
**Nanotechnologies — Occupational risk
management applied to engineered
nanomaterials —**

**Part 1:
Principles and approaches**

*Nanotechnologies — Management du risque professionnel relatif aux
nanomatériaux manufacturés —*

Partie 1: Principes et approches



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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

In other circumstances, particularly when there is an urgent market requirement for such documents, a technical committee may decide to publish other types of document:

- an ISO Publicly Available Specification (ISO/PAS) represents an agreement between technical experts in an ISO working group and is accepted for publication if it is approved by more than 50 % of the members of the parent committee casting a vote;
- an ISO Technical Specification (ISO/TS) represents an agreement between the members of a technical committee and is accepted for publication if it is approved by 2/3 of the members of the committee casting a vote.

An ISO/PAS or ISO/TS is reviewed after three years in order to decide whether it will be confirmed for a further three years, revised to become an International Standard, or withdrawn. If the ISO/PAS or ISO/TS is confirmed, it is reviewed again after a further three years, at which time it must either be transformed into an International Standard or be withdrawn.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO/TS 12901-1 was prepared by Technical Committee ISO/TC 229, *Nanotechnologies*.

ISO/TS 12901 consists of the following parts, under the general title *Nanotechnologies — Occupational risk management applied to engineered nanomaterials*:

- *Part 1: Principles and approaches*

Introduction

The field of nanotechnologies continues to advance rapidly through the development of new materials, products and applications. At the same time, many questions have been raised relating to the potential risks to human health and to the environment of some of these new nanomaterials. Internationally, a large programme of research is underway to understand better and quantify these risks. Although some research is now published, this effort will need to continue for some time. However, those involved in the development and use of nanomaterials now still require to make assessment of the risks and to implement effective risk management approaches based on the best available evidence. International standardization on nanotechnologies should contribute to realizing the potential of this technology for the betterment and sustainability of our world through economic development, improving the quality of life, and also for improving and protecting public health and the environment.

This part of ISO/TS 12901 supports this by describing the principles of an occupational risk management framework and gives practical advice on its implementation based on the best current emerging evidence concerning the potential risks of nanomaterials. ISO/TS 12901-2, which is under development, describes a specific approach based on control banding to further support the implementation of good practice in this area.

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Nanotechnologies — Occupational risk management applied to engineered nanomaterials —

Part 1: Principles and approaches

1 Scope

This part of ISO/TS 12901 provides guidance on occupational health and safety measures relating to engineered nanomaterials, including the use of engineering controls and appropriate personal protective equipment, guidance on dealing with spills and accidental releases, and guidance on appropriate handling of these materials during disposal.

This part of ISO/TS 12901 is intended for use by competent personnel, such as health and safety managers, production managers, environmental managers, industrial/occupational hygienists and others with responsibility for the safe operation of facilities engaged in production, handling, processing and disposal of engineered nanomaterials.

This part of ISO/TS 12901 is applicable to engineered materials that consist of nano-objects such as nanoparticles, nanofibres, nanotubes and nanowires, as well as aggregates and agglomerates of these materials (NOAA).

The term “NOAA”, as used in this part of ISO/TS 12901, applies to such components either in their original form or incorporated in materials or preparations from which they could be released to a certain extent during their lifecycle, including, as a result, downstream activities such as disposal.

2 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

2.1

agglomerate

collection of weakly bound particles or aggregates or mixtures of the two where the resulting external surface area is similar to the sum of the surface areas of the individual components

[ISO/TS 27687:2008, definition 3.2]

NOTE 1 The forces holding an agglomerate together are weak forces, for example van der Waals forces, or simple physical entanglement.

NOTE 2 Agglomerates are also termed secondary particles and the original source particles are termed primary particles.

2.2

aggregate

particle comprising strongly bonded or fused particles where the resulting external surface area may be significantly smaller than the sum of calculated surface areas of the individual components

[ISO/TS 27687:2008, definition 3.3]

NOTE 1 The forces holding an aggregate together are strong forces, for example covalent bonds, or those resulting from sintering or complex physical entanglement.

NOTE 2 Aggregates are also termed secondary particles and the original source particles are termed primary particles.

2.3

engineered nanomaterial

nanomaterial designed for a specific purpose or function

[ISO/TS 80004-1:2010, definition 2.8]

2.4

exposure

contact with a chemical, physical or biological agent by swallowing, breathing, or touching the skin or eyes

NOTE Exposure may be short-term (acute exposure), of intermediate duration, or long-term (chronic exposure).

2.5

hazard

biological, chemical or physical element or factor that adversely affect individuals, the environment, a process or a product

[ISO 14698-2:2003, definition 3.10]

2.6

health hazard

potential source of harm to health

[ISO 10993-17:2002, definition 3.7]

2.7

nanofibre

nano-object with two similar external dimensions in the nanoscale and the third dimension being significantly larger

[ISO/TS 27687:2008, definition 4.3]

NOTE 1 A nanofibre can be flexible or rigid.

NOTE 2 The two similar external dimensions are considered to differ in size by less than three times and the significantly larger external dimension is considered to differ from the other two by more than three times.

NOTE 3 The largest external dimension is not necessarily in the nanoscale.

2.8

nano-object

material with one, two or three external dimensions in the nanoscale

[ISO/TS 27687:2008, definition 2.2]

NOTE Generic term for all discrete nanoscale objects.

2.9

nanoparticle

nano-object with all three dimensions in the nanoscale

NOTE 1 If the lengths of the longest to the shortest axes of the nano-object differ significantly (typically by more than three times), the terms nanorod or nanoplate are intended to be used instead of the term nanoparticle.

NOTE 2 Adapted from ISO/TS 27687.

2.10

nanoplate

nano-object with one external dimension in the nanoscale and the two other external dimensions significantly larger

[ISO/TS 27687:2008, definition 4.2]

NOTE 1 The smallest external dimension is the thickness of the nanoplate.

NOTE 2 The two significantly larger dimensions are considered to differ from the nanoscale dimension by more than three times.

NOTE 3 The larger external dimensions are not necessarily in the nanoscale

2.11

nanoscale

size range from approximately 1 nm to 100 nm

[ISO/TS 27687:2008, definition 2.1]

NOTE 1 Properties that are not extrapolations from a larger size will typically, but not exclusively, be exhibited in this size range. For such properties the size limits are considered approximate.

NOTE 2 The lower limit in this definition (approximately 1 nm) is introduced to avoid single and small groups of atoms from being designated as nano-objects or elements of nanostructures, which might be implied by the absence of a lower limit.

2.12

particle

minute piece of matter with defined physical boundaries

[ISO/TS 27687:2008, definition 3.1]

NOTE 1 A physical boundary can also be described as an interface.

NOTE 2 A particle can move as a unit.

NOTE 3 This general particle definition applies to nano-objects.

2.13

risk

combination of the probability of occurrence of harm and the severity of that harm

[ISO/IEC Guide 51:1999, definition 3.2]

3 Symbols and abbreviated terms

ADME	adsorption, distribution, metabolism and elimination
ACGIH	American Conference of Governmental Industrial Hygienists
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
CB	control banding
CNT	carbon nanotube
COSHH	Control of Substances Hazardous to Health Regulations
CPC	condensation particle counter
DMPS	Differential Mobility Particle Sizer
EDX	energy dispersive X-ray analysis

ELPI	electrostatic low pressure impactor
ES	exposure standard
GHS	Globally Harmonized System
HEPA	high-efficiency particulate matter
LCL	lower confidence limit
LEV	local exhaust ventilation
LOAEL	lowest-observed-adverse-effect-level
MWCNT	multi-wall carbon nanotube
NEAT	nanoparticles exposure assessment technique
NIOSH	National Institute for Occupational Safety and Health
NOAA	nano-objects, and their agglomerates and aggregates greater than 100 nm
NOAEL	no-observed-adverse-effect-level
OECD	Organization for Economic Cooperative Development
OEL	occupational exposure limit
OPC	optical particle counter
PB-ECL	performance based exposure control limit
PPE	personal protective equipment
RPE	respiratory protective equipment
SEM	scanning electron microscopy
SWCNT	single wall carbon nanotube
TEM	transmission electron microscopy
TEM EDX	transmission electron microscopy energy dispersive X-ray analysis
TEOM	tapered element oscillating microbalance
TLV	threshold limit value
WEL	workplace exposure limit

4 Nanomaterial types and characteristics

4.1 General

This clause describes some of the more common types of engineered nanomaterials to which this guide might be applied. It is not intended to provide a full and comprehensive guide or definition for these nanomaterials types.

4.2 Fullerenes

Fullerenes comprise one of four types of naturally-occurring forms of carbon, first discovered in the 1980s^[6]. Their molecules are composed entirely of carbon and take the form of a hollow sphere. Fullerenes are similar in structure to graphite which comprises sheets of hexagonal carbon rings, but can also contain pentagonal or heptagonal rings which enable 3D structures to be formed. One of the most commonly described fullerenes is C₆₀, known as a Buckminster fullerene or a buckyball. Fullerenes are chemically stable materials and insoluble in aqueous solutions. Potential applications include drug delivery, coatings and hydrogen storage^[7].

4.3 Carbon nanotubes

Carbon nanotubes^[8] are allotropes of carbon with cylindrical structure, high-aspect ratio different tube diameters and lengths as well as tube structures *principally* consisting of one to many layers of tubular graphene-like sheets^[9]. The principal types are usually grouped into SW (single-walled), DW (double-walled), and MW (multi-walled) CNT. Diameters may vary from around 1 nm for SWCNT to more than 100 nm for MWCNT. Their lengths can exceed several hundred μm . Commercial CNT can often contain a significant amount of other carbon allotropes and inorganic nanoparticle catalysts.

