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Nanotechnologies — Health and safety practices in occupational settings

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National foreword

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Nanotechnologies — Health and safety practices in occupational settings

Nanotechnologies — Pratiques de santé et de sécurité en milieux professionnels

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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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

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For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 229, *Nanotechnologies*.

This second edition cancels and replaces the first edition (ISO/TR 12885:2008), which has been technically revised.

The main changes compared to the previous edition are as follows:

— widespread reference to 'nano-objects, and their aggregates and agglomerates greater than 100 nm' ('NOAAs'), in place of alternative terms;

— addition of annexes addressing:

  — primary chemical composition of nanomaterials;

  — nanomaterial-specific animal and cell culture toxicity studies;

  — characteristics of selected instruments and techniques for monitoring nano-aerosol exposure;

  — characteristics of biosafety cabinets;

  — advantages and disadvantages of different types of air-purifying particulate respirators;

— consolidation of bibliographical information.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

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Introduction

The field of nanotechnologies is advancing rapidly and is expected to impact virtually every facet of global industry and society. International standardization on nanotechnologies should contribute to realizing the potential of this technology through economic development, improving the quality of life, and for improving and protecting public health and the environment. One can expect many new manufactured nanomaterials coming to the market and workplace. The introduction of these new materials into the workplace raises questions concerning occupational safety and health. This document assembles useful knowledge on occupational safety and health practices in the context of nanotechnologies. Use of the information in this document could help companies, researchers, workers and other people to prevent potential adverse health and safety consequences during the production, handling, use and disposal of manufactured Nano-Objects, and their Aggregates and Agglomerates greater than 100 nm (NOAAs). This advice is broadly applicable across a range of NOAAs and applications.

This document is based on current information about nanotechnologies, including characterization, health effects, exposure assessments, and control practices. It is expected that this document will be revised and updated and new safety standards will be developed as our knowledge increases and experience is gained in the course of technological advance.

Nanotechnology involves materials at the nanoscale. ISO/TC 229 defines the "nanoscale" to mean size range from approximately 1 nm to 100 nm (ISO/TS 80004-1:2015)[1]. To give a sense of this scale, a human hair is of the order of 10 000 to 100 000 nm, a single red blood cell has a diameter of around 5 000 nm, viruses typically have a maximum dimension of 10 nm to 100 nm and a DNA molecule has a diameter of around 2 nm. The term "nanotechnology" can be misleading since it is not a single technology or scientific discipline. Rather it is a multidisciplinary grouping of physical, chemical, biological, engineering, and electronic processes, materials, applications and concepts in which the defining characteristic is one of size.

The distinctive and often unique properties which are observed with nanomaterials offer the promise of broad advances for a wide range of technologies in fields as diverse as computers, biomedicine, and energy. At this early stage the potential applications of nanomaterials seem to be limited only by the imagination. New companies, often spin outs from university research departments, are being formed and are finding no shortage of investors willing to back their ideas and products. New materials are being discovered or produced and for some, astonishing claims are being made concerning their properties, behaviours and applications.

While much of the current "hype" is highly speculative, there is no doubt that worldwide, governments and major industrial companies are committing significant resources for research into the development of nanometer scale processes, materials and products.

Ordinary materials such as carbon or silicon, when reduced to the nanoscale, often exhibit novel and unexpected characteristics such as extraordinary strength, chemical reactivity, electrical conductivity, or other characteristics that the same material does not possess at the micro or macro-scale. A huge range of nanomaterials have already been produced including nanotubes, nanowires, fullerene derivatives (buckyballs).

A few manufactured nanomaterials were developed already in the 19th and 20th centuries, at a time when the word "nanotechnology" was unknown. Among such nanomaterials are zeolites, catalyst supports such as $MgCl_2$, pigments and active fillers such as carbon black and synthetic amorphous silica. Market size of these commodity materials is well above the billion US dollars or million tons threshold.

Nanotechnologies are gaining in new commercial application. Nanomaterials are currently being used in electronic, magnetic and optoelectronic, biomedical, pharmaceutical, cosmetic, energy, catalytic and materials applications. Areas producing the greatest revenue for nanomaterials are chemical-mechanical polishing, magnetic recording tapes, sunscreens, automotive catalyst supports, electro-conductive coatings and optical fibres.

Among other factors, due to the great variability of physical and chemical properties of nanomaterials, our abilities to accurately predict the impact of some nanomaterials exposures on worker health are

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limited at this time. Similarly, there might be insufficient information about human exposures during work and our abilities to measure nanomaterials in the workplace (or more generally) are limited by current technologies. Overall, there is currently limited knowledge on chronic health effects of nanomaterials. In the case of some nanostructured materials, such as carbon black and synthetic amorphous silica, toxicological and epidemiological data are available.

A subset of nanomaterials, NOAAs are of particular concern in the workplace as they can be dispersed in the air and can represent health risks via inhalation exposures. NOAAs include structures with one, two or three external dimensions in the nanoscale from approximately 1 nm to 100 nm, which might be spheres, fibres, tubes and others as primary structures. NOAAs can consist of individual primary structures in the nanoscale and aggregated or agglomerated structures, including those with sizes larger than 100 nm. An aggregate is comprised of strongly bonded or fused particles (structures). An agglomerate is a collection of weakly bound particles and/or aggregates.

There are many gaps in current science about identifying, characterizing, and evaluating potential occupational exposures in the nanotechnology context. These gaps in our knowledge are best addressed at a multidisciplinary level. Occupational health practitioners and scientists and practitioners in the toxicology field including medical scientists and environmental scientists have vital roles to play in safeguarding health in this fast-moving field. Collaborative studies — ideally with international coordination — are essential in order to provide the critical information required within a reasonable time frame.

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Nanotechnologies — Health and safety practices in occupational settings

1 Scope

This document describes health and safety practices in occupational settings relevant to nanotechnologies. This document focuses on the occupational manufacture and use of manufactured nano-objects, and their aggregates and agglomerates greater than 100 nm (NOAAs). It does not address health and safety issues or practices associated with NOAAs generated by natural processes, hot processes and other standard operations which unintentionally generate NOAAs, or potential consumer exposures or uses, though some of the information in this document can be relevant to those areas.

2 Normative references

There are no normative references in this document.

3 Terms and definitions

For the purposes of this document, the terms and definitions given in the ISO/TS 80004 series apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp/ui

— IEC Electropedia: available at http://www.electropedia.org/

4 Symbols and abbreviated terms

ACGIH	American Conference of Governmental Industrial Hygienists
AIDS	acquired immune deficiency syndrome
APF	assigned protection factor
APR	air-purifying respirator
BEI	biological exposure index
BET	Brunauer-Emmett-Teller
BMD	benchmark dose
BSC	biological safety cabinet
CNF	carbon nanofibre
CNT	carbon nanotube
COSHH	control of substances hazardous to health
CPC	condensation particle counter
DC	diffusion charger

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DEMS	differential electrical mobility sizer
DMAS	differential mobility analysing system
DNA	DNA
DOE	U. S. Department of Energy
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
EPA	U. S. Environmental Protection Agency
GI	gastro-intestinal
GSD	geometric standard deviation
HEI	Health Effects Institute
HEPA	high efficiency particulate air filter
HSE	U. K. Health and Safety Executive
HVAC	heating, ventilation and air conditioning
EHS	environment, health and safety
ELPI®	Electrical Low Pressure Impactor
ICON	International Council on Nanotechnology
ICP-MS	inductively coupled plasma mass spectrometry
ICRP	International Commission on Radiological Protection
ICSC	international chemical safety cards
IDLH	immediately dangerous to life or health
ILSI	International Life Sciences Institute
IRSST	Canadian Institut de recherche Robert-Sauvé en santé et en sécurité du travail
LEV	local exhaust ventilation
LPI	low pressure impactor
MCDA	multi-criteria decision analysis
MMAD	mass median aerodynamic diameter
MPPS	most penetrating particle size
MWCNT	multiwall carbon nanotube
NIOSH	U. S. National Institute for Occupational Safety and Health
NMAM	U. S. NIOSH manual of analytical methods
NOAA	nano-objects, and their aggregates and agglomerates greater than 100 nm
NOAEL	no-observed-adverse-effect Level

