classification of a substance as carcinogenic, or not, by the International Agency for Cancer Research (IARC). A recent example of this is the outcome of the October 2014 IARC meeting to discuss carbon nanotubes as well as other fibrous materials (Monograph Volume 111). It is reported that the Working Group concluded that there was sufficient evidence for carcinogenicity in experimental animals with the multi-walled carbon nanotube 'MWCNT-7', considered to be one of better studied, yet only *limited* evidence for other multi-walled carbon nanotube samples with dimensions similar to MWCNT-7, and *inadequate* evidence for single walled carbon nanotubes (SWCNTs) (Grosse et al., 2014). This level of evidence was reflected in the Working Group's classification and MWCNT-7 specifically was classified as possibly carcinogenic to humans (Group 2B) whilst other forms of MWCNTs (excluding MWCNT-7) and SWCNTs were determined to be not classifiable as to their carcinogenicity to humans (Group 3). This category of Group 3 is used for agents for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals although it should be noted that a classification of Group is not a determination of non-carcinogenicity or overall safety, rather that further research is needed (IARC, 2006).

35 A similar high degree of evidence is needed for the derivation and adoption of a Workplace Exposure Limit (WEL) (for example, well-designed *in vivo* inhalation studies of a sufficient exposure period performed to internationally recognised guidelines) which from a human safety point of view is the most robust form of exposure limit. However, for many substances (not just nanoparticles), such information is not available and instead lower level toxicological assessments must be used with a corresponding increase in uncertainty and margin for error dependent on the data available.

36 When considering the hazard potential of particulate nanomaterials, it is important to understand that the word "nanoparticles" embraces an enormous variety of different materials in

different compositions, shapes and sizes (with one or more aspect in the nanometre range). There is therefore no single measure of toxic potency that can be attributed to *all* nanoparticles since there can be considerable variability in toxicity based upon physico-chemical characteristics; specifically, not all nanoparticles are toxic nor equally hazardous. Furthermore, it is important to note that the definition of the size cut-off for nanoparticles has no basis in toxicology, meaning that there is no step-change in toxicity when a particle becomes below 100 nm in any dimension.

37 When searching for hazard information, it is absolutely necessary to define the nanoparticles that are under consideration in as much detail as possible (see Nanomaterials' characterisation section). For example, "zinc oxide nanoparticles" or "carbon nanotubes" are very broad descriptions, and it would be better to give details such as "20 nm uncoated ZnO nanoparticles" or "multi-walled carbon nanotubes, in fibre form, with length range 620 nm – 52 µm, and 12% iron" as this enables a greater depth of consideration when attempting to describe the potential potency or toxic behaviour.

Hazard Information

38 There is now an evidence base of toxicology of various nanoparticles showing considerable differences in hazard between different nanoparticle types. However, the literature is dominated by studies that employ non-validated *in vitro* tests, which form an unsuitable basis for risk assessment in part because the relationship between *in vitro* toxicological data and *in vivo* effects is unclear. Currently, there are very few inhalation studies on which to base the development of WELs for nanoparticles and those that do exist are limited to a small number of nanoparticles with limited relevance to other forms of nanomaterials. An example of this latter issue was a point raised by the IARC working group considering carbon nanotubes, in that generalisation between different types of carbon nanotubes was precluded due to a lack of coherent evidence across the various distinct carbon nanotubes (Grosse et al., 2014).

39 This means that for the majority of nanoparticles there is unlikely to be the in-depth quantitative toxicological data required for the determination of a WEL. Therefore, when such a limit is presented within an MSDS, one should question if it is specifically for the nanoparticle in question, or if it relates to the bulk-scale compound or an analogous material (for example, a WEL for graphite being given for CNT) when it is unlikely to be accurate.

40 When looking rather generally at the current large toxicological evidence base across a wide breadth of nanoparticles it seems that:

- many nanoparticles are likely to pose a low hazard at plausible exposures to the lungs;
- skin is unlikely to be affected by the common nanoparticle types, which do not cross into the human body through skin to any significant extent. For example the European Commission's Scientific Committee on Consumer Safety (SCCS) has concluded that the use of ZnO and TiO_2 nanomaterials (at a concentration up to 25% as a UV-filter in sunscreens) can be considered to not pose any risk of adverse effects in humans after dermal application (SCCS, 2013a, SCCS, 2013b).

41 These are broad generalisations taken on balance, but it has been shown that some nanoparticles such as ZnO nanoparticles might adversely affect the lungs if there is on-going high exposure (Cho *et al.*, 2011). In addition, there are special cases of particulate nanoparticles that might pose unusual hazards due to their novel and unusual properties which do not arise in nature. This includes long (>15 µm) nanofibres and nanotubes, low density "fluffy" nanotube

bundles and large but very thin plate-like particles, all of which are large but with small aerodynamic diameters so that they are not dealt with by normal mechanisms.

42 Below are listed several attributes in the form of questions that may infer toxicity to nanomaterials and as such, the presence of one or more of these physico-chemical characteristics may suggest increased hazard potential. (Inclusion here is based upon generalisations and intended to help inform as to the potential risks and should not be seen as a replacement for robustly derived WELs if available.)

- *Is the particulate classified as a CMTR (carcinogen, mutagen, teratogen and reproductive toxicant) or sensitizer?*

  If the bulk-scale or parent version (if it exists) of a nanomaterial is already classified as a CMTR or skin/respiratory sensitizer, there is a high likelihood that the nanoparticulate form will also demonstrate this toxic potential. Indeed due to their characteristically large surface area, the nanoparticulate form may exhibit comparatively greater activity than that of the bulk-scale compound and should therefore be considered as potentially hazardous.

- *Is the nanomaterial composed of reactive metal(s)? Is the nanomaterial photoreactive? Does the nanomaterial have a highly charged surface?*

  The presence of reactive metals is known to drive the toxicity of various complex particulate mixtures such as welding fumes (McNeilly *et al.*, 2004). Therefore a nanomaterial possessing a significant proportion of such metals (for example, large amounts of catalyst remaining within unrefined carbon nanotubes) could be regarded as having a potentially hazardous component.

  When exposed to light, photocatalytic nanomaterials (for example, certain forms of TiO_2) can release free radicals (Konaka *et al.*, 1999) that may generate toxicity by causing inflammation, oxidative damage and genetic damage Hirakawa *et al.*, 2004; Carlotti *et al.*, 2009).

  The surface charge of a nanomaterial is known to influence its propensity to agglomerate/aggregate, but it can also play a prominent role during cellular uptake or interactions with charged molecules such as proteins.

  These attributes, singly or collectively, can contribute to the surface activity of a nanoparticle and are potential drivers of toxicity. The combination of high surface area and high reactivity may lead to the formation of a “double hazard” Duffin *et al.*, 2007; Karlsson *et al.*, 2009).

- *Is the (nano)material soluble?*

  The solubility of a (nano)particle can have a positive and/or negative influence on its propensity to cause harm. Specifically if a particle is soluble in an aqueous environment but *does not* release toxic components, a progressive reduction/removal of dose will occur as the particle dissolves. However, if the particle releases reactive or cytotoxic components such as toxic ions as it dissolves, its toxicity could increase.

  An attribute of nanoscale materials is the potential for changes in physico-chemical characteristics, including solubility, compared to the bulk-scale material; for example, bulk-scale silver is insoluble, but nano-silver releases free silver ions in aqueous solutions by

dissolution. Therefore, the contention that since the bulk-scale material is insoluble, the nanomaterial is also insoluble is not necessarily correct. As such when considering the hazardous nature of a material, it is pertinent to consider both the insoluble (particle) and soluble components in the hazard assessment.

- *Is the nanomaterial fibrous (i.e. possess a high aspect ratio)?*

  There is concern that fibrous nanomaterials such as carbon nanotubes or nanowires may represent a similar danger to health as hazardous fibres such as asbestos, refractory ceramic fibres or certain man-made vitreous fibres (MMVFs). The basis for this is the morphological similarity between these fibres and newly developed high aspect ratio (fibrous) nanomaterials (HARN). However, if the fibre hazard paradigm is to be enacted, certainty is needed that it is a fibrous sample that is being dealt with, i.e. it should meet the criteria of the definition of a fibre, such as that of the World Health Organisation (WHO).

  The WHO defines a respirable fibre as an object with length greater than 5 µm, width less than 3 µm and length to width ratio (aspect ratio) greater than 3:1 (WHO, 1997). Those particles which do not meet these base criteria would not be considered as fibres and are unlikely to represent a fibre-type hazard (although they may still represent a particulate-type hazard). Within fibre toxicology, a fibre begins to generate difficulties with normal clearance mechanisms in the lung when its length prevents its full enclosure by those cells tasked with clearing such particles (for example, alveolar macrophages). This is considered to be between 10-15 µm in length (Schinwald *et al.*, 2012a). A nanomaterial longer than 15 µm would therefore potentially frustrate clearance mechanisms if deposited in the distal lung and lead to hazardous effects similar to those associated with other harmful fibres. Due to the uncertainty around the identification of a lower cut-off length for pleural inflammation (Schinwald *et al.*, 2012b) than for the lungs, the WHO length criteria of 5 µm could be seen as presenting a suitably conservative approach.

  Since generalisations should not be based purely on the substance type when considering the potential hazard of a particulate; not all fibrous nanomaterials will necessarily represent a fibre hazard as outlined above and not all nanomaterials typically thought of as particulate, always exist in particulate form. For example, not all carbon nanotubes are true fibres, as many form highly curled, dense bundles and are particulate in nature. Conversely, not all TiO_2 nanoparticles are particulates, since like many materials, it can be formed into wires (Hamilton *et al.*, 2009) which could represent a fibre hazard.

It is therefore imperative that the true physico-chemical characteristics of the sample under consideration (and not just of the class of material) be established when considering the basis for hazard.

- *Does the nanomaterial possess a low aerodynamic diameter yet one or more high aspects?*

  As the basis for respiratory toxicity from fibres requires a low aerodynamic diameter for penetration into the distal airways yet a large physical aspect (for example, fibre length or particle diameter) causing frustration of normal cell-mediated clearance mechanisms, it is worth bearing in mind that other shapes, not just fibres, can possess these properties. Plate-like structures such as graphene/graphite platelets can have a very large (>15 µm) diameter yet be very thin (<100 nm) and as such possess a low aerodynamic diameter (Sanchez *et al.*, 2011), allowing them to be respirable. In addition, low density 'fluffy' bundles of fibres, often seen with carbon nanotubes, may also, due to their very low density, possess the potentially hazardous mix of low aerodynamic diameter with one or

more high aspects, making clearance from the distal lung difficult. However, much more research is needed into these particle types to understand if they are likely to represent a true hazard to humans.