4.4 Nanowires

Nanowires are small conducting or semi-conducting nanofibres with a single crystal structure, a typical diameter of a few 10s of nm and a large aspect ratio. Various metals have been used to manufacture nanowires, including cobalt, gold and copper. Silicon nanowires have also been produced. Potential applications include inter-connectors in nano-electronic devices, photovoltaics and sensors.

4.5 Quantum dots

Quantum dots are small (2 nm to 10 nm) assemblies of semiconductor materials with novel electronic, optical, magnetic and catalytic properties. Typically containing 1 000 to 100 000 atoms, quantum dots are considered to be something between an extended solid structure and a single molecular entity. Semiconductor quantum dots exhibit distinct photo-electronic properties which relate directly to their size. For example, by altering the particle size, the light emitted by the particle on excitation can be tuned to a specific desired wavelength. Applications include catalysis, medical imaging, optical devices and sensors.

4.6 Metals and metal oxides, ceramics

This category includes a wide range of compact forms of nanoparticles, including ultrafine titanium dioxide and fumed silica. Such nanoparticles can be formed from many materials, including metals, oxides and ceramics. Although the primary particles have compact form, these materials are often available only in agglomerated or aggregated form. They can be composites having, for example, a metal core with an oxide shell, or alloys in which mixtures of metals are present. This group of nanoparticles is generally less well defined in terms of size and shape, and likely to be produced in larger bulk quantities than other forms of nanoparticles. Applications include coatings and pigments, catalysis, personal care products, cosmetics and composites.

4.7 Carbon black

Carbon black is virtually pure elemental carbon in the form of particles that are produced by incomplete combustion or thermal decomposition of gaseous or liquid hydrocarbons under controlled conditions. Its physical appearance is that of a black, finely divided powder or pellet. Its use in tyres, rubber and plastic products, printing inks and coatings is related to properties of specific surface area, particle size and structure, conductivity and colour. The primary particle size of carbon black is most commonly less than 100 nm, but commercial forms are aggregated, typically with dimensions greater than 100 nm. Carbon black is one of the top 50 industrial chemicals manufactured worldwide, based on annual tonnage.

4.8 Dendrimers

Dendrimers are polymer particles in which the atoms are arranged in a branching structure, usually symmetrically about a core. Dendrimers are typically monodisperse with a large number of functionalizable peripheral groups. They are currently being evaluated as drug delivery vehicles.

4.9 Nanoclays

Nanoclays are ceramic nanoparticles of layered mineral silicates. Nanoclays can be naturally occurring or engineered to have specific properties. Naturally occurring forms include several classes such as: montmorillonite, bentonite, kaolinite, hectorite, and halloysite. Nanoclays also include organo-clays, i.e. clays that have been subjected to cation exchange, typically with large organic molecules, which partially or completely de-laminates the primary sheets.

5 Nanomaterial hazard, exposure and risk

5.1 General

It has been established for many years that inhalation exposure to many types of particles, including nanoparticles, can cause ill health in individuals or exposed populations. These data are from studies in workers, animals, and the general population exposed to particulate air pollution. The lung effects depend on the particle dose, physicochemical properties and the susceptibility of the individuals. Animal studies have shown that nanoparticles can be more potent at causing adverse lung effects on a mass basis than larger respirable particles due to their greater surface area per unit mass^[10]. There are many instances of adverse lung effects relating to exposure from industrial activity and environmental pollution. For example, in an occupational setting, exposure to coal dust is clearly linked to the onset of lung diseases, such as pneumoconiosis and chronic obstructive pulmonary disease (COPD), and exposure to asbestos is clearly linked with asbestosis, mesothelioma and lung cancer. In an environmental context, studies have reported associations between particulate air pollution and increased morbidity and mortality from respiratory and cardiovascular effects, primarily in susceptible populations such as the elderly or those with pre-existing conditions^[11].

However, many millions of the population are exposed to particles in environmental pollution on a daily basis without any apparent ill effects. For any material, the risk, or likelihood, of illness increases with increasing dose. Dose broadly refers to 'how much' gets to an organ and 'how long' it stays there. Toxicity, specifically for relatively insoluble particles, appears to relate to the total surface area of the particles. However, there are other physicochemical factors which can influence the toxicity of nanomaterials, such as the fibre-like toxicity of some carbon nanotubes^[12].

5.2 Potential risk considerations to health from inhalation of NOAAs

More than 30 major reviews and position papers have discussed the potential risks to health and to the environment from exposure to NOAAs^[13]. The potential risks to health from inhalation of NOAAs, specifically bio-persistent NOAAs¹⁾, may be summarized as follows:

- a) Due to their small size, nano-objects can reach parts of biological systems which are not normally accessible by larger particles. This includes the increased possibility of crossing cell boundaries, or of passing from the lungs into the blood stream and so on to all of the organs in the body, or even through deposition in the nose, directly to the brain. This process is known as translocation and, in general, nano-objects can translocate much more easily than larger structures.
- b) NOAAs have a much higher surface area than the same mass of larger particles. To the extent that surface area is a driver for toxicity, this clearly implies potentially increased toxic effects.

1) If particles are readily soluble, they will be taken up in the body the same way as other chemicals and classical toxicity, and particle toxicity will follow.

- c) An important rationale for developing nanomaterials is that they will have new, improved or enhanced properties compared to larger particles of the same material. Altered chemical and/or physical properties might be expected to be accompanied by altered biological properties, some of which could imply increased toxicity.
- d) A specific issue relates to comparisons between biopersistent high aspect ratio (ratio of length to diameter), NOAAs (e.g. some forms of carbon nanotubes or nanowires) and asbestos. Some biopersistent fibrous particles cause disease because they can be inhaled and enter the alveolar region of the lung and are not easily removed because (i) their physical dimensions mean they cannot be removed by lung clearance mechanisms, and (ii) they are highly durable and do not dissolve in the lung lining fluids. Hence they remain in the lung for a long period of time, causing inflammation and ultimately disease. Asbestos is an example of such a biopersistent fibre. High aspect ratio NOAAs of similar morphology (shape and rigidity) and durability are therefore likely to persist in the lungs, if inhaled.
- e) In addition, for some NOAAs, reduction in size has been shown to relate to increased solubility. This effect might lead to increased bioavailability of materials which are considered to be insoluble or poorly soluble at larger particle sizes²⁾.

Along with increasing production volumes, lower costs and an increased general presence of nanomaterials in industry and commerce, these issues indicate that more needs to be done to assess the potential risks associated with these NOAAs and that a suitably cautious approach should be taken in their handling and disposal.

The likelihood (or risk) of disease occurring depends on the physicochemical properties of the nanomaterial and the dose in the organ where disease can occur. Dose in humans is not assessed directly, but is estimated from the exposure, which for airborne particles is a combination of the concentration of particles in air, the inhalation rate, the particle size-specific deposition efficiency in the respiratory tract, and the length of time the exposure lasts. If there is no exposure, no dose will accumulate and, despite the potential toxicity of the particles, there will be no risk to health.

An appropriate response to the potential risks from NOAAs, particularly when hazard information is unavailable, is to understand the potential exposures which could occur throughout the life cycle of the nanomaterial and to put in place measures to eliminate or minimize these exposures. In this way the risks can be controlled.

5.3 Potential risk considerations to health from dermal exposure or ingestion

Concerns have also been raised about the potential risks to health arising from dermal exposure to some types of NOAAs, in particular nano-objects, based on the possibility of these materials penetrating the skin and entering the bloodstream. To date there have only been a few studies of this effect on skin models^{[14][15]} and these have not demonstrated skin penetration by NOAAs to any extent. However, the studies are preliminary and have not considered, for example, the effect on damaged skin.

A recent paper found that small amounts of Zn from ZnO particles in sunscreens applied outdoors are absorbed through human skin^[16]. In this study, volunteers applied two sunscreen products, one 'nano sunscreen' containing 19 nm nanoparticles and 'bulk sunscreen' containing > 100 nm particles. Stable isotope tracing was used to detect the presence of zinc. A small excess in blood and urine was detected. However it is not known whether ⁶⁸Zn has been absorbed as ZnO particles or soluble Zn or both.

Other studies are currently underway but, until consensus emerges, a prudent approach would be to limit exposure to the skin.

Potential health effects due to ingestion have also been postulated based on the possibility of nanoparticle transfer across the gastro-intestinal wall. However, there is presently no direct evidence of adverse health effects from ingestion of NOAAs but it would be prudent to minimize exposure by this route.

2) If particles completely dissolve and the substance acts only by its molecules or ions, then classical toxicology comes in and particle effects are no longer relevant.

5.4 NOAAs as hazardous materials

A hazardous material may be identified as follows:

- it may be listed in national publications, which lists substances which have been assigned an OEL^[17];
- it may be classified according to the United Nations Globally Harmonized System as a carcinogen, a mutagen, or very toxic, toxic, harmful, sensitizing (e.g. cause of occupational asthma), corrosive, irritant or toxic to reproduction;
- it may be identified as a hazardous material in a safety data sheet, with information about the specific hazards e.g. carcinogen or mutagen;
- it may be identified in national or international publications which list hazardous chemicals.

However, with the limited knowledge about the toxicity of some NOAAs and the concern that current safety data sheets do not adequately reflect the hazardous nature of such NOAAs, it is recommended that all nanomaterials in a particulate form, or in a form where particles potentially could be released are considered potentially hazardous unless sufficient information to the contrary is obtained.