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NRV	nano reference value
OSHA	U. S. Occupational Safety and Health Administration
PAPR	powered air-purifying respirator
PPE	personal protective equipment
PTFE	Polytetrafluoroethylene
RDECOM	research, development and engineering command
RPE	respiratory protection equipment
SAR	supplied-air respirator
SCBA	self-contained breathing apparatus
SCENIHR	E. C. Scientific Committee on Emerging and Newly Identified Health Risks
SDS	safety data sheet
SEM	scanning electron microscopy
SOP	standard operating procedures
SPE	skin protective equipment
SWCNT	single-wall carbon nanotube
TEM	transmission electron microscopy
TEOM	Tapered Element Oscillating Microbalance
USACHPPM	U. S. Army Center for Health Promotion and Preventive Medicine

5 Nanomaterials: Description and manufacturing

5.1 Manufactured nanomaterials

Manufactured nanomaterials are nanomaterials intentionally produced to have selected properties or composition[1]. Manufactured nanomaterials encompass nano-objects and nanostructured materials (see Figure 1). The former are defined as discrete piece of materials with one (nanoplate), two (nanofibre) or three external dimensions (nanoparticle) in the nanoscale (i.e. length range approximately from 1 nm and 100 nm)[1][2]. Examples of nanostructured materials are nanocomposites composed of nano-objects embedded in a solid matrix or nano-objects bonded together in simple random assemblies as in aggregates and agglomerates or ordered as in crystals of fullerenes or carbon nanotubes[3]. Discussion in this document focuses primarily on nano-objects and their simple assemblies.

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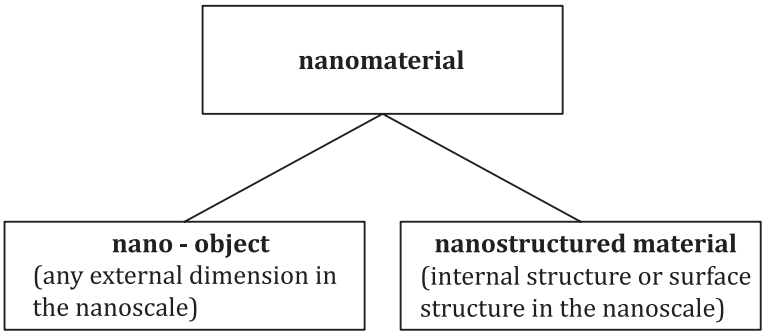


Figure 1 — Nanomaterials framework (Based on ISO/TS 80004-1:2015)[1]

Relatively simple nanomaterials presently in use or under active development can be classified in terms of dimensionality and the primary chemical composition. However, even simple nanomaterials are often coated and have complex chemical and physical structure. Any attempt to classify nanomaterials is highly artificial with many materials falling into several classification categories. Thus, the following description is for organizational purposes only.

Quantum dots and fullerenes are confined to the three-dimensional nanoscale domain. Nanotubes (i.e. hollow nanofibre), nanowires (i.e. electrically conducting or semi-conducting nanofibre), nanorods (i.e. solid nanofibre), other nanofibres and nanofibrils have at least two nanoscale dimensions, while nanoplates such as nanoscale surface coatings, thin films and layers have at least one nanoscale dimension (see Figures 2 and 3). In Annex A, nanomaterials are described according to the primary (or core) chemical composition of nano-objects: carbon nano-objects (e.g. fullerenes, carbon nanotubes); oxide nanomaterials (e.g. TiO_2 and ZnO); metal nanomaterials (e.g. Au); semiconductor nanomaterials (e.g. quantum dots); organic polymeric nanomaterials (e.g. dendrimers); and bio-inspired nanomaterials (e.g. capsid nanoparticles, the protein shell of a virus). Within these classes, different nanomaterials are listed in the order of decreasing necessary number of dimensions in nanoscale from 3D particles to fibres to layers.

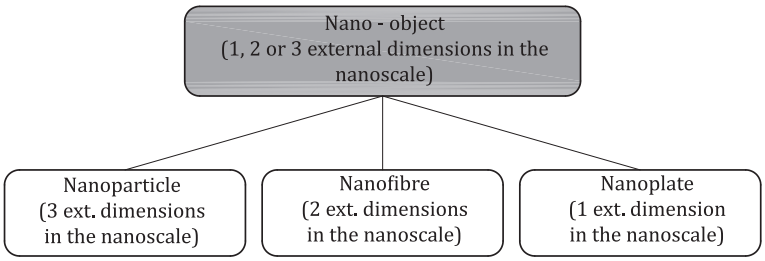
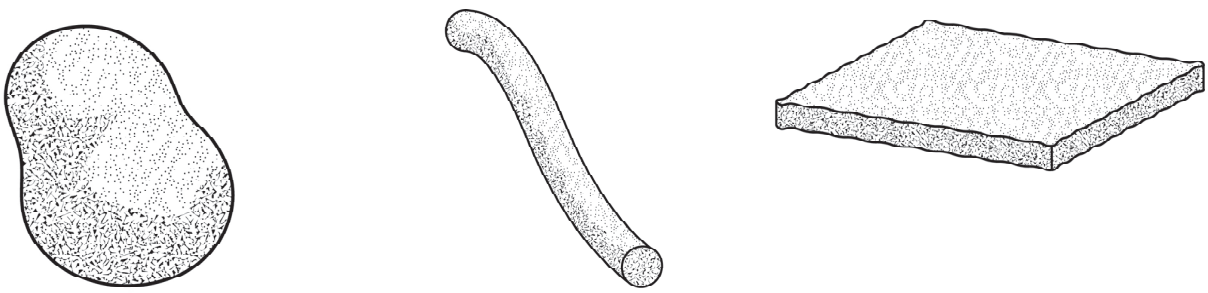


Figure 2 — Fragment of hierarchy of terms related to nano-objects (ISO/TS 80004-2:2015)[2]



a) Nanoparticle (3 external dimensions in the nanoscale) **b) Nanofibre (2 external dimensions in the nanoscale)** **c) Nanoplate (1 external dimension in the nanoscale)**

Figure 3 — Schematic diagrams showing some shapes for nano-objects (ISO/TS 80004-2:2015)[2]

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5.2 Production processes

5.2.1 Typical production processes

Examples of methods typically used for the manufacturing of nanomaterials are:

— aerosol generation such as flame pyrolysis, high temperature evaporation and plasma synthesis;

— vapour deposition;

— liquid phase methods: colloidal, self-assembly, sol-gel;

— electropolymerization and electrodeposition;

— electro-spinning for polymer nanofibre synthesis;

— mechanical processes including grinding, milling and alloying.

5.2.2 Aerosol generation methods

The aerosol generation method is used to produce a wide range of nanomaterials. This method is based on homogeneous nucleation of a supersaturated vapour and subsequent particle growth by condensation, coagulation and capture[4]. The formation of vapour typically occurs within an aerosol reactor at elevated temperatures, where often a super saturate of a solid is cooled into a background of gas. The methods used to produce nanomaterials are usually categorized by the heating or evaporation process and include[5]:

— flame pyrolysis;

— furnace/hot wall reactors;

— laser induced pyrolysis.