Hazard Banding

43 As discussed above, the currently available toxicology data for the majority of nanomaterials would be considered to be minimal or suggestive and this is incompatible with the rigorous data demands needed for the development of a WEL. As a practical interim solution to aid in the risk assessment of such materials, a hazard and control banding approach could be utilised.

44 Hazard banding as an approach has been adopted within the pharmaceutical industry with early publications on the subject from the mid-1990s (Naumann *et al.*, 1996). It was developed as a means to deal with the problem of the rapid development of new compounds for which few toxicological data existed. Indeed for some of these compounds, the mechanisms by which they had their effects were poorly understood, yet they were becoming increasingly potent with unknown short and long term health effects. A practical approach to mitigating the risks associated with such unknown compounds was to classify them based on limited toxicological data into bands, which inform as to the relative hazard, maximum exposure levels and are aligned with control schemes. This would mean in practice that a nanoparticle classed as “highly hazardous” could only be handled within full containment and associated low airborne mass concentration exposure limit, whilst those classified as “low hazard” and could be handled with good ventilation and appropriate PPE.

45 A problem equally as relevant to nanomaterials as to chemicals and pharmaceuticals is what to do with materials for which *no* information exists. An approach may be to use “physico-chemical or structural alerts”, such as those discussed earlier, many of which are incorporated into control banding tools. Identification of such alerts may suggest a basis for hazard and promote a nanoparticle up the category scheme, necessitating tighter controls and exposure measures. Another approach is to adopt a default *preliminary* category associated with sufficient exposure control measures that would protect workers should a compound later be shown to be toxic. Movement out of such a category would be based upon toxicological evidence to allow its transfer to a lower or higher hazard category as appropriate. The latter approach is conservative whilst the former allows a case-by-case basis that reduces the number of non-toxic nanoparticles being encumbered by what may subsequently be shown to be excessive control methods.

46 Whilst it is possible to identify some nanoparticles in relation to their hazard (for example, certain forms of TiO_2 considered as low hazard), the hazard banding approach is still under development and has yet to be validated for nanomaterials. Further development as well as expert and regulatory agreement of the criteria for inclusion of nanoparticles into different bands are required.

Exposure Control

47 UK and European law requires workplace exposure to substances hazardous to health to be controlled adequately. This applies to nanomaterials particularly where there is uncertainty about the risk. To achieve adequate control involves applying "good control practice", which is a consensus view of hardware, systems of work and other measures that need to be put in place to control the risk.

48 An employer's overriding duty and first priority is to consider how to prevent employees being exposed to substances hazardous to health (including nanomaterials) by all routes. Employers who do not do this are failing to comply with a fundamental requirement of COSHH. The principles of the hierarchy of controls, which is based on inherent reliability and likely effectiveness, should be applied. The duty to prevent exposure should be achieved by measures other than the use of personal protective equipment.

Risk Assessment

49 A risk assessment must be carried out before an employee is allowed to work with nanomaterials. This risk assessment must be a suitable and sufficient assessment of the risk to health caused by the work. The HSE publication, "A step by step guide to COSHH assessment" describes in general terms the procedures to be followed in making an assessment. The COSHH general Approved Code of Practice (ACOP) also gives guidance.

50 Assessment of the risk should include identifying all potential sources of exposure. If the exposure cannot be prevented, assess the potential level of exposures.An action plan / check list for assessment would involve addressing the questions:

- What are the tasks or processes which could lead to the release of particulate nanomaterials into the air or onto a surface?
- Is exposure likely?
- Who is likely to be exposed?
- Can the exposure be prevented?

51 Work activities involving nanomaterials which require special attention when assessing exposure include:

- handling of powder containing particulate nanomaterials;
- manufacturing of particulate nanomaterials (especially production of particulate nanomaterials in a gas phase) and associated maintenance of equipment;
- machining of materials containing nanomaterials (for example, sawing, polishing, grinding);
- spraying of liquids containing particulate nanomaterials;
- processing particulate nanomaterials in a liquid where a high energy output is involved;
- recycling and waste disposal of nanomaterials.

52 In making the assessment, careful attention should be paid if there is a possibility of inhalation of the particulate nanomaterials.

53 In all cases, the assessment should be written down and reviewed if circumstances change, new information becomes available on the hazard of the nanomaterials being used or the composition of the nanomaterial is changed.

Prevention and control of exposure

54 Having made an assessment of the risk from exposure to nanomaterials, employers must ensure that such exposure is either prevented, or if that is not reasonably practicable, adequately controlled.

55 Employers need to consider the following precautionary measures in their prevention and control procedures, and adapt them to suit their circumstances. Employers should arrange to regularly review the adequacy of the precautions taken, particularly if the circumstances of use change or in the light of new technical developments or information on the nanomaterials.

Prevention of exposure: Substitution

56 As with all substances potentially hazardous to health, the employer must give first priority to preventing workers being exposed to nanomaterials. This can be achieved in a number of ways, for example by using a substitute material or process, which does not involve nanomaterials, or by changing the method of work. When considering substitution, it is important to take account of any hazards of the substitute materials or process and balance the risks these might present against the benefits.

Workplace Exposure Limits

57 At the time of publication, there are no UK legal Workplace Exposure Limits (WELs) specific for any nanomaterials. Therefore, in compliance with COSHH, the potential for exposure should be eliminated or adequately controlled by all routes by applying the principles of good control practice.

58 There have been many references made in the literature to proposed limits. None of these limits are based on health effects; some ascertain they are achievable with good control practices; others are based on extrapolation from toxicological studies. In the United States, the National Institute for Occupational Safety and Health (NIOSH) has issued a recommended occupational exposure limit (REL) for CNTs and ultrafine TiO_2, but currently there is no legal basis to use these limits in the UK. These limits should be used with extreme caution. It should also be noted that measuring nanomaterials in the workplace is a challenge and there is considerable debate about which metric to measure.

59 **It should be noted that the UK WEL for airborne 'Carbon Black' of 3.5 mg/m^3 (3500 µg/m^3) is not considered appropriate for carbon nanotubes.**

60 Measurement of airborne particulate nanomaterials is not a simple, quick or straightforward task and therefore the preferred/practical option in most research environments is to prevent potential exposure with rigorous containment via engineering controls rather than an extensive airborne nanomaterial monitoring regime.

Approaches to selecting control measures

61 Several approaches may be taken to identify the necessary control measures required to prevent exposure to particulate nanomaterials in the laboratory and workplace. Traditional

approaches for risk assessment of substances cannot always be applied to all nanomaterials due to the missing data or uncertainties with existing information. An alternative approach is the utilisation of control banding, which is a simplified approach to evaluate the risks from activities and the substances they involve into bands according to the potential for exposure and the hazard. For each risk band, control measures are then suggested. A number of tools are being developed (Table 1), albeit with important assumptions and limitations, which may help *inform* the assessment and management of risks from working with all nanomaterials and indeed other chemical substances.

Table 1: Examples of current control banding tools being developed for nanomaterials (N.B. These tools have been developed independently of each other and are not standardised. This may lead to different outcomes from each model for the same data inputs).

Name	Type	URL
Precautionary Matrix	Risk Prioritisation	http://www.bag.admin.ch/nanotechnologie/12171/12174/index.html?lang=en
NanoCB Tool	Control Banding	http://www.controlbanding.net/Home.html
ANSES nano	Control Banding	https://www.anses.fr/en/content/tool-control-banding-risks-associated-nanomaterials
Stoffenmanager Nano 1.0	Risk Prioritisation	http://nano.stoffenmanager.nl
NanoSafer	Risk Evaluation (semi-quantitative)	http://nanosafer.i-bar.dk
ISO Technical Specification: "Nanotechnologies - Occupational risk management applied to engineered nanomaterials Part 2: Use of the control banding approach". PD ISO/TS 12901-2:2014	Control banding	http://www.iso.org/iso/catalogue_detail.htm?csnumber=53375

62 The control banding approach of COSHH Essentials can be applied to nanomaterials http://www.hse.gov.uk/coshh/essentials/coshh-tool.htm. This is a tried and tested, robust approach for many chemical hazards, although it is important to acknowledge that there currently are no COSHH Essential control sheets for nanomaterials.

Control of exposure to particulate nanomaterials

63 Use of good laboratory/good workplace practice is a pre-requisite to controlling exposure to all substances hazardous to health. Where information on the toxicity of a specific particulate nanomaterial is unknown or unclear, a precautionary approach should be adopted; i.e. it should be assumed, until proven otherwise, that the specific particulate nanomaterial represents a hazard to health.

64 Therefore, wherever reasonably practicable, exposure to particulate nanomaterials by all routes (inhalation, dermal and ingestion) should be eliminated or controlled by the use of engineering controls. If total prevention of exposure to particulate nanomaterials is not reasonably practical, the duty under COSHH is to reduce exposure and risk. (Appendix 2 shows a particulate nanomaterial control measures selection flowchart).

65 If engineering controls and good laboratory/good workplace practice are not adequate to control exposure, consideration should be given to using additional controls, such as respiratory protective equipment to prevent inhalation. Whatever system is chosen, there is a need to check that it is, and remains, effective.

66 In most cases the principal potential exposure route to particulate nanomaterials in the laboratory or workplace is via inhalation. Therefore, wherever possible the release of airborne particulate nanomaterials should be minimised or prevented by the use of appropriate processes, practices, systems and engineering controls.

Inhalation risk

67 Where there is a risk of particulate nanomaterials becoming airborne, the following measures should be used where possible to control and prevent exposure:

- minimise the quantity of particulate nanomaterials in use at any one time;
- minimise the number of people potentially exposed;
- minimise the potential exposure time;
- ensure that all those potentially exposed to particulate nanomaterials have had suitable and sufficient information, instruction and training;
- use engineering controls such as Local Exhaust Ventilation (LEV) to control airborne exposure;
- where other control measures are either not reasonably practicable or fail to achieve adequate control, the use of Respiratory Protective Equipment (RPE) is a valid control strategy. RPE should only be used however when all other reasonably practicable measures have been taken but these have not, in themselves, achieved adequate control;
- avoid contact with the skin. Always wear suitable disposable, single-use gloves;
- where dust exposure from contamination of work clothing could be significant, use clothing made from a low dust-retention and low dust-release fabric;
- keep all bottles/vessels containing particulate nanomaterials sealed when not in immediate use since it has been shown that the action of opening vessels containing free particulate nanomaterials can cause them to be drawn from the vessel so that they become airborne;
- where possible, keep the particulate nanomaterial wet or damp, or use slurries, and avoid energetic processes that might generate airborne dusts to reduce the risk of particulate nanomaterials becoming airborne;
- use a damp sheet of paper towel or tissue on the bench when weighing out particulate nanomaterials and dispose of it in a sealed plastic bag whilst it is still damp;
- use a damp paper towel or tissue to wipe up spilt particulate nanomaterials and dispose of it in a sealed plastic bag whilst it is still damp.