5.5 Risk of fire and explosion from NOAAs

Explosive dust clouds can be generated from most organic materials, many metals and even some non-metallic inorganic materials. The primary factor influencing the ignition sensitivity and explosive violence of a dust cloud is the particle size or specific surface area (i.e. the total surface area per unit volume or unit mass of the dust). As the particle size decreases the specific surface area increases. The general trend is for the violence of the dust explosion and the ease of ignition to increase as the particle size decreases, though for many dusts this trend begins to level out at particle sizes in the micrometer range. There is limited experimental data available. Moisture content can also play a role in the ignition sensitivity and explosion violence. High moisture content leads to lower explosion properties. Generally, the explosibility of NOAAs is broadly similar to conventional micron-scale powders. Thus, their large surface-to-volume ratio has not produced greater explosion violence than the equivalent material at micron-scale. However, the minimum ignition energies of some NOAAs have been found to be lower than the equivalent material at micron-scale. This indicates that some NOAAs might be more susceptible to ignition, but once ignited the explosion violence is no more severe than micron-scale powders^[12].

6 General approach to managing risks from NOAAs

In most countries, the law relating to the use of chemicals or other hazardous substances at work requires employers to control exposure to hazardous substances to prevent ill health to both employees and others who could be exposed. For example, in the United Kingdom (UK), The Control of Substances Hazardous to Health Regulations (COSHH) 2002^[11], which are based on a risk assessment approach, provide a framework for assessing and managing the potential risks from NOAAs. This framework comprises eight main steps:

- a) identify the hazards and assess the risks;
- b) decide what precautions are needed;
- c) prevent or adequately control exposure;
- d) ensure that control measures are used and maintained;
- e) monitor the exposure;
- f) carry out appropriate health surveillance;
- g) prepare plans and procedures to deal with accidents, incidents and emergencies;
- h) ensure employees are properly informed, trained and supervised.

The approach proposed in this part of ISO/TS 12901 closely follows this framework.

This approach generally relies on having good information about the hazardous nature of materials, the effectiveness of control approaches and convenient and accessible ways to monitor exposure. One of the difficulties in applying this approach to nanomaterials is that the information available might be incomplete or, worse, incorrect (this is also true of many low volume substances).

The knowledge gaps concerning the health hazards of new nanomaterials introduce significant uncertainty into any risk assessment. It is inappropriate in the absence of knowledge to assume that a nanoparticle form of a material has the same hazard potential as it has in a larger particulate form. In general, the greater the gaps in knowledge are, the more cautious the control strategy should be.

The general approach adopted in this guide to managing risks from NOAAs is illustrated in Figure 1, which is also a guide to the rest of this part of ISO/TS 12901. This figure provides a step-by-step approach to managing the risks from NOAAs, recognizing the associated uncertainties and developing and implementing an effective strategy to control exposure and manage the risks.

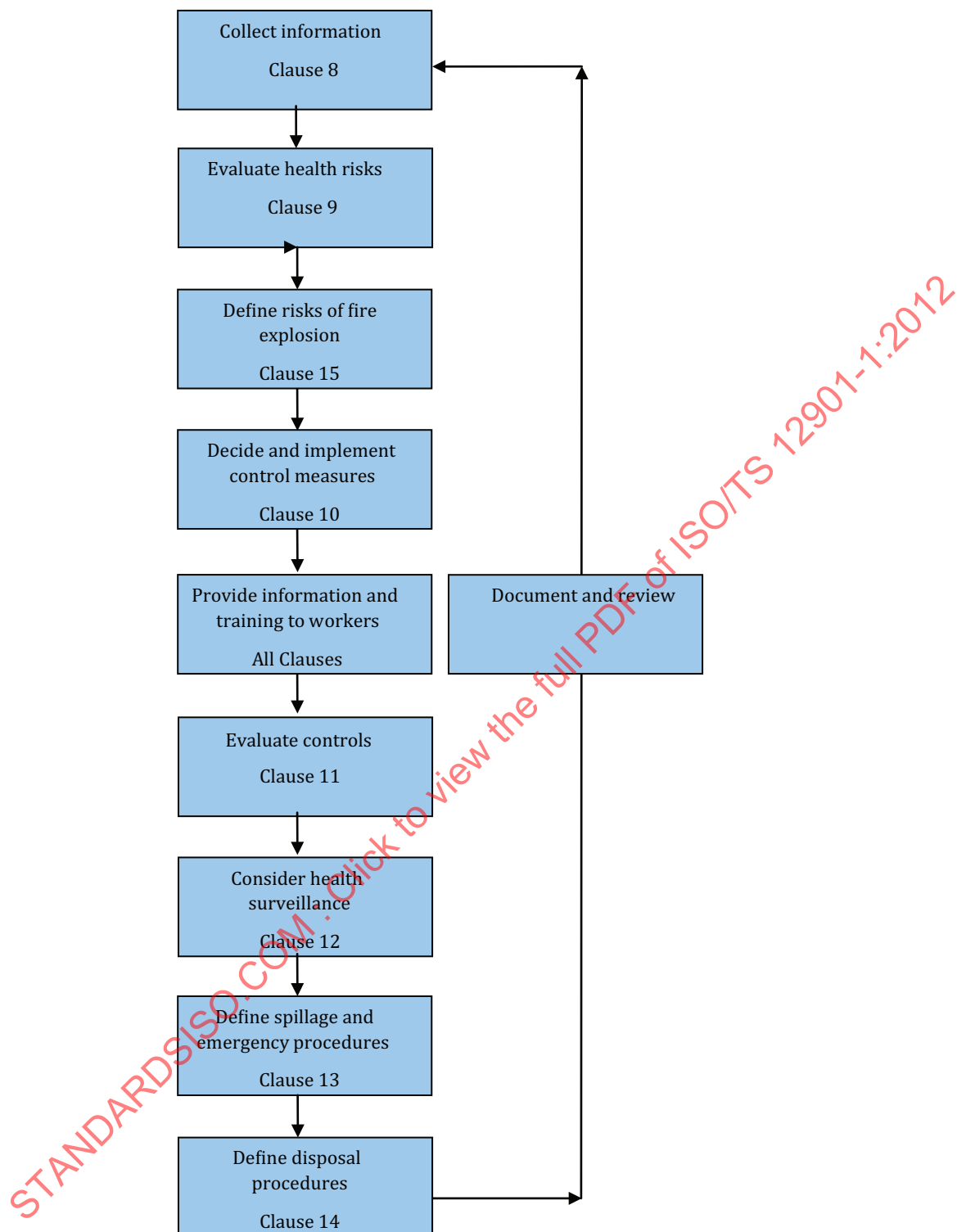


Figure 1 — Approach to managing risks from NOAAs

7 Identification and competence of person conducting risk assessment

An initial decision relates to who will carry out the risk assessment. As in general chemical risk assessments processes, several people might be involved, such as those involved in the development or implementation of a process, managers, or professional occupational hygienists. The current state

of knowledge concerning NOAAs suggests that it will be difficult for an individual with no background knowledge of nanoparticle risk issues to make effective judgments about the appropriate steps to take. While this part of ISO/TS 12901 helps address this situation, it is strongly recommended that those involved in developing risk assessments for NOAAs seek information more widely on these issues or undertake some external training. For further information on risk assessment, see ISO/TR 13121^[13].

8 Information collection

This is a key step in the risk assessment. If little is known about the material, it will be necessary to treat it as hazardous and apply tighter exposure controls.

It is therefore necessary to begin by collecting information about the material, the work and the working practices. It is important to consider both operational and other practices, such as maintenance and cleaning, including non-routine practices.

This should focus on the collection of information that can help to conduct a comprehensive risk assessment. The following are examples of the types of information, including those drawn from BSI PAS 6699-2^[14], and are not exhaustive:

- a) What are the commercial (or common) and technical names for the material?
- b) Is there a safety datasheet (SDS)³⁾?
- c) What is the chemical composition?
- d) What is the form of the nanomaterial (e.g. powder, agglomerated, pelletized)?
- e) Is nanomaterial present? In what proportions?
- f) Are the particles long and thin?
- g) What is the particle size distribution?
- h) How dusty is the material? How easily are particles released into the air?
- i) Is the material water soluble?
- j) How hazardous or toxic is the material?
- k) Are there materials which could be used instead of the nanomaterial that are potentially less hazardous, but still achieve the required end properties?

It is important to document both the information which is available and the information gaps. For commercial NOAAs, some of the information will be available on product safety data sheets. In using these sheets, however, it is necessary to evaluate the extent to which suppliers have taken account of the nanoscale nature of the substance.

It is also necessary to identify those who could be exposed. This could include production employees, ancillary or support-services employees, such as cleaners or maintenance workers, contractors on site, visitors, supervisors and managers, students, office workers and people outside.

9 Health risk evaluation

9.1 General

Risks are associated with the toxicity of material and the exposures that people have to that material. Information shall be collected that helps assess what the risks might be.

3) Guidance on the preparation of SDS for manufactured nanomaterials is given in ISO/TR 13329.

9.2 Assessing the hazard

For most particulate materials that can become airborne and be inhaled, particularly those that are poorly soluble, the primary health concern is for effects resulting from respiratory exposure. This should be the first consideration for any nanomaterial that is being manufactured or used. However, consideration should also be given to other means of exposure, such as skin contact or ingestion, and other potential hazards, such as fire and explosion (see Clause 15).

An assessment of hazard, (coupled with an assessment of the likelihood of exposure), can be used to decide on a control strategy. Clearly, the more information available, the better this categorization will be. Information on the hazardous nature of some NOAAs continues to increase and a number of sources are now available which can provide input for decision making^{[15][16]}. The information needs to be evaluated critically in terms of quantity and quality. Gaps in the information regarding hazard shall also be identified. Decisions can be informed by peer-reviewed science, anecdotal evidence or professional judgment. Emerging scientific evidence should be appropriately considered, and efforts made to keep up to date with the latest information. Relevant information will be available on Safety Data Sheets, but it has been indicated that at the current time many of these do not adequately represent the nano forms of the material^[17].