5.2.3 Vapor deposition methods

These methods are traditionally based on already well known and established methods for the manufacture of semiconductors. Here, vapour is formed in a reaction chamber by pyrolysis, reduction, oxidation and nitridation. The first step is the deposition of a few atoms. These first atoms form islands which spread and coalesce into a continuous film. Later, growth continues until thicker film develops[5][6]. Examples include[7]:

— physical vapour deposition (i.e. process of depositing a coating by vaporizing and subsequently condensing an element or compound, usually in a high vacuum);

— sputter deposition (i.e. physical vapour deposition technique employing energetic ions to transfer atoms from a target to a substrate);

— chemical vapour deposition (i.e. deposition of a solid material by chemical reaction of a gaseous precursor or mixture of precursors, commonly initiated by heat on a substrate).

These methods have been used to produce nanofilms including TiO_2, ZnO and SiC[5]. Vapour deposition processes mediated by a catalyst are used to produce carbon nanotubes commercially. Chemical vapour deposition emerged as an efficient graphene and synthetic diamond production method[8].

5.2.4 Colloidal/self-assembly methods

Self-assembly is defined as the autonomous action by which components organize themselves into patterns or structures[7]. The colloidal methods are also well established conventional wet chemistry precipitation processes in which solutions of different ions at required concentrations are mixed under controlled conditions of temperature and pressure which form insoluble precipitates[5].

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Recently, a rapidly expanding sub-set of colloidal methods is the so-called sonochemistry method, which uses acoustic cavitation to control the process[9]. Cost-effective, eco-friendly, energy efficient, and nontoxic methods of producing nanomaterials using diverse biological entities have been receiving increasing attention in the last two decades in contrast to physical and chemical methods that use toxic solvents, generate unwanted by-products, and high energy consumption[10].

5.2.5 Electrodeposition

Electrodeposition is the deposition of material onto an electrode surface from ions in solution due to electrochemical reduction[7]. Polymer nanofibre and metal nanowire films as well as nanoparticle films can be fabricated on an substrate through a controlled electropolymerization (polymers) or electrodeposition (metals) process[11][12].

5.2.6 Electrospinning

Electrospinning is the use of electrical charge to induce drawing of very fine fibres from a liquid[7]. Electro-spinning method is a major method in the manufacture of polymer nanofibres.

5.2.7 Attrition methods

In attrition methods, size reduction is accomplished by grinding and milling and production of materials such as clay, coal, some metals and semiconductors have been made[13]. Production rates in the order of tons per hour can be obtained using these methods.

6 Hazard characterization

6.1 Health effects

6.1.1 General

The potential health risk of a substance is generally associated with the magnitude and duration of the exposure, the persistence of the material in the body, the inherent toxicity of the material, and the susceptibility or health status of the exposed person. Since hazard properties of some manufactured nanomaterials are not well characterized, there are uncertainties as to whether the unique properties of these nanomaterials also pose unique health risks. These uncertainties arise because of gaps in knowledge about the factors that are essential for evaluating health risks (e.g. routes of exposure, translocation of materials once they enter the body, and interaction of the materials with the body's biological systems). An important issue is whether the nanoscale version of a particular material poses risks that are significantly different in type or intensity than the micrometer-scale forms of the same material.

Results of existing studies in cell cultures (*in vitro*), animals (*in vivo*) or humans (epidemiological) on exposure and response to nanoscale or other respirable particles[14][15][16][17], as well as available toxicity information about a given material in microscopic form, provide a basis for preliminary estimates of the possible health effects from exposures to similar engineered materials on a nanoscale. However, it should be recognized that there are significant uncertainties and variables associated with predicting human health effects based on animal studies. Presently, *in vitro* cell culture methods are used mostly to delineate mechanisms of toxicity, and to screen and compare relative toxicities. There are only a limited number of *in vitro* assays validated for determination of safety of chemicals, which is, so far, mainly restricted to hazard identification (e.g. embryotoxicity, irritation testing).

NOTE Information on validated alternative methods for animal experiments can be found at for example: European Union Reference Laboratory for Alternative to Animal Testing (EURL-ECVAM)[18]; Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) of the National Toxicology Program, USA[19]; Japanese Center for the Validation of Alternative Methods (JACVAM)[20].

In general, these *in vitro* data cannot be extrapolated to humans without additional information (e.g. *in vivo* data). Initial experimental studies in animals have shown that the biological response (whether

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beneficial or detrimental) to certain incidental or manufactured NOAAs can be greater than that of the same mass of larger particles of similar chemical composition[21][22][23][24][25][26][27][28]. However, the dose expressed as mass might not be the best descriptor for the toxic effect observed. For lung inflammation induced by nano-TiO_2 and nanosilver the dose described as total surface area was a better dose descriptor than mass[29][30]. In addition to particle size, other particle characteristics might influence the biological response, including solubility, shape and aspect ratio, charge and surface chemistry (corona formation — proteins and lipids), catalytic properties, adsorbed pollutants (e.g. heavy metals or endotoxins), photoreactivity, as well as degree of agglomeration[29][31][32][33]. Often nano-object surfaces are intentionally modified with coatings or functionalized in order to prevent agglomeration of particles and to achieve desired properties, e.g. pharmacological activity. Such modifications, as well as the contamination of particle surfaces with impurities can lead to changes in biological responses. In addition, some nanomaterials are produced using rather toxic intermediates and/or solvents. So, when evaluating NOAA toxicity it should always be considered whether the solution used for NOAA dispersion and/or production residues present as contaminants might be responsible for the observed toxicity. In Annex B some further animal and cell culture studies upon NOAA are discussed in detail.

Recently OECD WPMN published the dossiers resulting from the nanomaterial safety testing sponsorship programme. In the dossiers, mainly animal testing results obtained by applying OECD test guidelines were collected and some *in vitro* genotoxicity studies were also included in the dossiers. Therefore, in Annex B, the results on the dossiers were summarized and readers of this TR can go into the dossier site[34] and look for detailed results.

Recent studies on histopathology show the occurrence of engineered and incidental nanoparticles inside pathological lesions in organs (such as liver, kidney, pancreas, bladder, brain affected by a few forms of cancer)[35][36] and their possible linkage to fetal malformations and miscarriages[37][38]. The authors suggest that these nanoparticles might have caused the harm.

6.1.2 Basic principles and uncertainties

The existing literature on particles and fibres provides a scientific basis from which to evaluate the potential hazards of manufactured NOAAs. While the properties of manufactured NOAAs can vary widely, the basic physicochemical and toxicokinetic principles learned from the existing studies are relevant to understanding the potential toxicity of NOAAs. For example, it is known from studies in humans that a greater proportion of inhaled nano-objects will deposit in the alveolar region of the respiratory tract (both at rest and with exercise) compared to larger particles[39][40]. In addition to the International Commission on Radiological Protection (ICRP) model[39], the Multiple Path Particle Dosimetry (MPPD) model can be used for modelling deposition in human and animal respiratory tract[41]. However, it has to be realized that nano-objects might agglomerate and that these agglomerates can deposit in other areas of the respiratory tract or possibly cannot be inhaled at all. Further, animal studies indicate that nano-objects after initial exposure can be translocated to other organs in the body, although it is not well known how this might be influenced by the chemical and physical properties of the nano-objects[42][43][44][45][46]. Additional uncertainties are introduced by the difficulties in predicting human health effects based on animal studies. There might also be the potential for greater dermal and gastro-intestinal uptake of NOAAs when compared to larger particles, although in general uptake from the GI-tract of nano-objects was found to be relatively low[47][48][49][50]. Evidence from nanotoxicological studies (*in vitro* and animal studies) suggests that exposure to some NOAAs might have the potential to cause cell, tissue, or systemic toxicity. Due to their small size, nano-objects have the potential to cross cell membranes and interact with subcellular structures, such as mitochondria and the nucleus (and some nano-objects have been shown to cause oxidative damage and impair some function of cells in culture)[51][52]. Animal studies have indicated that some NOAAs are more biologically active due to their greater surface area per mass compared with larger-sized particles of the same chemistry when dose response relationships are expressed as mass[21][22][23][24][25][26][27][28][29][30]. The greater surface area per mass of NOAAs compared to larger particles is a fundamental contributor to the greater chemical reactivity and utility of nano-objects for industrial, commercial, and medical applications, but it also raises concern about the potential for adverse health effects in workers exposed to NOAAs. NOAAs that are able to shed ions and/or slowly dissolve, e.g. Ag-NP, nano-ZnO, nano-CuO, can have toxicity mechanism similar to the ionic form of these materials.