Dermal and ingestion risk

68 Where there is a risk of particulate nanomaterials contacting the skin, the following measures, **in addition** to those detailed above for preventing exposure by inhalation, should be used to control and prevent exposure:

- change the disposable gloves after every task;
- ensure gloves are removed in a safe manner and disposed of safely;
- if possible, use instruments/tools to prevent contact with the skin;
- good housekeeping is important with easy to clean surfaces, containment of spills and keeping the workplace surface clean using wet wipes;
- good personal hygiene/skin care is also important; suitable welfare facilities should be provided;
- always wash hands before leaving the laboratory/work area.

Engineering Control Measures

69 Engineering control measures will vary depending on the requirements of each workplace. It may be necessary for those working with particulate nanomaterials to use a combination of methods to control exposure. These methods range from total enclosure of the process and automatic handling techniques, to partial containment by LEV, such as extracted enclosures and fume cupboards. Total enclosure or partial enclosures such as fume cupboards will be reasonably practicable for many operations with particulate nanomaterials, including manufacture/synthesis and weighing. For cutting, sawing or polishing, simpler extracted enclosures and other LEV devices such as capturing/receiving hoods or down-draught benches may be appropriate. However, certain work activities may lead to higher potential exposure and therefore additional control measures may be necessary.

70 All LEV equipment should be designed and installed to a high standard. It should also be commissioned to demonstrate control effectiveness (see HSG 258).

HEPA Filtration Efficiency

71 Wherever reasonably practicable, the exhaust air from an LEV system should be filtered through a High Efficiency Particulate Air (HEPA) filter, preferably H14, to remove the airborne particulate nanomaterials before venting to a safe place outside the building. This is particularly important when handling HARNs such as carbon nanotubes or other fibrous/rod like nanomaterials. If it is not reasonably practicable to vent the exhaust air to a safe place outside, it must never be re-circulated directly back into the workplace unless it has been effectively filtered to remove airborne particulate nanomaterials by at least one HEPA H14 filter (see Appendix 1). Particulate nanomaterials have also been shown to be captured by electrostatic collectors.

72 HEPA filters H14 are designed to remove at least 99.97% of airborne particles at the Most Penetrating Particle Size (MPPS) for which filtration is at a minimum. Larger and smaller particles may be filtered with even higher efficiency. Recent studies indicate that HEPA filters of this grade are reasonably efficient at capturing the relatively limited number of particulate nanomaterials (as small as 2 nm in diameter) tested. It should be noted that different grades of HEPA filter have

differing efficiencies in the nanoparticle range. In addition, different particulate nanomaterials may have differing MPPSs and penetration rates depending on their shape, density and charge.

73 Ultra Low Penetration Air (ULPA) filters are designed to remove 99.9975% of airborne particles with a diameter of 120 nm, but to date, little information is available on their performance with particulate nanomaterials.

Local Exhaust Ventilation (LEV)

74 The most effective class of LEV are enclosures. In the laboratory setting there are generally two types: full or partial. Full enclosures (for example, a glove box with HEPA filtration) are the most effective as they provide physical separation between the worker and the material. However, their inherent features can make them impractical as a control option and therefore partial enclosures are frequently used. These may be designed specifically for the process or be commercially available units. Examples of partial enclosures suitable for handling particulate nanomaterials include: HEPA-filtered fume cupboards, HEPA-filtered containment cabinets or a HEPA-filtered microbiological safety cabinets (MSCs). Using double HEPA-filtered cabinets increases the level of protection and can provide a safer means of carrying out filter changes.

75 The small size and ”low inertia” of particulate nanomaterials means they move with the air generated by the process in a manner more akin to gases than conventional particles. Therefore, correctly designed LEV systems should be an effective control measure.

76 The effectiveness of any control measure cannot be automatically assumed when handling particulate nanomaterials. Respirators, HEPA-filtered cabinets and most importantly fume cupboards were not specifically designed for this task, and so evidence should be sought as to their effectiveness before use. For newer installations, information may be sought in the LEV commissioning report (see HSG 258 and BS EN 14175).

77 It is important to make sure that the LEV achieves and maintains adequate control of exposure at all times. The system requires regular maintenance/periodic monitoring to ensure controls are working and thorough examination and testing “once a year” (COSHH allows a maximum of 14 months between tests). In addition to face velocity measurements, flow visualisation using smoke will show whether the LEV is truly effective. Furthermore, a smoke test performed with the process/operation running will show:

- the extent, velocity and behaviour of the airborne contaminant cloud;
- the capture zone and boundaries of capture hoods;
- whether containment is maintained within an enclosure;
- draughts, their direction and size;
- the general movement of air around an enclosure;
- eddying and encroachment into the operator’s breathing zone.

78 If there is any doubt about the capability of a fume cupboard, then it may be necessary to carry out a containment test, as detailed in BS EN 14175-3:2004

79 All users should be trained in how to check and use the LEV and records should be kept of all LEV checks.

Ducted Microbiological Safety Cabinets (MSCs*)*

80 Ducted MSCs can be used to handle particulate nanomaterials in a similar way to other HEPA-filtered containment cabinets. A Class I MSC operates in a similar way to a fume cupboard and protects the worker by drawing air through the front opening. Class II and III MSCs provide protection for both the user and the material in the cabinet. All these cabinets exhaust air through a HEPA filter.

81 It should be noted that Class II MSCs are NOT suitable for handling HARNs and are only suitable for handling small (<1 g) quantities of particulate nanomaterials because they re-circulate up to 70% of their air inside the cabinet and are only specified to a containment level of 10^{-5}.

Ductless re-circulating HEPA-filtered containment cabinets and re-circulating MSCs

82 Ductless re-circulating HEPA-filtered containment cabinets and MSCs that "re-circulate" air back into the room from the cabinets interior through a HEPA filter, can be used for small quantities (<1 g) of particulate nanomaterials **in the absence of hazardous vapours or gases**. However, the use of a ductless re-circulating cabinet or enclosure to control any hazardous substance must be subject to rigorous risk assessment and should only be considered where external venting to a safe place outside is not reasonably practicable. The containment cabinet should be set aside for use with particulate nanomaterials or chemically similar materials because some other chemicals, particularly those with the potential to evolve corrosive vapours or fumes, may affect the effectiveness and integrity of the fitted filter.

83 HEPA-filtered re-circulating cabinets do NOT absorb or capture gases or vapours, for which external venting to a safe place would be required in addition to the HEPA filter. If corrosive vapours or fumes could be generated, a glass fibre rather than cellulose HEPA filter should be used and the exhaust vented to a safe place outside.

84 The International Organization for Standardization Technical Report (ISO/TR 12885, 2008) on nanotechnology proposes a series of qualifications on the use of MSCs based on their mode of operation and the quantity of nanomaterial that could be safely handled in them (Appendix 1).

85 If using a re-circulating safety cabinet or re-circulating MSC, it should conform to BS7989:2001 3 and the following must be considered:

- filter must be HEPA; charcoal filters alone must not be used;
- cabinet should have a filter blockage warning/alarm;
- cabinet must have a low airflow warning/alarm;
- how a saturated filter is to be safely changed;
- how the contaminated filter is to be safely disposed of (incineration is recommended);
- cabinet must be subject to regular maintenance including a filter integrity test.

The cabinet must be subject to thorough maintenance, examination and testing (including a filter integrity test) at periods not greater than 14 months, and more frequently if the assessment identifies higher risk; every 6 months would be good practice.

Maintenance, examination and testing of control measures

86 Regulation 9 of COSHH requires that every employer who provides any control measure to meet the requirement of Regulation 7 shall ensure that it is maintained in an effective state, in an efficient working order and in good repair.

87 In order to comply with Regulation 9 it should be ensured that:

- all measures used to control exposure to nanomaterials are maintained in good working order and in good repair. (The manufacturer/supplier of plant should be able to help with appropriate information.);
- competent persons undertake frequent visual checks and periodically carry out thorough examinations of equipment to ensure they are being maintained adequately;
- all LEV plant is examined and tested at least every 14 months (a record of such tests must be kept for at least 5 years after the date on which they were made).

88 Further general information about LEV is contained in HSG 258.

Personal Protective Equipment (PPE)

Eye protection

89 Suitable eye protection must be worn when handling any chemicals including particulate nanomaterials (minimum of close fitting safety glasses).

Respiratory protective equipment

90 There will be situations where other control measures are either not reasonably practicable or fail to achieve adequate control. In these circumstances, the use of Respiratory Protective Equipment (RPE) is a valid control strategy. RPE should only be used however when all other reasonably practicable measures have been taken but these have not, in themselves, achieved adequate control.

91 It must be emphasised that the use of RPE as a means of preventing exposure should be a last resort (COSHH) and must not be undertaken lightly or without full consideration of the practicality of using engineering controls.

92 Disposable masks (no less than FFP3 standard) are only suitable as a secondary precautionary measure against accidental “spillage” not as a first line of protection. Full-face P3 APF40 (Assigned Protection Factor 40) particulate respirators that protect the eyes and lungs are required for any work in an atmosphere containing airborne-engineered particulate nanomaterials.

93 All RPE, including disposable masks, must be suitable for the task, manufactured to the appropriate standard and face-fit tested for the individual by a competent face-fit tester.

94 Those using RPE should be trained in its use and if the equipment is re-usable, it should be regularly cleaned, checked to ensure that it remains effective and monthly maintenance

records kept. For further information on the selection, use and maintenance of RPE, see http://www.hse.gov.uk/coshh/basics/ppe.htm.

Gloves

95 The gloves selected should be suitable and manufactured to an appropriate standard. For many particulate nanomaterials, good quality, disposable, single-use gloves should be adequate. However consideration must also be given to other chemicals used in the procedure/process. Organic liquids, including solvents, can not only permeate through gloves quite quickly in their own right but may facilitate the penetration of small particulate nanomaterials through gloves.