For all of the categories of NOAAs identified it is a reasonable assumption that these materials have a hazardous potential which is equal to or greater than that of the larger, non-nanoscale forms of the material (if existing).

9.3 Assessing exposure

The key deliverable from this step is an exposure characterization; a summary and synthesis of the gathered exposure information. The exposure characterization should include:

- a) a statement of purpose, scope, level of detail, and the approach used in the assessment;
- b) estimates of exposure for each relevant pathway, both for individuals and populations (e.g. groups of workers);
- c) an evaluation of the overall quality of the assessment and the degree of confidence in the exposure estimates and conclusions drawn, including sources and the extent of uncertainty.

Questions to consider to support that information gathering include:

- What are the processes which could lead to the release of NOAAs into the air or onto a surface?
- What are the tasks where people are potentially exposed to NOAAs (e.g. production, cleaning, accidental releases, maintenance, transport, storage and disposal)?
- Who can potentially be exposed during each task? The individual undertaking the task, adjacent workers, visitors, contractors, managers and others might be exposed.
- What are the potential routes of human exposure (e.g. inhalation, ingestion, dermal penetration and accidental injection)?
- What is the chance of the exposure occurring? Consider operational work, accidental releases and maintenance (including non-scheduled maintenance).
- How often is exposure likely to occur (e.g. continuous over a working shift, intermittently or rarely)?
- What concentrations are people exposed to and for how long? This might require collection and assessment of existing data or collection of new data (see Clause 11).
- Which control measures can be applied for each task? These can include segregation of personnel from the source by enclosing them or the process, or by using local exhaust ventilation, training the workers and supplying personal protective equipment (PPE).

In addition, any relevant existing measurement data should be collected.

It is quite likely, given current knowledge about nanoparticles, that the information collected will be considered insufficient. As uncertainty about the levels of exposure increases, the need for caution in the assessment increases. It is therefore necessary to err on the side of caution and determine where significant doubt exists. Based on this assessment, a prioritized plan should be developed to collect additional information about exposure levels. This could include a programme of exposure measurements, methods for which are summarized in Clause 11.

9.4 Assessing and prioritizing health risk

At this stage, potential hazards should have been identified and an assessment made of the likely exposures. Consideration of hazard and exposure leads to an assessment of the risks. The next stage is to decide what to do about them. If the risks are significant or could become so, or if there is uncertainty about the level of risk, then precautions are required.

Not all risks can be addressed immediately and priorities for action will be required. Priorities are decided on the basis of assessments of:

- the most serious risks to health;
- numbers of workers potentially exposed;
- the risks that are likely to occur the soonest;
- the potential for chronic disease due to repeated exposure (e.g. in workers);
- the risks that can be dealt with the soonest.

The most important of these is the seriousness of the risks. If a risk is serious it should be dealt with immediately. Less serious risks should not assume greater priority merely because they can be dealt with more easily or might occur more quickly.

9.5 Document and review

The findings of the risk assessment should be recorded when the assessment is made or as soon as is practicable afterwards. In some circumstances not all the findings will occur at the same time. Some might require further information before they can be resolved, e.g. where there is a pilot operation which runs for a period before being assessed completely or where air monitoring results are awaited. In these circumstances, the record of the significant findings should be completed or updated as information becomes available.

Given the emerging state of knowledge concerning the risks of NOAAs, it is probable that important new knowledge will become available at some time. It is critical therefore that the assessment is reviewed at least annually and that those involved in the process take steps to ensure that their knowledge is kept up-to-date.

10 Control of risk

10.1 Hierarchy of control

Exposure should be prevented preferably by avoiding, so far as is reasonably practicable, the use of a hazardous substance by substituting it, or the process, to a safer alternative, if existing. If, however, this is not possible, then exposure should be controlled by applying protection measures appropriate to the activity and consistent with the priority order given in Figure 2, which describes the hierarchy of control.

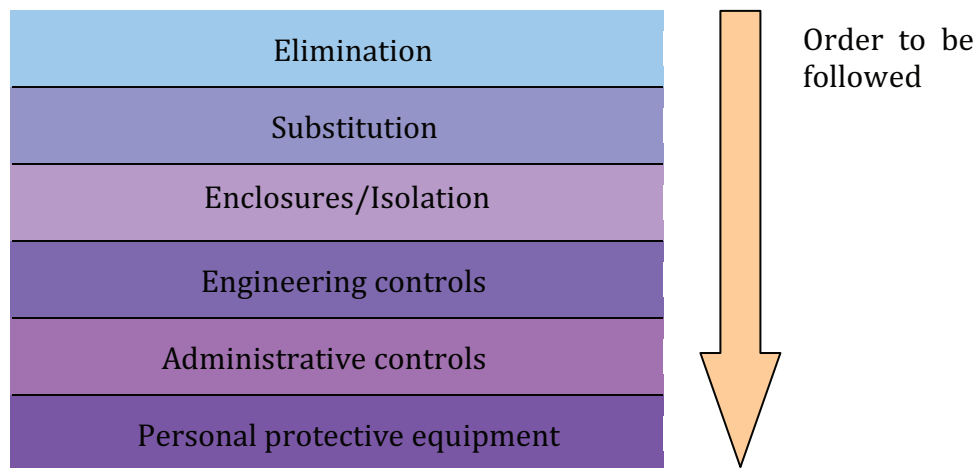


Figure 2 — Hierarchy of control

10.2 Control of exposure

If exposure cannot be prevented, it should be adequately controlled. The hierarchy of control measures as applied to inhalation and dermal risks comprises the following:

- Elimination.** Avoid using the hazardous substance or the process which causes exposure. This is unlikely to be an option if the nanomaterial has been selected for its specific properties. However, consideration should be given as to whether the improved properties of the nanomaterial justify any enhanced risks associated with its use, including to the environment.
- Substitution/modification.** Change the nanomaterial or process to one which has less risk to human health, safety and the environment. Although it might not be possible to substitute that material or modify it without impacting on desired end properties, it might be possible to reduce the likelihood of exposure by, for example, binding powder nanomaterials in liquid or solid media. Dispersions, pastes or pelletized forms should be used instead of powder substances wherever this is technically feasible^[1].
- Enclosures/isolation.** All operations in which there is deliberate release of NOAAs into the air or which involve the likely release of NOAAs into the air should be performed in contained installations, or where personnel are otherwise isolated from the process (e.g. in a cabin). This includes gas phase nanomaterial production and spray drying. All other processes involving the use of dry nanomaterials should be performed in enclosed installations where possible. More information about process enclosure is available^[18].
- Engineering controls.** All processes where there is a likelihood of dust formation should be carried out with extraction ventilation. Many types of extraction ventilation systems are available, including fume cabinets, fume hoods and dust extractors. Selection of appropriate controls will depend on the level of risk. More information about engineering control approaches is available^[18].

Regular maintenance and performance testing of extraction facilities should be carried out. Extracted air should not be re-circulated without exhaust air purification. General ventilation may also be appropriate.

Dermal exposure can be reduced by re-engineering the work process to avoid splashes or immersion.

- Administrative controls.** Procedural controls should accompany engineering controls, though the risk assessment might indicate that procedural controls alone are sufficient in some circumstances. Procedural controls include reducing the number of personnel exposed or the time spent by personnel on the process, limiting the process to specified areas and denying unauthorized persons

access to these areas. The personnel involved should be informed of the specific hazards of free nanoparticles, the need for special measures, and the potential health effects of exposure to dusts. Relevant information in the operating instructions might be included. Routine monitoring should be carried out as needed. The use of medical surveillance should be considered. Recommendations on the use of medical surveillance for workers potentially exposed to NOAAs have been published by NIOSH^[39].

Work wear should be cleaned by the employer and stored separately from private clothing. Cleaning of workplaces should be carried out regularly, in line with risk control plans.

f) **Personal protective equipment (PPE).** Personal protection is a last option or a supplemental option to help support all of the other methods of exposure control.

1) **Protection from inhalation exposure.** Certified respirators have been shown to provide stated level of protection for NOAAs^{[19][20]} and so are likely to form an important element of a control strategy where control of emissions at source is not practical. Information on the selection and use of respirators can be found in various guidance documents, for example the International Classification for Standards (ICS) 13.340^[21]. Appropriate types of RPE include disposable filtering face-pieces, half and full facemasks and a range of powered (air supplied) hoods, helmets, blouses and suits. All wearers of tight fitting respirators (half-mask and full facemasks) should undergo face-piece fit testing to ensure correct fitting and proper wearing^{[22][23]}.

PPE, especially respiratory protection, needs a significant investment in training, supervision and maintenance if it is to provide the intended level of protection. Incorrect selection or fitting or insufficient use can render it ineffective.

2) **Protection from dermal exposure.** The risk assessment might indicate a need for protective gloves, protection goggles with side protection and protective clothing.

Golanski et al.^[24] found that there was no penetration of nanoparticles through a range of glove-types tested (air type material). However, the tested gloves were found to be porous for helium, and the porosity varied with the type of glove. Nanosafe2 notes that this result does not inform about the efficiency of gloves in preventing penetration of nanoparticles from liquid dispersions, and recommend the use of two layers of gloves^[25]. A number of other publications also note that it may be beneficial to use two layers of gloves^[26]. In regard to protective clothing, Golanski et al. report that: "For protective clothing, air-tight fabrics made of non-woven textile seem to be much more efficient to protect workers against nanoparticles than cotton. However these types of protective clothing may be less comfortable to wear".

Simply selecting gloves solely on the basis of glove manufacturers' published data is insufficient in ensuring adequate protection. There are four basic criteria for the selection of protective gloves: they should be appropriate for the risk(s) and conditions where they are to be used; they should be suitable for the ergonomic requirements and state of health of the intended wearer; they should fit the intended wearer correctly; and they should prevent exposure without increasing the overall risk. This assumes that the gloves are worn and maintained correctly.