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6.1.3 Potential relevance of health effects information about incidental or naturally-occurring NOAAs

While there is limited information on the health effects of manufactured NOAAs, there is a larger body of research on the health effects of incidental NOAAs (e.g. diesel exhaust particulate[53][54] and welding fumes[55]). The biological mechanisms of particle-related lung responses (e.g. oxidative stress, inflammation, and production of cytokines, chemokines, and cell growth factors) appear to be a consistent lung response to incidental respirable, including nanoscale, particles[29][56][57]. However, contaminants present such as transition metals[58] might also contribute to the lung response[59]. Although the composition and thus the physicochemical characteristics of incidental and manufactured NOAAs can differ substantially, the toxicological and dosimetric principles derived from studies of incidental NOAAs might be relevant to assessing the health effects of manufactured NOAAs especially for respiratory exposure which is considered to pose the highest risk.

There is a very large body of research on the health effects of certain respirable fibres. For example, it is well established that particular forms of asbestos are causative factors in otherwise rare, occupationally-derived, malignant mesotheliomas[60] and other lung disorders (including pulmonary interstitial fibrosis, pleural plaques, calcification and thickening)[61]. The harmful effects of fibres are driven by three important factors: length, diameter and persistence[62][63][64][65]. It is difficult to draw conclusions regarding the health effects of manufactured nanoscale fibres based on asbestos studies, but they suggest that particle properties of size, shape and composition are important factors influencing the toxicity of NOAAs. For some CNT and structures of CNTs with characteristics similar to blue asbestos (long fibres, rigidity, persistence) granulomatous inflammation and mesothelioma induction was observed[66][67][68]. In contrast, for CNT lacking these characteristics such reactions were not reported[69]. The International Agency for Research on Cancer (IARC) has recently classified multiwall carbon nanotubes (MWCNTs) other than MCWCNT-7 and MCWCNT-7 as Group 3 and Group 2B respectively (for additional details see B.1.2.1). There have been shorter-term studies of the effects of single-wall carbon nanotubes (SWCNTs)[70][71] and multiwall carbon nanotubes[72] in the lungs of rats and mice (administered by intratracheal instillation or pharyngeal aspiration). These studies have shown unusual inflammatory and fibrogenic reactions in the lungs, including transient inflammation followed by early onset of fibrosis at mass doses lower than those causing fibrosis from quartz or carbon black[70][71].

6.1.4 Relationship between toxicity and surface area, surface chemistry, and particle number

To the extent that NOAAs might pose increased hazards, the most significant factors might relate to the greater number or surface area of NOAAs compared with that for the same mass concentration of larger particles. This hypothesis is based primarily on the pulmonary effects observed in studies of rodents exposed to various types of poorly soluble nanostructured materials in the form of agglomerated and aggregated nano-objects or larger respirable particles (e.g. titanium dioxide, carbon black, barium sulfate, diesel soot, coal fly ash, and toner). These studies found that for a given mass of particles, poorly soluble nanostructured materials in the form of agglomerated and aggregated nano-objects produced greater observable effect than larger particles of similar chemical composition and surface properties. Dose-response relationships obtained in animal studies for poorly-soluble and low toxicity particles appear consistent across particle sizes when dose is expressed as particle surface area[21][22][23][24][25][26][27][28][29][30][73][74][75][76][77]. The mechanisms by which these materials exhibit higher levels of toxicity at smaller particle sizes (on a mass basis) appear to involve pulmonary inflammation, oxidative stress, and tissue injury[29][56][57]. The biological activity of particles is affected by their number and their physical and chemical properties, including size, surface area, solubility, shape, crystal structure, charge, catalytic activity and chemistry[21][22][23][24][25][29][31][78][79][80][81]. It should be considered whether a dose expressed as mass, although convenient when using NOAAs in experiments, is the proper metric to express dose response relationships for NOAAs. For several toxicological end points other dose metrics e.g. volume, surface area and/or number was found to better express the dose response relationship[29][30][82].

Through engineering, the properties of nanomaterials can be modified. For example, recent *in vitro* studies have shown that the *in vitro* cytotoxicity of fullerenes (measured as cell death) and carbon nanotubes can be reduced by several orders of magnitude by modifying the surface chemistry of the fullerene molecules and carbon nanotubes (e.g. by hydroxylation)[83][84]. Cytotoxicity studies *in vitro*

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with quantum dots have shown that the type of surface coating can have a significant effect on cell motility and viability[85][86][87].

6.1.5 Inflammatory response to NOAAs

A variety of NOAAs ranging from carbon-based combustion products to transition metals, having entered tissues and cells, can elicit generalized inflammatory and acute phase responses which incorporate the release of signalling molecules such as chemokines, cytokines, C-reactive protein and fibrinogen (a coagulant)[88][89][90][91][92][93][94]. In addition, macrophage and neutrophil activation is also associated with the production of reactive oxygen species. Macrophages are the well-known surveillance cells in the tissues which react with particulate matters, including NOAAs to produce these biological responses. Exposure to different NOAAs has been found to modulate, in different ways, the defence/inflammatory capacities of macrophages[95]. In response to cytokines and chemokines, plasma proteins and neutrophils migrate from the blood to start inflammation. One of the roles of neutrophils in the inflammation is to destroy foreign bodies by proteolysis as well as reactive oxygen species. However, the excess or prolonged defence reactions against foreign bodies by these cells damage the tissues, too. When the process of macrophage ingestion and (attempted) proteolytic breakdown go awry or when nanoscale particles become internalized in non-immune-related cell types (e.g. parenchymal cells), intracellular molecular defenses are initiated which result in the new expression of protective genes. When these protective mechanisms (e.g. antioxidants) are depleted, tissue injury and disease might occur[57][96]. Several broad intracellular protective responses are known, from cell culture and animal studies, to be induced by the exposure to particulate/fibrous materials (carbon black, carbon nanotubes, ambient air particles, and nanostructured titania): the pro-inflammatory cytokines and relevant genes; the antioxidant-response element-inducible genes and proteins; and the stress (or "heat shock") response proteins[88][89][90][91][92][93][94]. Consequently, effects such as persistent inflammatory responses and gene inductions are likely to represent precursors of downstream pathological conditions. It is important to note that contaminants, such as metal catalysts or bacterial endotoxins (lipopolysaccharides), contributed to the induction of inflammatory responses observed in experimental toxicological studies of NOAAs. Specifically, the unpurified single-wall carbon nanotubes which contained more than 20 % by weight of iron induced stronger pulmonary inflammation than purified counterparts[58]; and the conventional formulations of gold NOAAs which contained significant amounts of endotoxins stimulated immune cells *in vitro,* and the improvement of formulation process, which diminished the endotoxin contamination, also effectively reduced the biological responses[97].

6.1.6 Observations from epidemiological studies involving fine and nanoscale particles

Initial epidemiological studies in workers exposed to aerosols, including incidental fine and nanoscale particles, have reported lung function decrements, adverse respiratory symptoms, chronic obstructive pulmonary disease, and fibrosis[14][15][16][17][55][98][99]. In addition, some studies have found elevated lung cancer among workers exposed to certain incidental nanoscale particles, e.g. diesel exhaust particulate[53][54] and welding fumes[55]. Human case studies have reported pulmonary oedema in workers exposed to polytetrafluoroethylene (PTFE) fume and an accidental death in a worker when an equipment malfunction caused overheating of the PTFE resin and release of the PTFE pyrolysis products in the workplace[100][101]. The implications of these studies for manufactured NOAAs, which might have different particle properties, are uncertain.