96 Glove material thickness is a major factor in determining the diffusion rate of chemicals through gloves and consideration may need to be given to wearing two layers of disposable gloves for some materials. Guidance on choosing the appropriate gloves to protect skin from a variety of substances can be found at http://www.hse.gov.uk/skin/employ/gloves.htm.

97 Currently the only criterion that can be readily accessed to validate gloves as potentially suitable for use with particulate nanomaterials is the virus penetration test (ASTM F1671-97b/ISO 16604), which uses a 28 nm diameter bacteriophage. If the risk assessment indicates that latex gloves are the safest choice, then only low protein, powder-free gloves should be used.

98 All those working with particulate nanomaterials should be properly trained in how to put on and remove gloves without contaminating themselves. Guidance on removing single-use gloves can be found on the HSE training video, available at: http://www.hse.gov.uk/skin/videos/gloves/removegloves.htm.

Protective clothing

99 When working with particulate nanomaterials, suitable lab coats, coveralls or where appropriate, disposable overalls should be worn. Provision must be made to allow clean overalls/laboratory coats to be put on and dirty ones removed in a manner that does not contaminate the individuals or the general workplace.

100 If dust exposure from contamination of work clothing could be significant, clothing made from a low dust-retention and low dust-release fabric such as polyethylene textiles is recommended. The European Nanosafe 2 project reported in 2008 that particulate nanomaterials can permeate through some intact disposable overall materials and by implication, woven reusable materials. The Nanosafe 2 report recommended non-woven Tyvek/Tychem polyethylene overalls for use with particulate nanomaterials in preference to paper or cotton.

101 If re-usable laboratory coats or overalls are used, provision should be made for their regular laundering and the prevention of secondary exposure. (In the event of a “one-off” gross contamination, consideration should be given to treating even “re-usable” PPE as disposable.)

Cleaning spillages

102 The work area and all equipment should be thoroughly cleaned after use or following a spillage by wet-wipe cleaning.

- **Do not** brush.
- **Do not** use compressed air for cleaning.

- **Do not** use a standard vacuum cleaner.

103 If a vacuum cleaner is the only reasonable practical means of cleaning, it must be a **dedicated, commercial, HEPA-filtered** cleaner and the filter and bag that contain the particulate nanomaterial dust regularly changed under controlled conditions. The filter and bag must be disposed of appropriately and safely. The cleaner itself must only be used for this task and will need to be decontaminated at the end of its life before it is disposed of, taking a precautionary approach.

Specific Advice for High Aspect Ratio Nanomaterials (HARNs)

104 Fibrous nanomaterials including certain CNTs and nanowires are substances of high concern and unless, or until, sound evidence is available on the hazards from inhalation, a strict precautionary approach should be taken to the risk management of all HARNs. It should also be noted that as described in the HSE guidance "*Using nanomaterials at work*", plate-like structures (sometimes called nanoplatelets), where only one dimension falls within the nano size range, are also considered to be HARNs (HSE, 2013).

105 If the use of HARNs cannot be avoided, then the implementation of a risk management programme in the workplace can help to minimise the potential for exposure to HARNs. Such a programme should include the following:

- assess the worker's job and tasks to determine the potential for exposure;
- use appropriate work processes, systems and engineering controls, and provide suitable equipment and materials to minimise the likelihood of release i.e. minimise the amount of HARNs produced, or produce HARNs in a form that reduces the chance of them becoming airborne. Where possible, use equipment that fully encloses the process;
- control exposure at source by carrying out all tasks, including packaging for disposal, in a ducted fume cupboard with a HEPA filter, or in other suitable LEV fitted with a HEPA filter. When using other types of LEV, try to enclose the process as much as possible. Ductless, HEPA filtered safety cabinets and re-circulating HEPA filtered Class I or III MSCs can be used with small quantities of CNTs ,and other HARNs as long as they are subject to rigorous maintenance and checks are carried out to ensure they are effective at all times. See Appendix 2 for more information;
- reduce the number of employees handling HARNs and minimise the level and duration of exposure and the quantities used;
- if possible, keep the material wet or damp to reduce the risk of it becoming airborne;
- provide RPE for emergencies, and only for use in addition to other control measures. All employees who use RPE must be trained and have had face-fit testing performed. HSE recommends RPE with an assigned protection factor (APF) of 40 or higher;
- provide personal protective equipment (for example, gloves, non-woven coveralls). Use single-use disposable gloves where possible. Glove material thickness is a major issue in determining diffusion of particulate nanomaterials and therefore at least two layers of gloves are recommended when handling HARNs. If the risk assessment indicates that latex is the safest choice, then only use low protein, powder-free gloves. Provide protective clothing such as polyethylene textiles (for example, Tyvek) which performs better and does not retain dust or allow dust to penetrate - do not use wool, cotton or knitted material;

- consider maintenance, filter replacement, storage and disposal in risk assessments for the control of exposure to HARNs;
- use 'wet-wiping' wherever practicable for cleaning and avoid the use of vacuum cleaners. If vacuum cleaners are the only reasonably practical option, they must be appropriately HEPA filtered and decontaminated before further use. Contaminated wet wipes should be double bagged and treated as hazardous waste;
- emergency procedures should be in place to deal with spills, accidents and emergencies;
- educate and train workers in the proper handling of particulate nanomaterials (for example, good work practices) and keep records of all training carried out.

Information, Instruction and Training

106 To comply with Regulation 12 of COSHH, employers should give all their employees who may be exposed to nanomaterials at work, sufficient information, instruction and training to understand the risks to their health caused by potential exposure to nanomaterials and the precautions that should be taken to avoid or minimise exposure.

107 In academia, it is important that the person carrying out the research carries out risk and COSHH assessments and is trained in how to perform these tasks. A senior member of staff should check and sign them off, but should not write them *per se*. A central record of all health and safety training in COSHH and risk management should be kept within the department with or for students, and this can be used for future employment.

108 Employers should provide adequate supervision, particularly to new and inexperienced workers. The training should detail how control measures are to be used. Employees should be instructed to report any obvious defects in the control measures to their supervisor.

109 Where RPE is used, employees should be trained to check that it fits properly, and given clear instructions about when it should be used, serviced or, if it is disposable, thrown away.

110 Information, instruction and training should in particular enable employees to:

- understand the risks to health arising from exposure;
- use the control measures provided effectively;
- use PPE effectively where necessary.

111 A record of all the information, instruction and training should be kept for each employee.

Monitoring

112 One of the general principles of risk management includes taking measures to prevent or minimise exposure of workers to nanomaterials and their releases into the environment. Monitoring is important to assess whether potential exposure occurs and whether the engineering controls are adequate. Exposure to nanomaterials can occur by ingestion, skin penetration or inhalation. However, inhalation is the primary route of exposure for airborne particulate nanomaterials. There is currently no consensus on which is the most appropriate metric or method to measure airborne nanomaterials in the workplace. Sampling strategies based on extensive real-time measurements and off-line characterisation of airborne engineered nanoparticles have been described in PD ISO/TR 27628:2007, ISO/TR 12885:2008, PD6699-3:2010 and Brower *et al.* (2009). However, workplace exposure measurement surveys based on extensive monitoring using a large set of sophisticated equipment require training and expert knowledge.

113 Guidance documents, particularly those from ISO/BSI and NIOSH provide recommended approaches to undertaking exposure monitoring. Approaches based on simple to use, hand-held instruments have been developed. NIOSH has proposed the Nanoparticle Emission Assessment Technique (NEAT) (Methner *et al.*, 2010a, and b). An OECD document (2015) presented a three-tiered approach for conducting field-based measurement of airborne particulate nanomaterials with tier 2 focusing on conducting a basic exposure or release assessment using a straightforward approach for determining whether an exposure to engineered nano-objects may occur. The approach utilises easy-to-use, portable equipment.

Limitations to monitoring

114 The monitoring of airborne particulate nanomaterials in the workplace is challenging due to the lack of portable and personal instruments that are selectively sensitive to engineered nanomaterials against a background of non-engineered nanomaterials (which can fluctuate). Background is defined as airborne particles present in the workplace and differs from engineered particulate nanomaterials/nanomaterials released during manufacturing, use or handling. It includes “ultrafines” originating from different sources including urban pollution.

Instruments used

115 The sampling method described in Appendix 5 uses hand-held Condensation Particle Counters (CPC) and Optical Particle Counters (OPC). Hand-held CPCs and OPCs measure particle number concentrations in the size range from 10-20 nm to 1 µm and 0.5 µm to about 15 µm or greater respectively. They are portable, easy to use, cost effective fast response instruments capable of detecting transient releases. The use of an OPC instrument in addition to a CPC instrument can be beneficial. In some circumstances, when monitoring powder-handling activities, the OPC can be useful as the nanoparticles agglomerate to form larger particles and can be detected using the OPC rather than the CPC. Samples should be collected for off-line analysis by electron microscopy and or X-ray fluorescence (XRF) / Inductively Coupled Plasma Mass Spectrometry (ICPMS). .

Sampling strategy

116 The protocol described in Appendix 5 is designed to be a pragmatic first stage approach to rapidly assess particle release and whether the control measures or changes implemented are effective. It requires at least a CPC, OPC and a sampler for subsequent EM and or XRF / ICPMS

analysis. A combination of off-line electron microscopy analysis and thermogravimetic analysis (for example, for elemental carbon analysis) can be used for carbon nanotubes. All these instruments should be placed close to the task. Another CPC and OPC, positioned away from the task/process, can also be used. See Appendix 5 for more information.

117 It is important that the background level of nanomaterials is established before any production or processing of the nanomaterial is started. This is because there is a natural background level of nanomaterials in the air, the amount of which will depend on the location.

Limitations

118 As the hand held CPC and OPC instruments in their basic form give no or limited size discrimination in the size range detected, the source must be "detected" by increased in particle counts relative to the background, over a wide size range. There are limitations to the performance of real-time instruments and samplers used for the monitoring of airborne particulate nanoparticles. More sophisticated instruments are available which offer much improved size discrimination and may help to better define the source but still rely on a comparison to the background count. Off-line analysis of the particles collected can confirm the presence or absence of the particles of concern. In the future, surface area monitors may play a more important role. The protocol describes "current best practice"; however, given the developmental nature of this field in doubt, this approach should be supported by external expert advice where necessary.