The development of a glove management system, which emphasizes and reinforces the factors that need to be considered and addressed, how these interlink with each other and when they should be reviewed, should help ensure adequate protection. Packham^[27] emphasizes several of the key elements to be considered in a glove management system, including an assessment of tasks/exposure scenario, glove material selection, ergonomics, training (both managers and workforce), monitoring the system and storage, maintenance and disposal.

10.3 Selection of controls

10.3.1 General

In general, the purpose of applying controls is to ensure that exposure of the workforce is as low as reasonably practicable. In general, it is advisable to adopt a control as high in the control hierarchy as

is technically and economically feasible. However, this needs to be balanced against the level of control required to provide a safe working environment and the efficacy of the control measures. The risk assessment should help to decide the appropriate control, taking account of necessity, practicability and cost. In all cases, selection of controls should as a minimum be based on national regulatory requirements and supplemented with additional controls, as appropriate.

Beyond this, it is difficult to make specific recommendations concerning the control approaches to be used in specific exposure situations. However several generic approaches can be applied which might be helpful.

10.3.2 Hazard-based control

The basis of this approach is to allocate control methods based on knowledge of or assumptions about the hazardous nature of the materials being used. This approach has been used for example by the UK's Health and Safety Executive in their guidance document on "Risk management of carbon nanotubes"[28]. In this document they state that they consider all CNTs as being substances of very high concern and a precautionary approach should be taken to the risk management of all CNTs. They state that if their use cannot be avoided HSE expects a high level of control to be used. This includes a recommendation to "control exposure at source by carrying out all tasks, including packaging for disposal, in a ducted fume cupboard with a HEPA filter, or by using other suitable effective LEV with a HEPA filter. When using other types of LEV, try to enclose the process as much as possible." A similar approach is taken in the United States in the NIOSH document "Approaches to Safe Nanotechnology Managing Health and Safety Concerns with Engineered Nanomaterials"[29].

10.3.3 Control banding

Control banding (CB) is an approach by which control methods are selected based on knowledge or assumptions about the hazardous nature of the materials being used and the exposure potential of the situation. CB has frequently been used in risk management guidance for other particles and chemicals and is usually based on a matrix having the axes exposure and hazard into which various control approaches are placed. CB therefore requires the user to have knowledge of, or make judgments concerning, the relative hazard of the materials being used and/or the relative exposure potential of the material and situation.

Paik et al.[30] have described the development of a pilot control banding tool for NOAAs. ISO/TS 12901-2 describes a specific tool based on control banding to further support the implementation of good practice in this area[31].

10.3.4 "State of the art" approaches

A limited number of studies have been published in the peer-reviewed literature which describe the application and effectiveness of various control approaches for various exposure scenarios. While these studies have not been specifically optimized and are not definitive, they evaluate possible approaches utilizing the state of the art. For the scenarios described, these studies provide an evaluation of control approaches currently in use. Published studies are listed in A.1.

While control approaches in general seem to be effective, there is evidence which indicates the potential for particle release into workplace atmospheres[36]. Use of all control methods should therefore be supported by measurements of exposure or measurements of emissions, wherever possible.

10.4 Evaluation of the effectiveness of control

The effectiveness of control approaches should be assessed. Measurement methods which can be used to carry out this assessment are provided in Clause 11. The purpose of applying controls as part of a precautionary approach, when hazard information is unavailable or when there is limited hazard information, is to ensure that exposure of the workforce is as low as practical. Collection of exposure information associated with the implementation of controls enables demonstration, and documentation, that effective control has been achieved. Methods for the measurement of exposure and emissions are

in Clause 12. Judgements considering whether effective control has been achieved could be made by comparison of measured levels with:

- the prevailing national OEL;
- proposed national or international benchmark levels specifically for types of NOAAs;
- other self-imposed (in-house) exposure limits, considering any proposed margin of safety to take account of known or assumed differences in the toxicity of NOAAs when compared to larger versions of the same material.

The only current example in national guidance of a specific OEL for NOAA, differentiated from larger forms (where such larger forms exist) of the same material is for TiO_2 ^[4] (however some nanomaterials which only exist in the form of agglomerated and aggregated nanoparticles such as carbon black and fumed silica do have specific OELs). General considerations of how size differentiated OELs could be established for NOAAs are described in A.2. An example of this approach is given in A.3 which describes the development of an OEL for nanoscale TiO_2 . Clause A.4 describes a set of pragmatic benchmark exposure levels.

10.5 Information, instruction and training

Arrangements should be put in place to ensure that all control measures are properly and fully applied. Clear allocation of managerial responsibilities and accountabilities is particularly important in this respect. The arrangements should include training/refresh training of those individuals who have to use the control measures and procedures for ensuring measures are working as they should.

Everyone who is involved or could be affected should be provided with the information, instruction and training required to ensure their safety. It is necessary to inform and involve the employees in the risk assessment process. Without the informed and competent participation of employees, any risk management measures identified as necessary in the risk assessment are unlikely to be fully effective. It is therefore necessary that the employees know at least:

- the names of the substances to which they are liable to be exposed and the risks to health created by exposure;
- any relevant OEL or similar self-imposed (in-house) exposure limit that applies to the substances;
- the information on any safety data sheet that relates to the substances;
- the significant findings of the risk assessment;
- the precautions they should take to protect themselves and their fellow employees;
- the results of any monitoring of exposure, especially if these exceed any OEL; and
- the collective results of any health surveillance (see Clause 12).

11 Measurement methods for evaluating controls

11.1 Need for measurement

Clause 11 focuses on measurement of airborne NOAAs. Particle sampling and measurement is often needed to understand exposure and risk in workplace scenarios. Measurement can be used to support various activities, including:

- a) identification of sources of nanomaterial emissions;
- b) assessment of the effectiveness of any control measure implemented;
- c) ensuring compliance with any OEL or self-imposed (in-house) exposure standard;

- d) identifying any failures or deterioration of the control measures which could result in a serious health effect.

Each of these tasks requires specific and often different types of instrumentation. A range of instrumentation is available [see 11.2]. In the workplace, airborne NOAAs will be a combination of primary particles and agglomerates (mainly) and aggregates. The need to detect and measure all these forms is a significant factor in determining an appropriate sampling strategy [see 11.3]. More information about these instruments and particle measurement generally is provided in ISO/TR 27628^[30].

11.2 Selection of instruments

Many instruments are available which could be used to measure airborne NOAAs. New instruments are also being developed. A summary of currently available devices and methods for direct measurement of number, mass and surface area concentration is provided in Table 1, which is an updated version of that found in ISO/TR 27628.

**Table 1 — Devices for direct measurement of number, mass and surface area concentration
(adapted from ISO/TR 27628)**

Measurand	Devices	Remarks
Measured particle number concentration	Condensation particle counter (CPC)	CPCs provide real-time number concentration measurements between their particle diameter detection limits. They operate by condensing vapour onto sampled particles and detecting/counting the droplet formed. Typically used with a 1 000 nm size selective inlet and able to detect down to around 10 nm.
	Differential mobility particle sizer DMPS	Real-time size-selective (mobility diameter) detection of number concentration, giving number-based size distribution.
	Electron microscopy: SEM, TEM	Off-line analysis of electron microscope samples can provide information on size-specific aerosol number concentration.
Measured mass concentration	Size selective static sampler	Assessment of the mass of nano-objects can be achieved using a size-selective personal sampler with a cut-off point of approximately 100 nm and the sample analysed by gravimetric weighing or by chemical analysis. Although there are no commercial devices of this type currently available, some cascade impactors (Berner-type low pressure impactors or Micro-orifice impactors) have selection points around 100 nm and can be used in this way.
	TEOM	Sensitive real-time monitors, such as the TEOM, can be used to measure nano-aerosol mass concentration on-line, with a suitable size-selective inlet.

Table 1 (continued)

Measurand	Devices	Remarks
Measured particle surface area concentration	Diffusion charger	Real-time measurement of aerosol active surface area. Note that active surface area does not scale directly with geometric surface area above 100 nm. Not all commercially available diffusion chargers have a response that scales with particle active surface area below 100 nm. Diffusion chargers are only specific to nano-objects if used with an appropriate inlet pre-separator.
	Electrostatic low pressure impactor ELPI	Real-time size-selective (aerodynamic diameter) detection of active surface area concentration. Note that active surface area does not scale directly with geometric surface-area above 100 nm.
	Electron microscopy: SEM, TEM	Off-line analysis of electron microscope samples can provide information on particle surface area with respect to size. TEM analysis provides direct information on the projected area of collected particles, which could be related to geometric area for some particle shapes.

Currently there is no standard for gravimetric analysis (mass measurement) of particulate forms of nanomaterials; it is recommended to use either the US EPA protocol for PM_{2.5}^[32] or the European protocol^[33] depending on the type of filter selected.

Several of the instruments and methods listed in Table 1 also enable information about particle size to be generated. Table 2 gives methods for deriving indirect estimates of number, mass and surface area concentration using the size information provided, based on assumptions about the interrelationships between these metrics.

**Table 2 — Devices for indirect measurement of number, mass and surface area concentration
(adapted from ISO/TR 27628)**

Metric	Instruments	Remarks
Number by calculation	ELPI	Real-time size-selective (aerodynamic diameter) detection of active surface area concentration, giving aerosol size distribution. Data may be interpreted in terms of number concentration. Size-selected samples may be further analyzed off-line.
Mass by calculation	ELPI	Real-time size-selective (aerodynamic diameter) detection of active surface area concentration giving aerosol size distribution. Mass concentration of aerosols can be calculated, only if particle charge and density are assumed or known. Size-selected samples may be further analyzed off-line.
	DMPS	Real-time size-selective (mobility diameter) detection of number concentration, giving aerosol size distribution. Mass concentration of aerosols can be calculated only if particle shape and density are known or assumed.
Surface area by calculation	DMPS	Real-time size-selective (mobility diameter) detection of number concentration, giving aerosol size distribution. Mass concentration of aerosols can be calculated only if particle shape and density are known or assumed.
	DMPS and ELPI used in parallel	Differences in measured aerodynamic diameter and mobility can be used to infer particle fractal dimension, which can be further used to estimate surface area.