Epidemiological studies in the general population have shown associations between particulate air pollution and increased morbidity and mortality from respiratory and cardiovascular diseases[102][103][104][105]. Some epidemiological studies have shown adverse health effects associated with exposure to the incidental nanoscale particulate fraction of air pollution[106][107][108][109][110], although uncertainty exists about the role of incidental nanoscale particles relative to the other air pollutants in causing the observed adverse health effects. The associations in these studies have been based on measurements of the particle number or mass concentrations of particles within certain size fractions (e.g. PM2.5). In an experimental study of healthy and asthmatic subjects inhaling nanoscale carbon particles, changes were observed in the expression of adhesion molecules by blood leukocytes, which might relate to possible cardiovascular effects of incidental nanoscale particle exposure[111]. Controlled clinical studies in the laboratory have shown deposition of incidental nanoscale dusts throughout the pulmonary tree, accompanied by cardiovascular problems[29][112][113][114]. For diesel exhaust

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inhalation adverse vascular effects were attributed to the combustion derived nanoparticulates as demonstrated in a human volunteer study[115]. In addition, reducing personal exposure to air pollution using a highly efficient face mask appeared to reduce symptoms and improve a range of cardiovascular health measures in patients with coronary heart disease[116]. So, a link between inhalation exposure to incidental nanoscale particles and cardiovascular disease is likely.

Epidemiological studies aimed specifically at manufactured NOAAs have been performed only for TiO_2[28] and carbon black[15][16][17]. For both nanomaterials, epidemiologic studies found increase of lung cancer among workers, but did not find association with cumulative exposures to these nanomaterials. A recent 2016 meta-analysis did not find that carbon black exposure increases cardiac disease mortality[117]. The extrapolation of the findings associated with air pollution and particulates generally (which might include incidental nanoscale particles) to other manufactured NOAAs is uncertain. However, the potential risks from exposure to nanomaterials, including occupational exposure, should be considered.

6.2 Physical hazards

6.2.1 Fire (exothermic events)

Nanoscale combustible material might present a higher risk than coarser material of similar quantity due to exothermic events arising from catalytic reactions or due to a lowering of minimum ignition temperatures[118]. Decreasing the particle size of combustible materials can reduce minimum ignition energy and increase combustion rate, leading to the possibility of relatively inert materials becoming combustible. Dispersions of combustible nanomaterials in air might present a greater safety risk than dispersions of micro- and macro-materials with similar compositions. Dust explosiveness, minimum ignition energy and ignition temperature are typical means of characterizing safety relevant aspects of dusts[119].

Nano-objects and nanostructured porous materials have been used for many years as effective catalysts for increasing the rate of reactions or decreasing the necessary temperature for reactions to occur in liquids and gases. Depending on their composition and structure, some nanomaterials might initiate catalytic reactions and increase their fire and explosion potential that would not otherwise be anticipated from their chemical composition alone[120].

Additionally, some nanomaterials are designed to generate heat through the progression of reactions at the nanoscale. Such materials might present a fire hazard that is unique to manufactured NOAAs. The greater activity of NOAAs forms a basis for research into nanoenergetics. For instance, nanoscale Al/MoO_3 thermites ignite more than 300 times faster than corresponding micrometer-scale material[121].

6.2.2 Safety consideration in manufacturing NOAAs

The manufacture of NOAAs, as with any other novel materials, can be either on a small pilot scale, including research and development activities, or full scale. Presently, nanomaterial manufacturing can include several high-energy processes, such as flame pyrolysis, laser induced pyrolysis, laser vaporization, thermal plasma, microwave plasma, sputtering, and laser ablation, which present specific safety issues. Typical safety hazards in these processes include handling of high pressure cylinders, low pressure apparatus, inert and toxic gases, high temperature objects, operation of high electrical currents, electromagnetic radiation emitting devices, and high intensity light sources (including ultraviolet, infrared, and visible light) and lasers. Working under such hazardous conditions requires implementing appropriate work practices or following respective laboratory safety guidelines.

7 Exposure assessment to nanomaterials

7.1 General

This clause concerns the assessment of the exposure of workers as a result of the manufacture, handling and use of manufactured nano-objects and their agglomerates and aggregates (NOAAs). Occupational

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exposures to manufactured NOAAs can occur in a range of workplaces including construction, health care, energy, manufacturing and the chemical industry. New manufactured NOAAs are being developed and introduced into the workplace. One estimate has 400 000 workers worldwide employed in the field of nanotechnology[122]. The scientific framework for exposure assessment is discussed with a consideration of the routes of exposure and the most appropriate measurement metric to be used. This is followed by a summary of the instrumentation currently available and a discussion of possible sampling strategies.

Protecting workers' health involves minimizing occupational exposures to hazardous substances. At this time, there is insufficient information to determine specific occupational exposure limits (OELs) and/or reference values for many manufactured NOAAs[123][124][125]. However, first attempts have been made to propose occupational limit values which could be used in regulations. For example, provisional nano reference values (NRVs) have been developed in the Netherlands as pragmatic benchmark levels for different categories of nanomaterials[126][127][128][129]. Although NRVs are not health-based OELs, the Social and Economic Council of the Netherlands (SER) recommended their utilization as indicative guidance levels for exposure assessment until health-based OELs would become available. Some organizations have proposed OELs for selected manufactured NOAAs (see Clause 8 and Reference [130]). In addition, there are regulatory OELs for some traditional manufactured nanomaterials such as carbon black and synthetic amorphous silica.

Besides using these provisional OELs in assessing exposures, other approaches that are being used for exposure assessments include:

(1) Nanomaterial emission assessment approach: The nanomaterial emission assessment approach guides users in determining if there is a potential for exposure from such emissions. The nanomaterial emission assessment approach emphasizes identifying potential emission source(s) (i.e. area or workstation monitoring) and might not directly assess personal exposures. Upon determining the extent of emissions in the workplace, a control strategy (which might include the use of a control banding model) can be developed and implemented to minimize occupational exposures to manufactured NOAAs until there is sufficient scientific evidence to set an appropriate OEL on specific manufactured NOAAs in use. For example, OECD Safety of Manufactured Nanomaterials – No. 11 has suggested an (manufactured NOAAs) particle count level of 10 % above background levels[131].

(2) Tiered approach for exposure assessment: The tiered approach for exposure assessment is a formal methodology for conducting occupational exposure assessments and measurements of aerosols containing manufactured NOAA in work processes (see also 7.3.2). The tiered approach commonly contains three hierarchical tiers. Tier 1 focuses on data gathering prior to workplace assessment to identify possible sources of exposure. Exposure evaluation as part of the Control Banding approach (ISO/TS 12901-2:2014)[132] could be used in Tier 1. Tier 2 includes measurements and assessment of the workstation/breathing zone air and comparing it to the 'background'. Only if Tier 2 reveals a significantly increased particle number concentration, mass concentration or positive detection by electron microscopy or chemical analysis in the workplace, should Tier 3 comprehensive measurements be necessary (see, for example, Reference [133]).

Regardless of the approach used, measuring background levels is critical. One suggestion for the maximum background level to be used for monitoring purposes is three times the standard deviation of background particle number concentrations[124]. Further information on issues related to identifying and quantifying background can be found in review articles[124][134][135][136].