Health Surveillance

119 On-going research on the hazards of engineered particulate nanomaterials is needed along with the continual reassessment of available data to determine whether specific medical screening is warranted for workers who are producing or using particulate nanomaterials.

120 HSE proposes that best practice would involve keeping a record of all those staff who are working with particulate nanomaterials via the equivalent of a COSHH work activity record form, in a similar way to other substances of concern. Alongside such records of work activity, the type of particulate nanomaterials handled, the duration of work with the material, and the exposure scenarios should be documented. An example of a work activity record can be found in Appendix 4.

121 Health screening and health surveillance *specific* for hazardous particulate nanomaterials are not practical at the present time due to a lack of information about anticipated health effects and suitable biomarkers.

123 The health hazards related to the material, irrespective of the nanoscale form, should still be considered as part of the usual COSHH risk assessment. This should be informed by considering the likely routes of exposure for the material of concern.

Disposal of Laboratory Waste Nanomaterials

124 There is currently no waste regulatory framework in the UK specific for nanomaterials. Nonetheless, the Environmental Protection Act 1990 (Duty of Care) and Waste (England and Wales) Regulations 2011 (in Scotland, the Waste Management Licensing Regulations 2011, and in Northern Ireland, the Waste Regulations (Northern Ireland) 2011) apply.

125 The responsibility under UK law of any individual who is the holder of controlled waste is to ensure that the waste is managed properly, is recovered or disposed of safely, does not cause harm to human, animal or plant health or pollution of the environment, and is transferred only to someone who is authorised to receive it. In general, research laboratories produce relatively small quantities of hazardous waste (i.e. ≤ kg scale) compared to manufacturing which typically produces waste on a larger scale (for example, tonne scale).

126 Nanomaterial (for example, nanoparticles, nanotubes, nanofibres, etc) in powder form or dispersed in liquid may present a greater exposure risk than a solid matrix impregnated with nanomaterial. It is important that nanomaterial waste is identified and characterised (for example, dust filters contaminated with CNTs or HARNs, paper tissues impregnated with colloidal silver, metal oxide nanomaterials on carbon black), in order to determine which controls are needed to reduce the risk of exposure. In the absence of sufficient knowledge, the nanomaterial waste should be classified at least as hazardous as the non-nanoscale (or 'bulk') form of that substance. Consideration should be given to the possibility of increased hazard in the presence of one or more of physico-chemical characteristics listed in paragraph 42. If the non-nanoscale ('bulk') form is classified as hazardous waste, the nanomaterial waste should be classified as hazardous waste. For larger consignments of waste nanomaterials (for example, from manufacturing), see PAS 138:2012.

127 The fate of nanomaterials in the environment, an obvious concern (RSC, 2006) is outside the scope of this guidance: however, a summary is available (RCEP 2008) and more recently discussed (Kumar, 2014; Wagner, 2014; Kühnel, 2014).

128 Determining the method of waste disposal for nanomaterials is dependent on the nature and character of the nanomaterial waste; for example, the solubility of the particulate nanomaterial or whether the nanomaterial waste is a solid/powder, particulate nanomaterials in a liquid dispersion or particulate nanomaterials embedded in a matrix. The waste disposal route will also depend on whether or not the waste is hazardous waste according to waste classification. In addition, consideration should be given to the possibility of enhanced hazard from the nanomaterial due to the potential for enhanced (eco) toxicological, physical properties or increased mobility during disposal.

129 Drawing on previous guidance (MIT, 2008) nanomaterial waste can be broadly classified into the following waste streams:

- pure nanomaterials (for example, CNTs);
- items contaminated with nanomaterials (for example, wipes/paper towels);
- liquid suspensions containing nanomaterials (for example, colloids);
- solid matrices with nanomaterials that are friable or attached to the surface;
- nanomaterials embedded in a solid matrix that are unlikely to be released on contact with air or water: i.e. the nanomaterial is immobilised.

130 The level of controls necessary to dispose safely of nanomaterial waste will depend on its nature. Unless there is evidence that the materials to be disposed of do not present any hazards, a **precautionary approach** should be taken for handling, packaging, and disposal. Waste should be disposed of in such a manner that the risk of exposure to the nanomaterials is minimised.

131 It is recommended that waste nanomaterials or waste containing nanomaterials is double-bagged or doubly contained, labelled, and sealed in preparation for disposal. (OECD 2010).

Preparation of nanomaterial laboratory waste prior to disposal

132 The risk of exposure to nanomaterial waste must be either prevented or controlled; wherever possible. All nanomaterial waste should be contained. Generation of nanomaterial waste should be minimised

133 Containment can be achieved by employing suitable, sturdy, compatible containers (for example, plastic clip top containers), which prevent the escape of nanomaterials. Containers must be clearly labelled, providing a description of the waste and including the hazardous properties (either known or suspected).

134 In general, all nanomaterial waste including contaminated laboratory consumables such as paper towels, wipes, disposal gloves and suits, blotters and other moderately contaminated items should be double-bagged in preparation for disposal (i.e. transfer to the waste contractor). It is recommended that:

- prior to disposal, the contaminated waste is placed in a sealable, plastic bag inside a fume cupboard/ biosafety cabinet;
- the sealed bag should then be placed inside another sealable, plastic bag and clearly labelled identifying the contaminated material.

135 It is suggested that where possible, particulate nanomaterials dispersed in liquid or in a powder form are treated in an appropriate way to inactivate the nanomaterial (OECD, 2010). For example, liquid waste can be placed in a waste solvent stream (ultimately incinerated), fixed in a resin (Cornelissen, 2011) or adsorbed on to a solid substrate (for example, silica or carbon). Other examples of inactivation include: aggregating the particulate nanomaterials in solution (for example, by centrifuging gold nanoparticles), or dissolving the particulate nanomaterials in solution (for example, treating silver nanoparticles with aqua regia (a mixture of hydrochloric acid and nitric acid)). Solid nanomaterial waste (for example, powder), which presents a risk of exposure through inhalation, can be considered for disposal via existing solid hazardous waste streams, for example, in a similar manner to waste fine silica employed for column chromatography (hazardous by virtue of potential inhalation). Such waste is double-bagged, sealed, and transferred into a suitable sealable container (for example, a metal or plastic clip top drum) for collection by a licensed waste contractor.

136 It has been recommended (Cornelissen, 2011) where surfaces or materials have been decontaminated (for example, wiped or washed down), producing a contaminated residue, that the resulting residue/waste is treated as chemical waste (hazardous waste).

137 Nanomaterials should not be disposed of via “non-hazardous waste” disposal routes (through landfill or drains) unless it can be demonstrated that such nanomaterials are proven to be non-hazardous and disposal via these waste streams is safe and does not contravene environmental legislation. A **precautionary approach** has been generally adopted: (in the

absence of sufficient knowledge on the hazard) no free manufactured particulate nanomaterials should enter any non-hazardous waste stream or be disposed of via the drains (Cambridge, 2011).

Disposal by waste contractors

138 There is a legal obligation to comply with the Environmental Protection Act 1990 (Duty of Care) which requires that any waste for disposal should be fully described and this should include the presence of nanomaterials where there is any uncertainty to the risk they might pose. Further information is available from:
http://www.netregs.org.uk/library_of_topics/waste/more_waste_materials_topics/laboratory_waste.aspx

139 The Environmental Agency technical guidance, 'WM3', (EA, 2015), which has recently been amended to reflect Global Harmonised System (GHS) provides a detailed protocol for classifying waste whether it is hazardous or not. According to EA 'Hazardous Waste Assessment Methodology' (EA, 2011) where knowledge on the composition of the waste is deficient and if the information, which demonstrates the waste is non-hazardous, is insufficient then the waste is classed as 'hazardous'. The EA states in 'WM3' "This procedure is a general guide, it applies in most circumstances and must be used with the supporting appendices. If you're unsure seek advice from a competent person".

140 The EA guidance (EA, 2015) states threshold limits of ≥0.1% for 'HP6' ('Acute toxicity' 'Oral Tox. 1' and 'Inhal. Tox. 1'); 'HP7' ('Carcinogenic' 'Carc. 1A & Carc. 1B'); 'HP11' 'Mutagens' 1A & 1B and a range of limits from 1–25% for hazardous materials as described by GHS (ascribed 'HP' codes) by mass in 'bulk'. It is yet to be determined if this approach is applicable to nanomaterial waste. It has been suggested [PD 6699-2:2007] that most nanomaterial waste will fall into either "H5" or "H6" waste categories, i.e. 'harmful' or 'toxic' respectively if inhaled, or ingested, or adsorbed through the skin. In some cases, ascribing waste to either "H7" (carcinogenic) or "H13" (sensitizing) categories may be applicable as well.

141 Incineration of solid waste containing nanomaterials has been identified as the "conservative option" even though the nanomaterials are present at low levels (<1%) (HSE, 2004). With respect to CNTs and biopersistent HARNs, high temperature incineration is the preferred method of disposal (HSE, 2013). The disposal of nanomaterials by incineration has been reviewed (Holder, 2013).

Table 2: Summary of treatment and control conditions for laboratory waste nanomaterials

Waste nanomaterial (NM)	Pre-treatment Prior to disposal	Containment	Level of engineering Controls	Disposal method
Unbound NM (free nanoparticles for example, powder)	Wet/moisten	Double	Inside a LEV enclosure or glove box	Incineration
Contaminated solids (laboratory consumables)	Wet/ moisten if necessary	Double bag (plastic, sealable)	Inside a LEV enclosure or glove box	Incineration
Liquid solutions (colloids/blends/QM Dots)	Process solvent soluble with solvent waste stream. Aggregate nanoparticles Dissolve NP (form ions)	Drip tray/funnel Vial/container/drip tray Vial/container/drip tray	Inside a LEV enclosure Inside a LEV enclosure, and/or contained in a centrifuge. Inside a LEV enclosure	Incineration Mix with solid waste. Incinerate Either mix with other soluble waste or dilute to drain if appropriate.
NM bound in resin in or polymer	As for liquid solutions or package as 'NM in a solid matrix not friable'.	Single containment or double containment if liquid.	General ventilation	Incineration or licensed landfill.
NM in a solid matrix but friable	Wet/moisten	Double containment	Inside a LEV enclosure	Incineration or licensed landfill.
NM in a solid matrix not friable	None	Single containment	General ventilation	Incineration or licensed landfill.