This table shows the most established measurement devices. New devices are continually being developed but often thus far with limited experience of use. Other novel measurement approaches have recently been described by Kuhlbusch et al.^[80]

11.3 Sampling strategy

Currently, there is no single sampling method that can be recommended to be used to characterize exposure to all particulate forms of nanomaterials. Therefore, attempts to characterize workplace exposure to NOAAs usually involve a multifaceted approach incorporating more than one of the sampling techniques mentioned above^[34]. However, an emerging sampling strategy for measuring emissions in workplaces relevant to NOAAs is developing^{[35][36][37]}. This is typically a stepwise process which involves an initial assessment of particle number concentration using a simple device such as CPC (together with an OPC where larger agglomerated forms of NOAAs might be present). Identification of this release in itself may be sufficient to reconsider the control systems and adapt better engineering control measures to more effectively control the release.

If a possible release is identified, this is followed by a more extensive characterization of that release. This can take a number of forms. The NEAT method recommends that a sample is collected on a filter for subsequent off-line analysis by transmission electron microscopy (TEM) and energy dispersive X-ray spectroscopy (TEM-EDX) to analyse the size distribution and chemical composition of the material^[35]. Scanning electron microscopy (SEM) with Energy Dispersive X-ray analysis (EDX) and other chemical analysis methods, such as ICPMS may also be utilized^[35]. This is helpful in determining that the detected materials are related to the source. Other chemical analyses may be utilized provided they have adequate sensitivity to ensure reliable exposure measurements (see 11.4).

These methods continue to be developed and the reader is directed towards the scientific literature for the most current thinking^{[34][37]}.

Alternatively (or in parallel), particularly if there is no access to TEM facilities, more information may be collected on the size distribution, number, mass and surface area concentration using the instruments described above.

The above methods only provide information on emissions. If measuring exposures to specific NOAAs is of interest, personal sampling using filters or grids suitable for analysis by electron microscopy or chemical identification should be employed. Electron microscopy with EDX can be used to identify the particles, and can provide an estimate of the size distribution of the particle of interest. The use of a personal cascade impactor or a respirable cyclone sampler with a filter, though limited, will help to remove larger particles that are of limited interest and allow a more definitive determination of particle size. Analysis of these filters for air contaminants of interest can help identify the source of the respirable particles. Standard analytical chemical methodologies, including gravimetric analysis, should be employed.

By using a combination of these techniques, an assessment of worker exposure to NOAAs can be conducted. This approach will allow a determination of the presence and identification of NOAAs and the characterization of the important aerosol metrics.

11.4 Limitations

Measuring particle number concentration in isolation can be misleading. In all particle number concentration measurements, the integration limits over which a particular instrument operates are critical in understanding the reported results. CPC instruments become increasingly insensitive to particles smaller than 20 nm. Concentrations measured with instruments with different sensitivities might therefore differ substantially, particularly if the particle count median diameter is close to or in this range. In this case instruments will significantly underestimate the nanomaterial aerosol number concentration.

A further complication relates to the ambient airborne particles and the difficulties for the real time instruments discussed have to distinguish between task / process related emissions and background. Unless the workplace is operating under clean room conditions, airborne particles from external sources will enter the workplace and contribute to the levels of NOAAs in the area of the process under investigation. Unless this is considered, it can lead to an overestimation of the levels of NOAAs emitted from the process under investigation. Other nanoparticles, which might be produced in the vicinity of the task / process that is monitored, e.g. from heaters or from electric motors, may also contribute towards overestimation. One way to overcome this problem is to determine ambient or background particle counts prior to the commencement of manufacturing or processing of the NOAAs. Another method is to carry out simultaneous measurement in the "near field" (close to the process/task) and the "far field" (away from the task/process). The far-field should be representative of the background close to the near-field. In some cases, the far-field measurement is outside the workplace. The far field measurement is subtracted from the near-field to provide an estimate of the contribution of the task. This approach assumes that the far-field particles are present in the same size and concentration in the near field which may not always be the case^[38].

A further approach is to utilize differences in composition between NOAAs generated in the workplace and the ambient aerosol for discrimination purposes.

Filter sampling of airborne nanoparticles yields very small particle mass (less than 0,1 mg), and numerous errors are associated with gravimetric analysis of such low-mass samples. Errors caused by static electricity, vibration, and particle contamination should be eliminated, and filters should be conditioned and weighed under strict protocols designed to control effects of humidity and air temperature. For very lightly loaded filters (e.g. particle mass less than 0,05 mg) corrections for changes in air density (known as buoyancy corrections) are recommended^[39].

In the case of lightly loaded filters, the greater sensitivity of inductively-coupled plasma mass spectrometry (compared to optical emission spectroscopy) may be required to ensure that limits of quantification are exceeded. Note that precautions should be taken to avoid contaminating the filter sample with particles or metals while loading and unloading the filter cassette, and throughout all stages of handling and analysis. In the case of lightly loaded filters, the contribution of metals from inadvertent contamination might be greater than the contribution from the particles being sampled^[39]. Examples of precautions include appropriate use of nitrile gloves while handling filters and loading/unloading cassettes in a clean laminar flow hood^[40].

12 Health surveillance

In most jurisdictions, the primary criterion for health surveillance is a reasonable likelihood that an identifiable disease or ill-health effect associated with exposure to a particular substance will occur in the workplace concerned. It is also necessary that there are medically accepted techniques for detecting the disease or ill-health effect.

Currently, no studies in humans have shown associations between exposure to recently developed forms of engineered NOAAs and adverse health effects, but, based on experience with other particles such as crystalline silica and asbestos, it might be expected that there could be a long latency in development of disease associated with such exposure. However, studies in animals have shown adverse effects (e.g. pulmonary inflammation and fibrosis) at lower mass doses than for larger particles of the same chemical composition. This suggests the need to consider whether medical screening tests such as those used to detect occupational respiratory diseases might be appropriate for workers exposed to NOAAs^[41].

In any case, a prudent approach in the current uncertainty is to collect at least some limited information about the materials being used and the duration of use. Such information will help to build up a profile of potential exposures which could be important for future epidemiology studies, should any health effects emerge in the exposed population at a later date.

13 Spillages and accidental releases

Due to the potential for spillages and accidental releases of NOAAs, it is essential that employers have documented policies and procedures in place that are based on adequate pre-planning activities. This documentation should include incidental (small) and emergency (uncontrolled) spills/releases.

It is vital that suitable and sufficient risk assessments are completed to determine the exact course of action to be taken in the event of a nanomaterial spillage or accidental release. The methods used should be consistent with the level of hazard and the quantity of nanomaterial involved in the spill. All clean-ups should be carried out in such a way as to ensure that exposure to personnel is as low as practical. Personnel who might be required to deal with such events should receive adequate information, instruction and training on assessing the extent of any spill/accidental release, the clean-up measures to be taken, and the PPE which should be worn, as well as guidance on the safe disposal of any waste collected during the clean-up.

In the event of a spillage or accidental release, on-site personnel should determine the extent of the area potentially affected and demarcate the area to restrict access by non-essential personnel. Measures should also be put in place to reduce the likelihood of spreading NOAAs from the affected areas, for example the use of adhesive walk-off mats at the affected area's exit points.

In situations where on-site personnel might reasonably be expected to deal with a spillage or accidental release of NOAAs, consideration may be given to the use of wet wiping cleaning methods, barriers to minimize air currents across areas affected by a spillage and tested and certified "HEPA" vacuum cleaner methods for dealing with dry materials or residues from dried liquid spill areas. Dry sweeping should be avoided. When using HEPA filters it is recommended that the effectiveness of these should be verified at a frequency consistent with manufacturers' recommendations and, where possible, dedicated HEPA vacuum cleaners should be used for clean-up operations. It is also good practice to record the type of material collected and avoid mixing potentially incompatible materials in the vacuum cleaner or filters.

Employers need to consider and document which, if any, situations should trigger an evacuation of personnel from an affected area. Consideration should also be given to the severity of spillages and accidental releases which on-site personnel can be expected to deal with and when other agencies, such as the emergency services and environmental protection agencies, need to become involved.

All debris resulting from the clean-up of a spillage or accidental release (including any filters, wipes, absorbent mats and materials) should be considered as nanomaterial-bearing waste. Guidance on the disposal of collected debris and waste is provided in Clause 14.

14 Disposal procedures

14.1 Planning the storage and disposal of nanomaterials

A plan for storage and disposal of NOAAs or NOAAs contaminated waste should be developed, taking account of the hazard profile of the materials and the quantities involved.

When the nanomaterial has a known hazard profile, disposal should be planned in accordance to this profile in line with the relevant jurisdiction.

The waste management guidance given in this clause is based on guidance developed and used by the US Department of Energy (DOE 2007)^[42] and the UK Environment Agency (EA) Guidance for the disposal of hazardous materials (HWR01)^[43], and applies to hazardous or potentially hazardous nanomaterial-bearing waste streams (solid and liquid waste), including:

- pure NOAAs;
- items contaminated with NOAAs, such as containers, wipes and disposable PPE;
- liquid suspensions containing NOAAs; and
- solid matrices with NOAAs that are friable or have a nanostructure loosely attached to the surface such that they can reasonably be expected to break free or leach out when in contact with air, water, or other media when subjected to reasonably foreseeable mechanical forces.