In one example, Genaidy et al.[137] conducted a detailed risk analysis of a CNF manufacturing process and suggested the following potential sources of workplace exposure to NOAAs:

— leakage and spillage from reactors and powder processing equipment;

— manually harvesting product from reactors;

— discharging product into containers;

— transporting containers of intermediate products to the next process;

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— loading the powders into processing equipment;

— weighing out powder for shipment;

— packaging material for shipment;

— storing material between operations;

— cleaning equipment to remove debris stuck to side walls;

— changing filters on dust collection systems and vacuum cleaners;

— further processing of products containing NOAAs (e.g. cutting, grinding, drilling).

This detailed analysis identifies common processes that can lead to worker exposure to NOAAs.

7.2 Scientific framework for assessing exposure to nanomaterials

7.2.1 Routes of exposure

There are four main routes by which workers can be exposed to nanomaterials:

a) inhalation;

b) ingestion;

c) skin contact;

d) injection/parenteral route[29].

Inhalation. As with most particles in the workplace, inhalation is considered to be the primary route by which nanomaterials in the form of free, unbound, airborne particles (e.g. nano-objects and their agglomerates and aggregates) will enter the bodies of workers. Once inhaled, nanomaterials will deposit in the respiratory tract regions, depending upon their particle size. Specifically, nanoparticles will deposit in all regions of the respiratory tract. Figure 4 shows the fractional deposition of inhaled nanoparticles in the nasopharyngeal, tracheobronchial and alveolar regions of the human respiratory tract for nasal breathing, using the predictive mathematical model of the ICRP[138]. According to the ICRP model, 80 % of the 1 nm particles are deposited in the nasopharyngeal region, with 20 % in the tracheobronchial region and less than 1 % in the alveolar region. For 20 nm particles, however, 50 % deposit in the alveolar region and 25 % in the nasopharyngeal and tracheobronchial regions.

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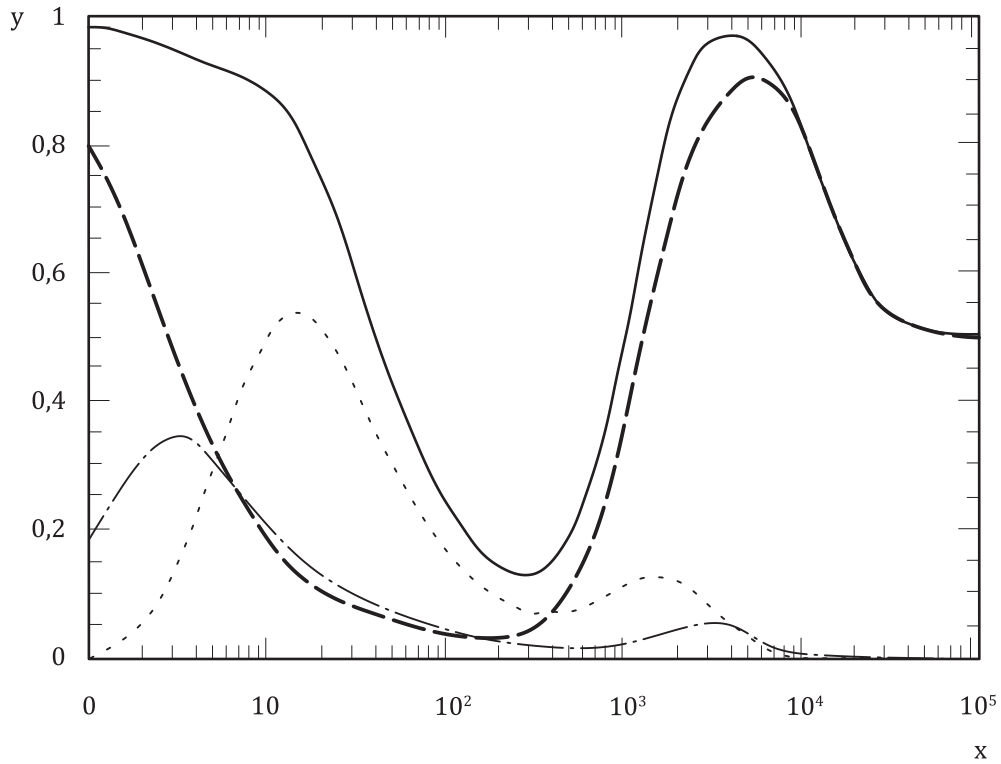

Key

x particle diameter (nm)

y deposition probability

——— total deposition

— — — — head region

—·—·— tracheobronchial

- - - - - - - - alveolar

Note Deposition Fraction includes the probability of particles being inhaled (inhalability). The subject is considered to be a nose breather, performing standard work.

Figure 4 — Predicted total and regional deposition of particles in the human respiratory tract related to particle size using ICRP 66 model[138]

Depending on the physicochemical characteristics of the inhaled manufactured NOAAs, the respiratory system can be considered to be a pathway for inhaled substances to reach other organs that are distant from the lungs[139]. Nano-objects have been reported to translocate to different organs in the body after penetrating the cell epithelium and entering the blood or lymph systems (see 6.1.2 and Annex B). Even after inhalation a major part of the inhaled particles are taken up by alveolar and lung macrophages that are subsequently cleared by the mucociliary cascade and will end in the GI-tract.

Ingestion. In the workplace, NOAAs could be ingested by swallowing the mucous that traps and clears particles deposited in the airways; by ingestion of contaminated food or water; or by oral contact with contaminated surfaces or hand. Only a few studies have been carried out to investigate the uptake and deposition of NOAAs to the GI tract[29]. In general uptake from the GI-tract of objects was found to be relatively low[47][48][49][50]. It was found that

1) NOAAs can directly affect nutrients absorption through disruption of microvilli or alteration in expression of nutrient transporter genes;

2) food components directly might affect NOAAs absorption through physicochemical modification;

3) the presence of food components might affect oxidative stress induced by NOAAs[140].

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Skin contact. In the workplace, skin might be exposed to NOAAs during their manufacture or use or by contact with contaminated surfaces. It is still under discussion if and to what extent NOAAs in general are able to penetrate the intact skin, which, depending on the nanomaterial, might cause adverse effects[141][142]. Most of the reported work has been carried out with individual materials, such as TiO_2 and ZnO, on intact skin. A limited number of studies explored the effects of flexing the skin, skin damage and nanoparticle surface functionalities on skin penetration by nanoparticles[143][144][145][146]. The role of solvents and normal force applied to the skin in dermal uptake of NOAAs in the occupational setting is also yet to be fully explored. Ocular route might be another important route of exposure requiring additional studies.

Injection/parenteral route. Exposure through parenteral route can occur in the workplace primarily due to accidents such as needle-stick injuries. Workers who could be at risk from needle-stick injuries include, but are not limited to, those in workplaces in the health care sector, law enforcement and the construction industry. Manufactured NOAAs have potential applications as drug delivery systems and in medical diagnostic procedures involving injections[147]. Consequently, workers could be at risk of accidental injections of such manufactured NOAAs. Once the worker's skin is broken, punctured or scratched by needles or other sharp objects, manufactured NOAAs can enter the bloodstream and hence can translocate throughout the body.

7.2.2 Metric for assessing exposure to airborne nanomaterials

The traditional method of assessing worker exposure to airborne particles in workplaces involves the measurement of the mass concentration of health-related fractions of particles in the worker's breathing zone (ISO 7708:1995)[14] and their chemical composition. The health-related aerosol fractions relate to the probability of penetration of airborne particles to the various anatomical regions of the respiratory system and provide a specification for the performance of sampling instruments (see Figure 5). The inhalable convention is the fraction of total airborne particles that enters the nose or mouth during breathing, The thoracic convention is the fraction of inhaled particles that penetrate the respiratory tract beyond the larynx, with 50 % penetration at an aerodynamic equivalent diameter (AED) of 11,64 µm (equivalent to 10 µm when expressed as a fraction of total aerosol) and the respirable convention is the fraction of inhaled particles that penetrate to the alveolar region of the lung, with 50 % penetration at AED 4,25 µm (equivalent to 4 µm when expressed as a fraction of total aerosol).