Labelling and Signs

142 A requirement and/or standardised approach to labelling and safety signs for use with nanomaterials does not currently exist. It is recommended that a diligent approach is taken using, for example, Hazard and Precautionary statements and warning signs to provide adequate, relevant and specific information on any actual or potential hazards and safety risks.

143 The European Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixture (CLP) was progressively implemented between 20 January 2009 and 31 May 2015 in all EU member states, including the UK. It adopts the Globally Harmonised System (GHS) on the classification and labelling of chemicals and replaces the former CHIP regulations in the UK from 1 June 2015. Although the CLP hazard pictograms are very similar to the former CHIP hazard symbols, they have a new shape, new design and a new colour.

144 Guidance from the European Chemicals Agency (ECHA) is available on how to label and package chemical substances and mixtures in accordance with the CLP Regulation (http://echa.europa.eu/documents/10162/13562/clp_labelling_en.pdf). Although not specific to nanomaterials, the guidance provides useful examples and aims to clarify:

- what aspects to consider when estimating the label size needed;

- what types of supplemental information are possible, and where to place this information on the label;
- the conditions for small packaging exemptions;
- the interaction between CLP and transport labelling rules;
- how to select the most appropriate set of Hazard and Precautionary statements for the label.

145 Hazard and Precautionary statements are used to convey information derived from the hazard, exposure and risk assessments, in Safety Data Sheets (SDS) and COSHH assessments

146 A Hazard statement is a phrase that describes the nature of the hazard in the substance or mixture. A hazard statement will be determined by the application of the classification criteria. Examples of hazard statements include “Causes serious eye damage”, “Toxic if swallowed”, “Toxic to the aquatic life with long lasting effects” and “May cause allergy or asthma symptoms or breathing difficulties if inhaled”. Hazard statements replace the ‘risk or R-phrase’ from the now defunct CHIP regulation.

147 A Precautionary statement is a phrase that describes recommended measure(s) to minimise or prevent adverse effects resulting from exposure to a hazardous substance or mixture due to its use or disposal. Examples of Precautionary statements include “Wear eye protection”, “Do not eat, drink or smoke when using this product”, “Avoid release to the environment” and “In case of inadequate ventilation wear respiratory protection”. Suppliers determine the appropriate Precautionary statements (usually no more than six) based on the required hazard statements. Precautionary statements replace the ‘safety or S-phrase’ from the now defunct CHIP regulation.

148 GHS aims to bring together the various national and regional hazard communication systems that control the supply of hazardous chemicals and to ensure that information on physical hazards and chemical toxicity is available in order to enhance the protection of human health and the environment during the handling, transport and use of these chemicals. Activity associated with GHS may, in the future, provide a consistent approach for labelling of nanomaterials, but the assignment of hazard and precautionary statements will always be contingent upon consideration of the hazardous nature of the material where data are available, and in the absence of data, will require a precautionary approach.

149 The selection of appropriate hazard labels, signs or pictograms should be based on the available hazard information for the material. In the absence of information, a precautionary approach to labelling should be adopted.

150 *Ad hoc* signs or pictograms should be posted in areas to provide visual indication of local instructions or rules in place, for example, on storage cabinets, fume cupboards, instruments dedicated for use with nanomaterials. The content and format of the signs should be consistent with any in-house requirements.

151 Generic pictograms, adopting the format of the yellow/orange warning triangle, have emerged for “nanomaterial hazards” and whilst these have no official recognition by authorities, their use may be considered to provide a visual indication of the presence of nanomaterials, as appropriate. It should be noted that these generic signs do not provide any information on the nature of the hazard, and any known or suspected hazards (for example, oxidising, explosive) should be adequately indicated.

References

Air Quality and Sustainable Nanotechnology, Institute of Energy and Environmental Technology e.V. (IUTA), Federal Institute for Occupational Safety and Health (BAuA), German Social Accident Insurance Institution for the Raw Materials and Chemical Industry (BG RCI), German Chemical Industry Association (VCI), Institute for Occupational Safety and Health of the DGUV (IFA), Research Group Mechanical Process Engineering, and Institute of Process Engineering and Environmental Technology, Technical University Dresden (TUD): "Tiered approach to an exposure measurement and assessment of nanoscale aerosols released from engineered nanomaterials in workplace operations. (2011).

ASTM F1671-97b "Standard Test Method for Resistance of Materials Used in Protective Clothing to Penetration by Blood-Borne Pathogens Using Phi-X174 Bacteriophage Penetration as a Test System: ASTM (American Society for Testing and Materials).

British Standards Publication PAS 138:2012 "Disposal of manufacturing process waste containing manufactured nano-objects - Guide 2012".

British Standards Publication PD 6699-2:2007 'Part 2: "Guide to safe handling and disposal of manufactured nanomaterials. 2007".

British Standards Publication PD 6699-3:2010 "Nanotechnologies. Guide to assessing airborne exposure in occupational settings relevant to nanomaterials".

British Standards Publication BS EN 14175-3:2004 "Fume cupboards. Type test methods." British Standards Institute: ISBN 978 0 580 50371 9.

British Standards Publication BS EN 14175-5:2006 "Fume Cupboards. Recommendations for Installation and Maintenance" British Standards Institute: ISBN 980 5 808 4614 3.

British Standards Publication BS7989:2001 "Specification for recirculatory filtration fume cupboards": British Standards Institute: ISBN 0 580 33277 2.

D. Brouwer, B. van Duuren-Stuurman, M. Berges, E. Jankowska, D.Bard, and D. Mark: "From workplace air measurement results toward estimates of exposure? Development of a strategy to assess exposure to manufactured nano-objects". J. Nanopart. Res. 11:1867-1881 (2009).

Carlotti ME, Ugazio E, Sapino S, Fenoglio I, Greco G, Fubini B. 2009 "Role of particle coating in controlling skin damage photoinduced by titania nanoparticles". Free Radic Res. Mar;43(3):312-22.

Cambridge, 2011. University of Cambridge: Chemical Safety Guidance. "Carbon Nanotubes and Other Synthetic Insoluble Fibrous Nanomaterials 2009 Revised 2011".

Cho, W. S., R. Duffin, S. E. Howie, C. J. Scotton, W. A. Wallace, W. Macnee, M. Bradley, I. L. Megson and K. Donaldson (2011). "Progressive severe lung injury by zinc oxide nanoparticles; the role of Zn2+ dissolution inside lysosomes." Particle and fibre toxicology 8: 27.

Cornelissen R, Jongeneelen F, van Broekhuizen P, van Broekhuizen F. 2011: "Guidance Working Safely with Nanomaterials and Nanoproducts: The Guide for Employers and Employees" FNV VNO-NCW CTV Document No. 1113-0. Version 1.0 2011.

COSHH. Control of Substances Hazardous to Health 2002 (As Amended) (6th Ed) ACOP.2013. HSE Books.

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. 2007 Aug;19(10):849-56.

EA (2015) Environment Agency Technical Guidance WM3 "Guidance on the classification and assessment of waste (1st edition 2015).

EA (2011a) Environment Agency guidance-HWR01. "What is a Hazardous waste? A guide to the Hazardous Waste Regulations". Version 5. 2011.

EA (2011b) Environment Agency Hazardous Waste Technical Guidance WM2 "Interpretation of the definition and classification of hazardous waste". Revised 2011.

Environmental Protection (Duty of Care) Regulations 1991 SI 2839

EU 2011/696/ EU Definition of Nanomaterial.

European Nanosafe 2 project report 2008: "Safe production and use of nanomaterials: Efficiency of fibrous filters and personal protective equipments against nanoaerosoles". DR-325/326-200801-1.

Grosse, Y., D. Loomis, K. Z. Guyton, B. Lauby-Secretan, F. El Ghissassi, V. Bouvard, L. Benbrahim-Tallaa, N. Guha, C. Scoccianti, H. Mattock and K. Straif (2014). "Carcinogenicity of fluoro-edenite, silicon carbide fibres and whiskers, and carbon nanotubes." Lancet Oncol 15(13): 1427-1428.

Hamilton, R.F. Jr., Wi, n., Porter, D., Buford, M., Wolfarth, M., Holian, A. 2009 "Particle length-dependent titanium dioxide nanomaterials toxicity and bioactivity", Part Fibre Toxicol, vol. 6, no. 36.

Hirakawa K, Mori M, Yoshida M, Oikawa S, Kawanishi S. 2004 "Photo-irradiated titanium dioxide catalyzes site specific DNA damage via generation of hydrogen peroxide." Free Radic Res.;38(5):439-47.

HSE (2004): "Nanomaterials: a risk to health at work?" 1st International Symposium on Occupational Health Implications of Nanomaterials. 2004 Report of Presentations at Plenary and Workshop Sessions and Summary of Conclusions.

HSE (2009) CNT Guidance "Risk Management of carbon nanotubes".

HSE (2011) Controlling airborne contaminants at work: A guide to local exhaust ventilation (LEV). HSG 258, 2nd Ed., HSE Books. ISBN 978 0 7176 6415 3. 2011.

HSE (2013). Using nanomaterials at work.

Holder A.L, Vejerano E.P, Zhou X, Marr L.C "Nanomaterial disposal by incineration" 2013 Environ.Sci: Processes Impacts 15, 1652-1664.

IARC (2014 Monograph 111). IARC monographs on the evaluation of carcinogenic risks to humans. Preamble. Lyon, IARC.

International Organization for Standardization ISO/TR 27628:2007 "Workplace atmospheres -- Ultrafine, nanoparticle and nano-structured aerosols -- Inhalation exposure characterization and assessment".

International Organization for Standardization ISO/TS 27687:2008 "Nanotechnologies -- Terminology and Definitions for Nano-Objects -- Nanoparticle, Nanofibre and Nanoplate".

International Organization for Standardization ISO/TR 12885:2008 "Nanotechnologies -- Health and safety practices in occupational settings relevant to nanotechnologies".

International Organization for Standardization ISO 16604:2004 "Clothing for protection against contact with blood and body fluids -- Determination of resistance of protective clothing materials to penetration by blood-borne pathogens -- Test method using Phi-X 174 bacteriophage".

Karlsson HL, Gustafsson J, Cronholm P, Möller L. 2009 "Size-dependent toxicity of metal oxide particles--a comparison between nano- and micrometer size". Toxicol Lett. 188(2):112-8.

Konaka R, Kasahara E, Dunlap WC, Yamamoto Y, Chien KC and Inoue M. 1999 "Irradiation of titanium dioxide generates both singlet oxygen and superoxide anion" Free Radic. Biol. Med. (3/4), pp. 294–300.