Any material that has come into contact with dispersible engineered NOAAs (that has not been decontaminated) should be considered as belonging to a nanomaterial-bearing waste stream. This includes PPE, wipes, blotters and other disposable laboratory materials used during research activities. Material from hazardous or potentially hazardous nanomaterial-bearing waste streams should not be put into the regular waste or down the drain. Surface contamination should be evaluated and decontaminated. Equipment used to manufacture or handle hazardous or potentially hazardous nanomaterials should be decontaminated before it is disposed of or reused. Wastes (cleaning solutions, rinse waters, rags, disposable PPE) resulting from decontamination should be treated as nanomaterial-bearing waste.

14.2 Storage of nanomaterial waste prior to disposal

The following are appropriate approaches for collection and storage of hazardous or potentially hazardous nanomaterial waste prior to disposal.

- a) **Storage in waste containers.** Package nanomaterial-bearing wastes in compatible containers that are in good condition and afford adequate containment to prevent the escape of the NOAAs. NOAAs or wastes should not be stored in storage silos or other large containers, particularly the more dispersible forms. Cleaning up spills could be very difficult if a large container fails. Label the waste container with a description of the waste and include available information characterizing known and suspected properties.
- b) **Storage in plastic bags.** Paper, wipes, PPE and other items with loose contamination should be collected in a plastic bag or other sealable container stored in the laboratory hood. When the bag is full, it should be closed and carefully placed into a second plastic bag or other sealing container, avoiding outside contamination. It should then be taken out of the hood and the outer bag be labelled with an appropriate waste label.

14.3 Disposal of nanomaterial waste

Disposal of nanomaterial waste should comply with national or regional regulations. Few national authorities have thus far made any specific recommendations regarding disposal of nanomaterial waste. The disposal process should depend on an assessment of the hazard and physicochemical characteristics.

One example in the UK, guidance provided by the Environment Agency (EA), provides a framework for assessing whether a waste material is hazardous and a process by which it can be disposed. EA currently considers, as a precautionary approach, classifying unbound carbon nanotubes as inorganic wastes containing dangerous substances with a threshold level of 0,1 % weight/weight. Their recommendation is that the waste can be rendered safe by incineration by exposure to temperatures above 850° C for at least 2 s or by being treated chemically in such a way as to destroy the nanodimensional structure which renders the material toxic. They consider high temperature incineration at a hazardous waste incinerator as the preferred disposal method. However, this approach will not be suitable for all NOAAs and the potential release of the original and/or transformed nanoparticles should be considered and prevented. Other technologies may be suitable if it can be demonstrated that they render the wastes safe^[44].

15 Prevention of fire and explosion

Prevention of fire and explosion is governed by national regulations. For example, in the UK issues of fire and explosion are covered by the Dangerous Substances and Explosive Atmospheres Regulations (DSEAR)^[12]. The effectiveness of methods for nanoparticle fire, explosion and catalysis prevention and control are yet to be fully evaluated. Potential risks from fire and explosion have been reviewed by the UK's Health and Safety Executive^[45]. Some types of nanoparticle products can be raised from a layer and become airborne more easily than coarser products, and can remain in suspension for a long time. Dense clouds of nanoparticle powder might be difficult to see, even though a suspension of the same product at the same concentration at a coarser grade is easily visible. The same principles applying to the management of fine powders, dusts or dusty materials should be considered for nanoparticles, with particular care taken in the case of easily oxidizable metallic dust. Explosion protection measures have been described for dust dispersions and for hazardous quantities of larger sized materials^[45], and these can be applied to the handling of potentially explosive nanoparticles. For reactive or catalytically active nanoparticles, contact with incompatible substances should be prevented.

Fire prevention has to take into account existing regulations, especially electrical requirements. The design of electrical equipment protection should take account of the fine granulometry and very long settling time of nanoparticles, which necessitate dust protection. In addition, further precautions should be taken to avoid the risk of auto-ignition of NOAAs^[42].

The selection of an extinguishing agent should take account of the compatibility or incompatibility of the nanomaterial with water. Some metallic dusts react with water to form, among other things, hydrogen, which ignites very easily. Chemical powders are available to extinguish burning metallic dust powders, though this has the effect of putting the metallic dust in suspension, thereby increasing the risk of deflagration. To reduce the risks of fire and deflagration, it might prove necessary to use controlled-atmosphere production and storage processes, using carbon dioxide, nitrogen or another inert gas. This could introduce further hazards into the system, notably the risk of asphyxiation.

Anti-static shoes should be worn in areas where the materials are handled to reduce the build-up of static charge, which could potentially ignite the materials.

Annex A (informative)

Control approaches

A.1 State-of-the-art in evaluating exposure control approaches

Only a few studies are available in the literature containing information on the performance of control approaches (enclosure, LEV, fume hood) for NOAA. The following studies have been identified as providing this information and as such represent the current state of the art.

Table A.1 — Evaluation of published exposure control approaches

Material	Process	Control used	Exposure without control	Exposure with control	Relevant bulk OEL	Reference	Comments
Carbon nanotubes (fibrous)	Blending for composites	Enclosure	172,9 f/ml to 193,6 f/ml	0,018 f/ml to 0,05 f/ml		Han [46]	
Zinc oxide (insoluble)	Sol-gel spraying	LEV	225 000 p/cm ³	7 200 p/cm ³ to 12 000 p/cm ³		Mohlmann [47]	
Manganese oxide (insoluble)	Reactor cleanout	LEV	3,6 mg/m ³	0,15 mg/m ³	0,2 mg/m ³	Methner [48]	Re: OEL ACGIH TLV for Mn (respirable)
Cobalt oxide (insoluble)	Reactor cleanout	LEV	0,71 mg/m ³	0,041 mg/m ³	0,05 mg/m ³	Methner [48]	Re: OEL Australian National ES and ACGIH TLV (respirable)
Silver oxide	Reactor cleanout	LEV	6,7 mg/m ³	1,7 mg/m ³	0,1 mg/m ³ (metallic silver, as Ag) 0,01 mg/m ³ (soluble silver compounds, as Ag)	Methner [48]	Re: OEL Australian National ES, UK OEL and ACGIH TLV
Nanomaterial (type not reported – assumed insoluble)	Gas phase manufacturing	Enclosure		0,188 mg/m ³ Steady state with process operating	3 mg/m ³	Demou [49]	Re: OEL Default ACGIH for nuisance dust (respirable)
Nanomaterial (type not reported – assumed insoluble)	Gas phase manufacturing	Enclosure		59 100 particles/cm ³ Steady state with process operating		Demou [49]	Average level over 10-hour shift is approximately 33 000 p/cm ³

Table A.1 (continued)

Material	Process	Control used	Exposure without control	Exposure with control	Relevant bulk OEL	Reference	Comments
Nanomaterial (insoluble and soluble, many types)	Nanoparticle production by flame spray pyrolysis	Fume hood with extraction		0,037 mg/m ³ PM1 (max) differentiated from background	3 mg/m ³	Demou [50]	Re: OEL Default for insoluble. ACGIH for nuisance dust (respirable)
Nanomaterial (insoluble and soluble, many types)	Nanoparticle production by flame spray pyrolysis	Fume hood with extraction		10 000 p/cm ³ p/cm ³ Steady state with process operating		Demou [50]	Maximum increase over background of 103 900 p/cm ³
Nanoalumina	Pouring/transferring of nanomaterial	Fume hood with extraction (various)		1 575 p/cm ³ to –13 260 p/cm ³		Tsai [51]	Breathing zone measurements

A.2 General approaches towards establishing OELs

In occupational settings, protection from toxic effects is achieved by reducing exposures to the toxic substance below established levels, which are intended to protect workers' health up to a full working lifetime. However, feasibility limitations (e.g. in the measurement and control of exposures) might result in OELs associated with some residual risk of health effects in workers. In such cases, additional efforts to protect workers may be needed (e.g. use of PPE, medical screening, as well as research to improve the sampling and analytical methods). Toxicological effects can be broadly characterized as threshold and non-threshold. For the former, it is possible to identify an exposure below which no adverse health effects are observed and for the latter, any exposure results in a non-zero probability of adverse health effect occurrence. However, a threshold assumption is not always reasonable. For example, when a toxicant adds to a response associated with another environmental exposure. Moreover, an average threshold assumption does not take into account the distribution of responses in the human population[52].

For threshold toxicological effects, quantitative determination of "safe" levels includes the following steps:

- determination of a NOAEL or LOAEL;
- extrapolation of animal levels to human levels by adjusting for species-specific differences in adsorption, distribution, metabolism, and elimination (ADME). For inhaled particles, animal-to-human effect level extrapolation takes into account the differences in air intake, deposition efficiency, exposure pattern and duration, and target tissue size (surface area, mass, or volume), as well as clearance; and solubility and metabolism if applicable;
- derivation of occupational exposure limits with consideration of technical feasibility and other factors.

This approach is an example of methods used to estimate exposure limits for non-carcinogens which assume a threshold model. In this case, uncertainty factors are typically applied to the derived exposure limit for humans (often factors of 10 each to account for animal-to-human extrapolation, inter-individual variability, sub-chronic study, and LOAEL if no NOAEL). In addition, the recent National Research Council (NRC) risk assessment guidance[52] advocates the development of risk-specific exposure limits for both carcinogens and non-carcinogens, e.g. by estimating the percentage of the population above or below a defined acceptable risk and the degree of confidence (versus assuming no risk in a population for exposures below a threshold-based exposure limit).

Instead of using a LOAEL or NOAEL, risk-based methods typically fit statistical models to the dose-response data to estimate a benchmark dose (BMD) (which is the maximum likelihood estimate of the

dose associated with a specified level of risk that is in the lower range of the data, e.g. 10 %) and a BMDL (which is the lower 95 % confidence limit of the BMD). A BMDL is typically used as the point of departure to extrapolate to lower risk levels. A BMDL is also sometimes used in place of a NOAEL in applying uncertainty factors to derive an exposure limit^[52].