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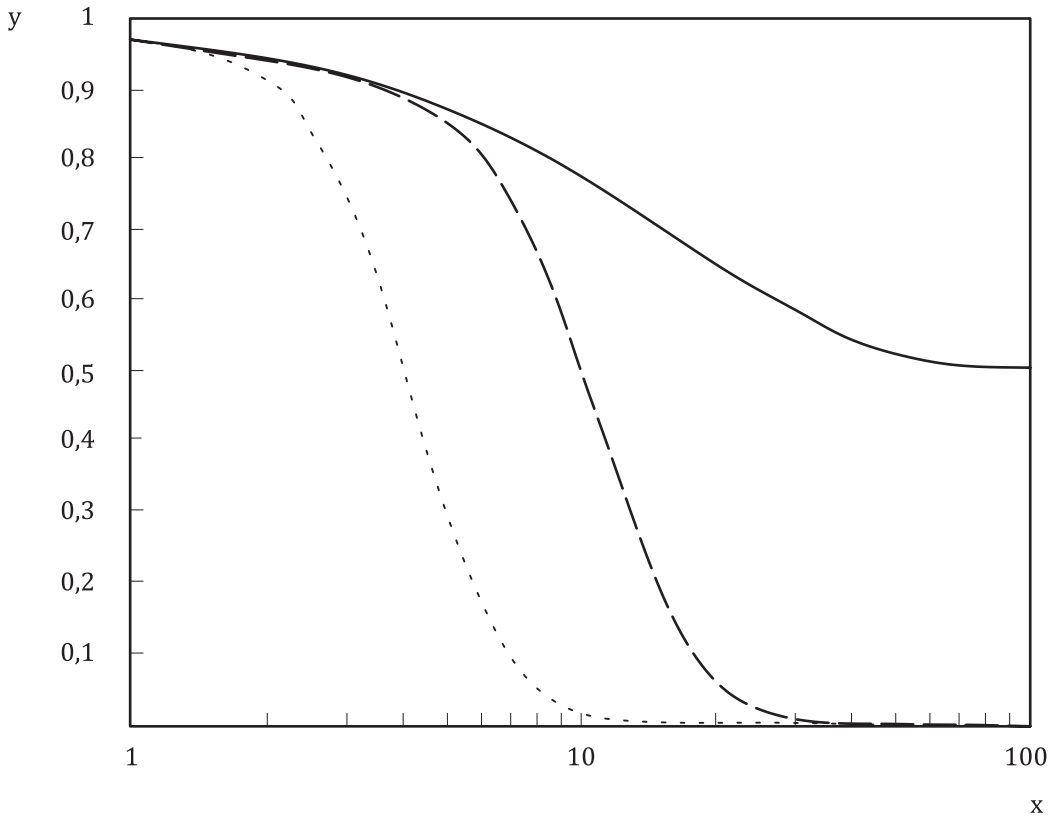

Key

x particle diameter (nm)

y fraction of ambient particles in convention

———— inhalable

— — — — thoracic

- - - - - - - - - respirable

Figure 5 — Health-related sampling conventions for workplace aerosols from ISO 7708[14]

The main exceptions to this methodology are particle-number-based metrics of exposure used:

a) for fibres such as asbestos (defined as of length > 5 µm, width < 3 µm and length: width aspect ratio ≥ 3:1, Note: the definition and sampling methodology of asbestos fibres can vary for different jurisdictions; this definition of fibre is based on World Health Organization definition[148]), for which the standard method is to collect them on a membrane filter sampler and to count them using optical or electron microscopy[149]; and

b) for microorganisms, for which the standard method is to collect them on a growth medium and to count the number of colony-forming units[150][151].

If not combined with other parameters, the mass dose metric (exposure concentration of air or lung dose) has been shown to be a poor predictor of toxicity for poorly soluble nano-aerosols/nano-objects (when compared with larger respirable particles), but it is a widely used metric. To be used in exposure assessment, this metric needs to be associated with other information like constituent/primary particles size, aggregation or agglomeration state, agglomerate density[152]. Particle surface area dose and particle volume have been reported to be better predictors of lung responses in rats or mice across a range of particle sizes[25][29][30]. Agglomeration can influence the deposited dose since airborne particle size determines the deposition efficiency in the respiratory tract[25]. The deposition probabilities are described in ISO 13138[153]. A number of studies have indicated that the toxicity of insoluble materials increases with decreasing particle size, on a mass for mass basis[29][154][155]. The mechanisms by which these materials exhibit higher levels of toxicity at smaller particle sizes have

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yet to be explained, although there are many hypotheses. A number of studies indicate that biological response depends on the surface-area of particles deposited in the lungs[25][26][29]. It has also been suggested that due to their small diameter, nano-objects are capable of penetrating epithelial cells, entering the bloodstream from the lungs[156], and even entering the brain via the olfactory nerves[40]. As particles in the nanometer size range have a high percentage of surface-atoms, and are known to show unique physicochemical properties, it would be expected that nano-objects would demonstrate biological behaviour closely associated with particle diameter, surface-area and surface activity.

It is apparent from the above discussion that measuring exposures to nano-aerosols in terms of mass concentration alone is not sufficient to assess potential health risk. In addition, there is strong evidence to suggest that occupational nano-aerosols should be monitored with respect to surface-area. However, in this context, aerosol surface-area is not well defined and it is dependent on the measurement method used. Geometric surface-area refers to the physical surface of an object, and is dependent on the length-scale used in the measurement. Measurement length-scale determines the upper size of features that are not detected by the measurement method. For example, methods utilizing molecular surface-adsorption have a length-scale that approximates to the diameter of the adsorbed molecules[157]. Similarly, biologically relevant surface-area will most likely be determined by the smallest biological molecule that interacts with particles within the body.

While a strong case might be made for using aerosol surface-area as an exposure metric, it is also necessary to consider characterizing exposures against aerosol mass and number concentration until further information is available. In the case of a nanomaterial with consistent composition, size and shape, one can measure the specific surface area and correlate it to mass concentration. However, the correlation coefficient will not be transferable to other nanomaterials with different distributions in composition, size and shape. For each of these exposure metrics, but particularly in the case of mass concentration, particle size selective inlets will need to be employed to ensure only particles within the relevant size range or in the particular respirable fraction, are sampled[158].

The actual particle cut-off size for assessing potential human health impact is still open to debate and depends upon particle behaviour and subsequent biological interactions. The currently proposed cut-off size for nanoparticles is 100 nm, although this is not derived from particle behaviour in the respiratory tract following deposition and it excludes larger particles of nanomaterials. However, at this scale it is thought that the properties of materials can be different from those at a larger scale. For instance, it could be possible to develop a health-related description of a nanoparticle based on the deposition probability in the lungs (see the curves in Figure 4). Particle deposition efficiency in the respiratory tract reaches a minimum at about 200 nm to 300 nm in diameter, and increases for particles of lesser diameter. In addition, as particles become smaller, surface curvature, the arrangement (and percentage) of atoms on the particle surface and size-dependent quantum effects play an increasingly significant role in determining physicochemical behaviour.

It is currently unclear whether the biological impact of discrete nanoparticles depositing within the respiratory system, is distinct from or similar to the impact of large agglomerates or aggregates of nanoparticles containing the same mass of material. Several factors can affect biological response. First, the location of deposition depends on aerodynamic particle size which will change with degree of agglomeration and aggregation. Next, if agglomerates or aggregates of nanoparticles either de-agglomerate or disaggregate completely following deposition, it is conceivable that the resulting biological impact will be similar to an equivalent exposure of discrete nanoparticles. In addition, if biological response is associated with the surface-area of the deposited aerosol, then for a given volume of material, the response to deposited agglomerates and aggregates with an open fractal-like structure will conceivably be similar to that from an equivalent dose of discrete particles. However if the nanostuctured particles do not de-agglomerate then it is likely that they will not translocate to other organs in the body as readily as the discrete nanoparticles and so the biological impacts will be different. So, knowledge of the ease with which the specific particles will de-agglomerate will be required before deciding at which particle size to exclude unwanted particles (bulk particles which are not nanostructured materials) and might vary with the particle properties.