Kühnel D, Marquardt C, Nau K, Krug H, Mathes B, Steinbach C "Environmental impacts of nanomaterials: providing comprehensive information on exposure, transport and ecotoxicity- the projectDaNa2.0" Envron.Sci. Eur. 2014, 26:21.

Kumar A, Das S, Munusamy P, Self W, Baer D, Sayle D, Seal S "Behavior of nanoceria in biologically-relevant environments" 2014 Environ.Sci.:Nano 1, 516-532.

McNeilly JD, Heal MR, Beverland IJ, Howe A, Gibson MD, Hibbs LR, MacNee W, Donaldson K "Soluble transition metals cause the pro-inflammatory effects of welding fumes in vitro." Toxicol Appl Pharmacol. 2004 Apr 1;196(1):95-107.

M. Methner, L. Hodson, and C. Geraci: "Nanoparticle emission assessment technique (NEAT) for the identification and measurement of potential inhalation exposure to engineered nanomaterials - Part A." J. Occup. Environ. Hyg. 7:127-32 (2010).

M. Methner, L. Hodson, A. Dames, and C. Geraci: "Nanoparticle Emission Assessment Technique (NEAT) for the identification and measurement of potential inhalation exposure to engineered nanomaterials - Part B: Results from 12 field studies". J. Occup. Environ. Hyg. 7: 163-176 (2010).

MIT (2008). Massachusetts Institute for Technology. "Nanomaterials Toxicity. Potential risks of nanomaterials and how to safely handle materials of unknown toxicity". Posted 2010. and "Best Practices for Handling Nanomaterials in Laboratories" 2008.

Naumann BD, Sargent EV, Starkman BS, Fraser WJ, Becker GT, Kirk GD.1996 "Performance-based exposure control limits for pharmaceutical active ingredients". Am Ind Hyg Assoc J; 57(1):33-42.

OECD (2010). "Series on the Safety of Manufactured Nanomaterials. No. 28. Compilation of nanomaterial exposure mitigation guidelines relating to laboratories". IOMC. 2010.

OECD (2015). Harmonized tiered approach to measure and assess the potential exposure to airborne emissions of engineered nano-objects and their agglomerates and aggregates at workplaces. ENV/JM/MONO(2015)19.

RCEP (2008) "Novel Materials in the Environment: The case of nanotechnology". Royal Commission on Environmental Pollution 27th Report 2008.

RS/RAEng (2004) "Nanoscience and nanotechnologies: opportunities and uncertainties." The Royal Society, London.

RSC "Chemicals in the Environment: Assessing and managing risk" Ed R.E. Hester and R.M. Harrison. Issues in Environmental Science and Technology Vol. 22. RSC Publishing 2006.

Sanchez VC, Jachak A, Hurt RH, Kane AB. 2011 "Biological Interactions of Graphene-Family Nanomaterials: An Interdisciplinary Review" Chem Res Toxicol. 2011 Oct 21. [Epub ahead of print].

SCCS (2013). Scientific Committee on Conusmer Safety (SCCS) Opinion on Titanium Dioxide (nano form), Scientific Commission on Consumer Safety.

SCCS (2013). Scientific Committee on Conusmer Safety (SCCS) Opinion on Zinc Oxide(nano form), Scientific Commission on Consumer Safety.

Schinwald, A., T. Chernova and K. Donaldson (2012). "Use of silver nanowires to determine thresholds for fibre length-dependent pulmonary inflammation and inhibition of macrophage migration in vitro." Particle and fibre toxicology 9(1): 47.

Schinwald, A., F. Murphy, A. Prina-Mello, C. Poland, F. Byrne and D. Movia (2012). "The threshold length for fiber-induced acute pleural inflammation: shedding light on the early events in asbestos-induced mesothelioma." Toxicological sciences: an official journal of the Society of Toxicology 128: 461 - 470.

Schulte P.A., Kuempel E.D., Castranova V., Geraci C., Hoover M.D. Stefaniak A., Hodson L., Zumwalde R., Murashow V . "Issues in Establishing Categorical Occupational Exposure limits for Nanomaterials". 2011 (poster).

Wagner S, Gondikas A, Neubauer E,Hofman T, von der Kammer F "Spot the difference: Engineered and Natural Nanoparticles in the Environment- Release, Behavior, and Fate" 2014 Angew. Chem. Int Ed. 53, 12398-12419.

World Health Organization (WHO). (1997 "Determination of airborne fibre number concentrations. A recommended method, by phase-contrast optical microscopy (membrane filter method)". Geneva.

APPENDIX 1: US Microbiological Safety Cabinet Characteristics and Applicability for Nanomaterials

The International Organisation for Standardisation Technical Report (ISO/TR 12885) with respect to the use of HEPA filtered cabinets for nanomaterials.

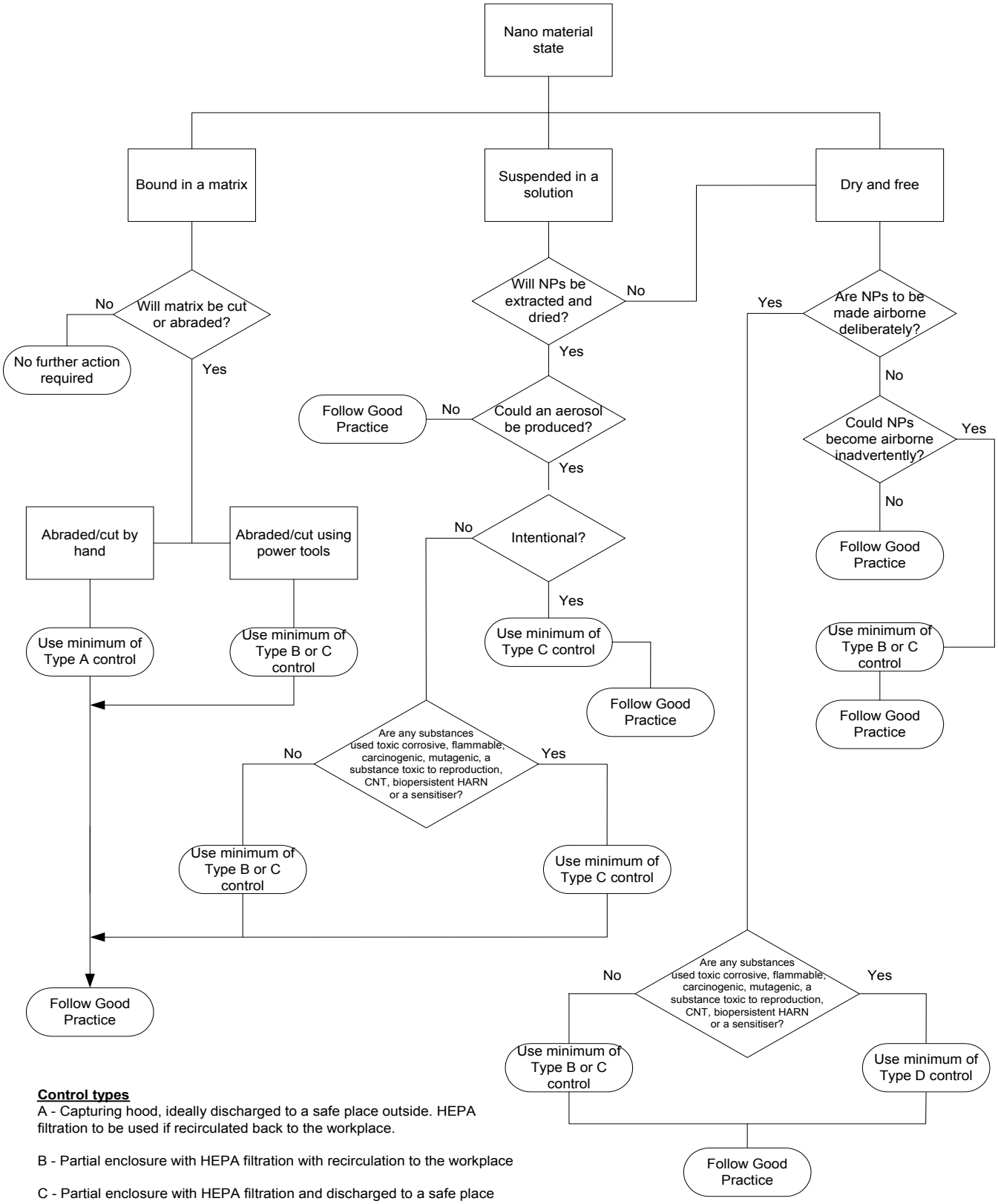
			Applications	
MSC Class	**Face Velocity m/s**	**Airflow Pattern**	**Non-volatile Toxic Chemicals**	**Volatile Toxic Chemicals**
I*	0.4	In at front then through HEPA to the outside or recirculate into the room through HEPA.	Yes	When exhausted outdoors [1,2]
II, A1	0.4	70% recirculated to the cabinet work area through HEPA; 30% balance can be exhausted through HEPA back into the room or to outside through a canopy unit.	Yes (minute amounts)	No
II, B1	0.5	30% recirculated, 70% exhausted. Exhaust cabinet air must pass through a dedicated duct to the outside through a HEPA filter.	Yes	Yes (minute amounts)[1,2]
II, B2	0.5	No recirculation; total exhaust to the outside through a HEPA filter.	Yes	Yes (small amounts) [1,2]
II, A2	0.5	Similar to II, A1, but has 100 lfpm intake air velocity and plenums are under negative pressure to room; exhaust air can be ducted to outside through a canopy unit.	Yes	When exhausted outdoors (Formerly "B3") (minute amounts) [1,2]
III	N/A	Supply air is HEPA filtered. Exhaust air passes through two HEPA filters in series and is exhausted to the outside via a hard connection.	Yes	Yes (small amounts) [1,2]

1. Installation may require a special duct to the outside, an in-line charcoal filter, and a spark proof (explosion proof) motor and other electrical components in the cabinet. Discharge of a Class I or Class II, Type A2 cabinet into a room should not occur if volatile chemicals are used.
2. In no instance should the chemical concentration approach the lower explosion limits of the compounds.

(Taken from Appendix A of ISO/TR 12885, Technical Report: Nanotechnologies - Health and safety practices in occupational settings relevant to nanotechnologies. Which in turn cites its source as the US Department of Health and Human Services publication 'Biosafety in Microbiological and Biomedical Laboratories, 2007')

*A Class I microbiological safety cabinet is similar in operation to a HEPA filtered fume cupboard or HEPA filtered cabinet, drawing in air through the front opening before HEPA filtering the exhaust.