Toxicological properties of NOAAs can arise from the intrinsic chemical composition of a material as documented for this material in a non-nano scale particulate form. Apart from that, the scientific community is considering whether there is additional toxicity for NOAAs due to the particulate nature and due to unique properties associated with the nanoscale^[53]. Toxicological studies are also being conducted on novel NOAAs such as carbon nanotubes, which do not have bulk analogues^[54].

Multiple toxicological findings have been reported for NOAAs. However, the existing toxicity studies were sometimes conducted with test materials which were not well characterized, mostly due to technological limitations. Thus, for the time being, only a limited amount of representative, validated hazard data from toxicological studies which can be used to develop scientific health-based occupational exposure limits is available. And, it is believed that such exposure limits will be available in the near future for only a few engineered nanoscale materials. One of the very few published examples of risk assessment of NOAAs includes a quantitative risk assessment of ultrafine titanium dioxide, ultrafine carbon black and diesel exhaust particulates^{[55][56]}. The study utilizes available pulmonary inflammation and lung tumour data from subchronic^{[57][58]} and chronic^{[59][60]} inhalation studies in rats. The data were evaluated using various modelling approaches to estimate the risk of disease in workers exposed to fine or ultrafine titanium dioxide for up to a 45-year working lifetime. In another example, a study in mice exposed to single-walled carbon nanotubes by pharyngeal aspiration was used to estimate an equivalent lung dose in humans and the associated workplace airborne concentration^[61]. A mouse lung dose linked to adverse lung effects, including a rapid fibrogenic response, was extrapolated to humans by estimating the fraction of airborne particles that would deposit in the human lungs at a relevant workplace airborne concentration.

The modelling results from dose-response data provide the quantitative basis for developing occupational exposure limits for these NOAAs. Occupational Exposure Limits were defined, in terms of mass concentration for a limited number of nanostructured material in the form of agglomerated and aggregated nanoparticles, such as carbon black^[62], zinc oxide fume^[63], fumed silica^{[64][65]}, and carbon nanotubes/nanofibres^[66].

At this point, given the current paucity of data, hazards based on toxicological properties of NOAAs have not yet been completely assessed. However it is currently considered that:

- the toxicological properties of NOAAs cannot always be predicted from the known toxicity of the substance in macroscopic form alone; and
- for some NOAAs, mass is not an appropriate metric for characterizing exposure and nanomaterial surface area, and number of nanomaterial particles have been proposed as better alternatives.

Thus, occupational exposure limits based on mass, for the equivalent non nanoscale material, might not be an appropriate metric for characterizing exposure across a range of particle sizes; for example, if the toxicity is associated with the particle surface area, or if the exposure level of concern is below the limit of detection by mass^{[56][67]}.

Developing exposure limits in the absence of complete data set for quantitative risk assessment is not novel (e.g. industry-wide and in-house exposure limits have been widely used in the absence of or in addition to existing OELs). It requires joint efforts by industry experts in the area of risk assessment and experts on site-specific hazards and exposures familiar with their product and site-specific work environment.

One proposed approach under development describes how to utilize available information about specific NOAAs to derive in-house OELs using existing limits for bulk forms of the same chemical compound^[14]. A simplified and more qualitative version of this approach was used in a BSI document to produce Benchmark Exposure Limits^[14].

An alternative could be to group NOAAs according to their hazard potential and develop exposure limit ranges or bands^[68]. Such hazard and exposure groupings could facilitate the further development of

techniques utilizing banding to assess and stratify risks to select appropriate risk control techniques for work with NOAAs. One proposed approach develops categories of NOAAs based on a variety of factors, including surface chemistry, particle shape, particle diameter, solubility, carcinogenicity, reproductive toxicity, mutagenicity, dermal toxicity, and toxicity of parent material^[52].

An even higher degree of qualitative analysis of hazard potential is found in performance-based approaches to control exposures, which focus on emission mitigation^[69]. In this approach, air monitoring and wipe test data are used to evaluate the effectiveness of performance-based controls and to detect breaches in a previously validated containment system. The level of monitoring depends on the hazard performance-based exposure control limit (PB-ECL) category.

In developing exposure limits and defining exposure bands, it is important to consider limitations of currently available exposure measurement techniques.

A.3 Development of an occupational exposure limit value for “ultrafine” TiO₂

In the US in 2011, the National Institute for Occupational Safety and Health (NIOSH) published a Current Intelligence Bulletin entitled “Occupational Exposure to Titanium Dioxide”^[4].

Titanium dioxide (TiO₂), an insoluble white powder, is used extensively in many commercial products, including paint, cosmetics, plastics, paper and food, as an anti-caking or whitening agent. It is produced and used in the workplace in varying particle-size fractions, including fine and ultrafine sizes.

The document is based on NIOSH’s rigorous assessment of the most current available scientific information about this widely used material.

The document recommends exposure limits of 2,4 mg/m³ for fine TiO₂ (particles greater than 0,1 micrometers in diameter) and 0,3 mg/m³ for ultrafine particles as time-weighted averages for up to 10 h per day during a 40 h work week. Exposures should be reduced to levels as low as feasible below those recommended limits.

Further analysis of this has recently been reported: the model average estimate of the working lifetime mean concentration of fine titanium dioxide associated with a 1/1 000 excess risk of lung cancer is 9,0 mg/m³, with a 95 % LCL (lower control limit) of 1,6 mg/m³. The corresponding estimate for ultrafine (including engineered) titanium dioxide is 1,10 mg/m³, with a 95 % LCL of 0,19 mg/m³^[70].

The document says that the differences in recommended limits for fine and ultrafine particles reflect findings from studies which suggest that ultrafine TiO₂ particles might be more potent than fine TiO₂ particles at the same mass. This may be due to the fact that the ultrafine particles have a greater surface area than the fine particles at the same mass.

The document concludes that the TiO₂ risk assessment could be used as a reasonable floor for potential toxicity, with the notion that toxicity can be substantially increased by particle treatment and process modification.

With this recommendation, NIOSH removes its current classification of TiO₂ as an occupational carcinogen for fine particles, but maintains its classification of a potential occupational carcinogen for ultrafine TiO₂.

The document states that further research is critically needed in the exposure assessment for workplace exposure to ultrafine TiO₂ in facilities producing or using TiO₂. Further research also is needed on 1) the exposure-response relationships of TiO₂ and other poorly soluble, low toxicity particles and human health effects, 2) the fate of ultrafine particles in the lung and associated pulmonary responses, and 3) the effectiveness of engineering controls for controlling exposures to fine and ultrafine TiO₂ particles.

A.4 Examples of approaches to setting benchmark levels for nano-objects

A.4.1 General

In the absence of specific OELs for many types of NOAAs some focus has been given to setting of benchmark levels to provide pragmatic guidance for those trying to estimate and control exposures. This section elaborates the process in relation to one such approach which has been promulgated in the original version by Institut fuer Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA) in Germany^[71].

A.4.2 Approach for particles

In setting benchmark levels to assess the effectiveness of protective measures, it is crucial to point out that they should not be confused with health-based workplace limit values. There is limited toxicological data to support these benchmark levels.

Any pragmatic proposal for assessment of the effectiveness of protective measures against exposure to NOAAs should take account of the following requirements.

- As a result of missing information on a product, a precautionary approach should be adopted.
- Under no circumstances may a general dust limit value (currently given in mg/m³) be exceeded as an upper limit.
- The proposed recommended bench mark level should permit simple technical monitoring. More far-reaching, complex, imaging study methods cannot be employed in routine operations.

To derive benchmark levels one has to consider the properties of NOAAs.

The OECD's Working Party on Manufactured Nanomaterials has agreed on a prioritized list of nanomaterials which are to be addressed^[72]. For the majority of these materials, Table A.2 shows the calculated particle number concentration, C_{PN} , that corresponds to a mass concentration of 0,1 mg/m³ for spherical particles with diameters, d of 20 nm, 50 nm, and 100 nm. 0,1 mg/m³ is one order of magnitude below the currently used dust limit values.

Table A.2 — Calculated particle number concentration C_{PN} , corresponding to a mass concentration of 0,1 mg/m³, for differently size spherical particles of various nanomaterials

Density ρ (g/cm ³)	Calculated number density of nano-particles of dimension 20 nm C_{PN} , (cm ⁻³)	Calculated number density of nano-particles of dimension 50 nm C_{PN} , (cm ⁻³)	Calculated number density of nano-particles of dimension 100 nm C_{PN} , (cm ⁻³)
1,05	$22,74 \times 10^6$	$1,46 \times 10^6$	$181,90 \times 10^3$
1,35	$17,68 \times 10^6$	$1,13 \times 10^6$	$141,47 \times 10^3$
1,65	$14,47 \times 10^6$	$0,93 \times 10^6$	$115,75 \times 10^3$
4,24	$5,63 \times 10^6$	$0,36 \times 10^6$	$45,40 \times 10^3$
5,61	$4,26 \times 10^6$	$0,27 \times 10^6$	$34,04 \times 10^3$
7,30	$3,27 \times 10^6$	$0,21 \times 10^6$	$26,16 \times 10^3$
7,87	$3,03 \times 10^6$	$0,19 \times 10^6$	$24,26 \times 10^3$
10,49	$2,28 \times 10^6$	$0,15 \times 10^6$	$18,21 \times 10^3$
19,32	$1,24 \times 10^6$	$0,08 \times 10^6$	$9,89 \times 10^3$

Particle number concentration, C_{PN} , is required for attainment of a mass concentration of 0,1 mg/m³ with nanoparticles of the stated size, in nm.