APPENDIX 2: Nanomaterial Control Measures Selection Flowchart



Control types

A - Capturing hood, ideally discharged to a safe place outside. HEPA filtration to be used if recirculated back to the workplace.

B - Partial enclosure with HEPA filtration with recirculation to the workplace

C - Partial enclosure with HEPA filtration and discharged to a safe place outside. e.g fume cupboard or a well designed bespoke partial enclosure

D - full enclosure with HEPA filtration and discharged to a safe place outside.

APPENDIX 3: Engineering Controls

Local Exhaust Ventilation (LEV):

Conventional ducted fume cupboards fitted with HEPA filtration and ducted microbiological safety cabinets may be used for HARNs, see below.

Fume cupboards

A fume cupboard is an enclosure designed to contain and exhaust vapours and gaseous contaminants generated inside it. A fume cupboard is a key engineering control device, therefore the selection of the appropriate fume cupboard design and the adherence to safe work practices are crucial to user safety.

For use with HARNs the fume cupboard exhaust air should be HEPA filtered, and wherever reasonably practicable vented to a safe place outside.

It is important that a fume cupboard complying with BS EN 14175 is used and that the fume cupboard does not lose containment during normal use. In most circumstances, velocity measurements and smoke test will show whether the fume cupboard is effective. Smoke tests, with appropriate detection, can be used to investigate a number of problems, such as:

- irregular air-flow and eddy characteristics resulting in air movement out of the cupboard;
- the possible negative effects of equipment on airflow;
- the possible negative effect of heat sources within the cupboard on airflow;
- leakage from the cupboard or ducting.

However, if there is any doubt about the integrity of the fume cupboard then it may be necessary to carry out a containment test as in BS EN 14175-3:2003**.**

Installation of fume cupboards **must be only** be undertaken by those with knowledge of British Standard BS EN 14175-5: 2006 'Fume cupboards, recommendations for installation and maintenance'. In particular fume cupboards must not be sited:

- on heavy pedestrian traffic routes;
- adjacent to doors;
- adjacent to opening windows.

As the above can cause air turbulence and wake affects that can affect the cupboards containment

- at the open end of a u-shaped laboratory bay, since a fire or explosion within the cupboard, may trap workers in the bay.

Microbiological safety cabinets

Ducted microbiological safety cabinets can be used, although it should be noted that a Class II cabinet is not suitable for handling HARNs because it re-circulates up to 70% of its air. The Class II and III microbiological safety cabinets, unlike the Class I type, provide protection for both the user and the material in the cabinet is working environment. All these cabinets exhaust air through a HEPA 14 filter.

Ductless recirculating HEPA filtered safety cabinets and recirculating microbiological safety cabinets

Safety cabinets and microbiological safety cabinets which recirculate air from the cabinets interior, thorough a HEPA 14 filter, back into the laboratory can be used for small quantities of HARNs in the absence of hazardous vapours or gases.

If using a recirculating safety cabinet or recirculating microbiological safety cabinet the following must be considered; Cupboard must conform to British Standard BS 7989:2001.3.

- The filter must be HEPA; charcoal filters alone must not be used†.
- The cupboard should have a filter saturated warning/alarm.
- The cupboard must have a low airflow warning/alarm.
- How is a saturated filter to be safely changed?
- How is the contaminated filter to be safely disposed of? (incineration)
- Ensure that the filter integrity test is performed.

- Subjected to thorough examination and testing at periods not greater than fourteen months and more frequently if the assessment identifies higher risk; every 6 months would be good practice.

Charcoal filters are designed to absorb gases and vapours and fumes, for which they have a finite capacity. When the capacity is exceeded, contaminate is returned to the workplace. Charcoal filters alone are not designed for filtering solid materials and for these reasons the use of such systems should be avoided.

Users should take steps to ensure that the standard of supervision, training, system of work and record keeping is up to date. The safety cabinet should be set aside for use with HARNs or chemically similar materials because some other chemicals may affect the effectiveness and integrity of the fitted filter.

HEPA filter recirculating fume cupboards or cabinets can be used to control any potentially airborne 'dusty' hazardous substance as long as it is subjected to a rigorous risk assessment **BUT** should only be considered where external venting to a 'safe place' is not reasonably practicable.

†NB: HEPA filtered recirculating cabinets do NOT absorb or capture, gases or vapours, for which external venting to a safe place would be required in addition to the HEPA filter.

APPENDIX 4: Record of Work Activity Form

Record of Work Activity Using Nanomaterials

COSHH Regulations require all individuals working with substances that can cause certain identifiable diseases or adverse health effects to be monitored. As a pre-cautionary measure the employer requires the completion of a Record of Work Activity for all individuals working with

- Nanomaterials (particles of approximately 100 nm or less in at least one dimension) with unknown toxicological properties.

For further information on the criteria for health surveillance see the HSE website:

http://www.hse.gov.uk/coshh/basics/surveillance.htm

Personal Details	
Surname:	Forenames:
Male/Female:	Date of Birth:
N.I. Number:	
Date commenced present job:	
Permanent address:	
Postcode:	Dept Tel No:
Status: Staff/ Undergraduate student/ Postgraduate student/ Visitor/ Other (Delete as appropriate)	
Department:	
Supervisor's name and contact telephone number:	
Signed:	**Date:**

PLEASE COMPLETE SUBSTANCE DETAILS OVERLEAF

THIS RECORD MUST BE KEPT BY THE DEPARTMENT FOR 40 YEARS FOLLOWING THE INDIVIDUAL LEAVING EMPLOYMENT.

SUBSTANCE DETAILS					
Name of substance	**Nature of hazard[1]**	**Physical state[2]**	**Quantity, amount[3]**	**Frequency/duration of use[4]**	**Control measures in use[5]**

Key:
1 Carcinogen, mutagen, substance toxic to reproduction, respiratory sensitiser, skin sensitiser or *'nanomaterial of unknown toxicity'*
2 Powder, liquid, solid –this includes free nanoparticles, nanoparticles in liquid suspension or nanoparticles in a solid matrix
3 Include amount and units
4 Daily, weekly, monthly, rarely
5 Fume cupboard, laminar flow bench, Local Exhaust Ventilation (LEV), glove box or other form of containment, personal protective equipment (please specify)

APPENDIX 5: Sampling Protocol to Assess Release of Particulate Nanomaterials to Air

This protocol is designed to assess the release of particulate nanomaterials into workplace air. It allows the effectiveness of the controls to be checked and if necessary to confirm that exposure to the particles of concern was taking place. Positive results should trigger a review, and improvement of the control approaches used. Other more comprehensive strategies (for example, Brouwer *et al.* (2009), OECD (2015)) are described in the literature which may give improved background discrimination. Given the developmental nature of this field of measurement, the detection limits for any of the strategies are not yet well-defined.

Real time measurements

An initial assessment without the process / task running should be carried out. A CPC and an OPC are moved around to investigate any other potential sources of non-engineered nanomaterials and the range in the background concentration. If possible these sources should be isolated or stopped during the monitoring period.

Measurements using a CPC and an OPC should be carried out before, during and after the activity under study takes place. The CPC and the OPC are stationary and positioned close to the worker's task (within an approximate 1m radius of the worker's head) taking care that they do not hinder or interfere with the workers' normal duties. Non-activity periods (before and after the activity period) should be monitored for at least 15 minutes if possible.

Measurements using a second CPC and a second OPC could be carried out before, during and after the activity under study takes place. The instruments are stationary and should be located at a distance from the activity, such that it measures airborne particle concentrations that are representative of the background concentration near the activity. A distance of at least 2/3 m is suggested. The non-activity periods (before and after the activity period) should be monitored for at least 15 minutes if possible.

A CPC could also be used with the telescopic probe attachment to monitor particle number concentration inside containment/fume cupboards during activity periods.

Be aware that any other extraneous sources of non-engineered nanomaterials such as: passing lorries/fork lift trucks, electric motors, smoke-generating systems, welding/soldering activities, open doors and windows can influence particle concentration readings greatly.

Smoke tubes, for the testing of fume-cupboards or local exhaust ventilation (LEV) efficiency, should not be used during the monitoring of the activities. It has been shown during previous studies that these can be a source of very high concentrations of airborne non-engineered nanomaterials.

All instruments should be calibrated at least every year and regularly checked to ensure consistent operation especially their performance to each other if several of the same instruments are used.

Collection of samples for off-line analysis

A number of sampling techniques for the collection of airborne particles and subsequent electron microscopy (EM) analysis are available and include:

- Filtration on to filters or carbon films supported on transmission electron microscopy (TEM) grids using conventional sampling pump. TEM grids with a holey carbon film can be attached to filters. Filters can be pre-coated with gold for subsequent scanning electron microscopy (SEM) analysis.

- Precipitation using thermal or electrostatic precipitators.

Samplers collecting the respirable mass fraction should be used for subsequent XRF / ICPMS analysis.

A sampler should be personal and or positioned close to the activity/process and at a distance of at least 2/3m from the process/task (optional) alongside the CPCs and OPCs. Samples collected inside containments/fume-cupboards are also very useful for comparison with samples collected outside containments/fume-cupboards.

Record and contextual information

The times at which the monitors and samplers were started and stopped together with the sampler flow rates should be recorded. It is also critical that detailed contextual information of all activities before, during and after the task/process takes place are recorded as an increase in particle number concentrations from the real-time instruments may be unrelated to the task/process.

Interpretation of Results

Particle number concentration should be plotted and arithmetic means, minimum and maximum concentrations before, during and after the task/process should be calculated. A difficult question to answer is if an increase in particle number concentration means there has been a corresponding emission of engineered nano-objects from the task/process. For that, the "task/process" particle number concentration must be higher than the "background" particle number concentration and this increase has to be statistically significant. However some critical judgement should also be applied. The background may greatly fluctuate or it can gradually increase or decrease with time. The contextual information is important in this decision-making as well as knowing whether other sources of non-engineered nano-objects are present. The off-line analysis of the sample (for example; EM, XRF/ICPMS) will confirm the presence or absence of the engineered nano-objects and if necessary may be used to quantify the number concentration and size distribution.

For risk management purposes, the monitoring data and analysis results can be used alongside an occupational hygiene assessment of the effectiveness of the control measures (using techniques such as, air velocity measurements, smoke tubes and expert knowledge to determine the level of control achieved).


THE UK NANOSAFETY
GROUP