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7.3 Review of methods for characterizing exposure to manufactured NOAAs

7.3.1 General

The principal purpose for most particle sampling is for the protection of workers by controlling the emissions of hazardous substances to air. This usually forms part of a risk management strategy which is ideally based on: hazard identification, hazard assessment, exposure assessment and risk assessment (see 8.2). However, for NOAA the hazard and risk assessment information currently available is often very limited and this means that targeted exposure sampling can be carried out for various purposes:

1) assessment of personal exposure for compliance with regulations,

2) assessment of personal exposure for linking with potential adverse health effects in epidemiological studies,

3) identification of major emission sources for establishing targeted control plan,

4) assessment of efficiency of control systems deployed.

Each of these tasks requires specific and often different types of instrumentation. For example, for personal exposure measurements the best solution is to use small, battery-powered samplers, mounted with the inlets close to the worker's breathing zone, so that move with him/her during the working shift. For source identification, personal or hand-held portable monitors can be used, generally giving continuous measurements of concentration that can be correlated with details of the location, ventilation and the specific work processes being undertaken. In order to assess the nanoparticles present and/or the overall efficiency of control measures in the workplace, many different types of monitoring instruments can be used, including larger static, mains-driven research orientated instruments, depending upon the information required.

However, for assessing exposure to manufactured NOAAs a major confounding factor in most workplaces is that of incidental nanoscale objects derived from ambient aerosols that penetrate workplaces to differing degrees[159][160], and incidental nanomaterials generated within the workplace itself[161]. These confounding particles can directly impact measurements of particle count, but also rapidly coalesce with nano-objects, including the NOAAs of interest[162], requiring careful design of measurement strategy. Possible methods of discriminating between exposures to manufactured NOAAs and to ambient incidental nanoscale particles will be discussed later. While discrimination will facilitate analysis of exposures, effective control of both manufactured and incidental NOAAs is essential for effective occupational health and safety management.

Measurement techniques and strategies need to be optimally combined to enable sensitive yet cost-effective determination of airborne manufactured NOAAs in the workplace. Measurement strategies might consider using tiered approaches as this can facilitate cost effective screening at workplaces. In addition, sampling methods that have been developed and/or proposed are often conducted using multiple instruments designed to capture multiple metrics (such as mass concentration, surface area concentration and NOAAs count concentration).

One of the challenges in obtaining exposure assessments of manufactured NOAAs in the workplace is the lack of reliable, standardized reference materials for developing and validating potential exposure assessment tools (including standardized sampling and monitoring methods, calibration protocols and instrumentation). However, unimodal test aerosols of particles in the nanoscale and above can be produced: e.g. cubic particles (NaCl and CsCl), spherical particles (Ag and DEHS) and agglomerates (carbon, diesel soot and ZnO) can be generated. Bimodal test aerosols can also be generated for instruments inter-comparison, calibration and performance testing[163][164][165]. A calibration method for the absolute number concentration has been proposed by Koch et al.[166]. Reference materials are a means to provide assurances to the quality of measurements, and to improve or revise potential sampling and monitoring methods. For manufactured NOAAs, developing standardized reference materials can help assess in conducting exposure and risk assessments; this might involve sampling and measuring specific properties of the manufactured NOAAs of interest[167].

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Ideally, according to Reference [168], the equipment for taking the occupational hygiene measurements should be:

— portable;

— capable of measuring multiple NOAA characteristics (particle count, mass, surface area, charge, size distribution, differentiate manufactured from background particles, temporal variation etc.);

— capable of obtaining breathing zone samples;

— capable of being used in industrial settings;

— battery-powered;

— real-time;

— relatively inexpensive.

At this time there is not a single instrument that meets all of these criteria. As well, many of the currently available hand-held, real-time aerosol instruments are more suited for measuring specific size-ranges of airborne spherical structures or NOAAs[169].

Particle number concentrations and particle number size distributions are some of the most commonly used metrics in many workplace exposure assessment studies. Advantages to this approach include the wide availability of measurement devices (e.g. CPC) and the instruments' high sensitivity to airborne nano-objects. Disadvantages include the inability to differentiate the background from the release of manufactured NOAAs from work-related practices. Challenges include the current lack of information of lower and upper detection limits (especially when compared with a measurement strategy being used). As well, uncertainty arises from the calibration of the devices which can differ by as much as 30 %[134].

A summary of currently available instrumentation is provided in Table 1, part of which is an updated version of that found in the ISO/TR 27628:2007 on Ultrafine, nanoparticle and nanostructured aerosols — Exposure characterization and assessment[170]. Some of the following subclauses contain information taken from ISO/TR 27628:2007, which will be updated periodically and might contain more up to date information than this document. Table 1 also integrates information from Reference [134] which contains a review of those instruments applied in occupational settings. Additionally a European Standard describes the different metrics in use and applicable instrumentation[171].

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Table 1 — Selected instruments and techniques for monitoring nano-aerosol exposure

Metric	Devices/Techniques	Remarks
Mass directly	Size selective static sampler	The only devices offering a cut point around 100 nm are cascade impactors (Berner-type low pressure impactors, or Microorifice impactors). Allows gravimetric and chemical analysis of samples on stages below 100 nm.
	TEOM® TEOM® is the registered trademark of a product supplied by Thermo Fisher Scientific Inc. This information is given for the convenience of users of this document and does not constitute an endorsement by ISO of the product named. Equivalent products may be used if they can be shown to lead to the same results.	Sensitive real-time monitors such as the Tapered Element Oscillating Microbalance (TEOM) might be useable to measure nano-aerosol mass concentration online, with a suitable size selective inlet.
Mass by calculation	Electrical Low Pressure Impactor (ELPI®) ELPI® is the registered trademark of a product supplied by Dekati Ltd. This information is given for the convenience of users of this document and does not constitute an endorsement by ISO of the product named. Equivalent products may be used if they can be shown to lead to the same results.	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. ELPIs can detect airborne particles between 6 nm – 10 µm. Size-selected samples might be further analysed off-line (as above).
	DMAS	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.
Number directly	CPC	CPCs provide real-time number concentration measurements between their particle diameter detection limits. Without a nanoparticle pre-separator, they are not specific to the nanometre size range. Generally, different types of CPCs can detect airbonre particles between 5,5 nm – 9 µm. P-Trak has diffusion screen to limit top size to 1 µm. Particle number concentration.
	DMAS	Real-time size-selective (mobility diameter) detection of number concentration, giving number-based size distribution.
	Electron Microscopy	Off-line analysis of electron microscope samples can provide information on size-specific aerosol number concentration.
Number by calculation	Electrical Low Pressure Impactor (ELPI®)	Real-time size-selective (aerodynamic diameter) detection of active surface-area concentration, giving aerosol size distribution. Data might be interpreted in terms of number concentration. ELPIs can detect airbonre particles between 6 nm – 10 µm. Size-selected samples might be further analysed off-line.

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Table 1 *(continued)*

Metric	Devices/Techniques	Remarks
Surface-area directly	Diffusion Charger	Real-time measurement of aerosol active surface area. Active surface area does not scale directly with geometric surface area for particles larger than 100 nm. Note that not all commercially available diffusion chargers have a response that scales with particle active surface area for particles smaller than 100 nm. Diffusion chargers are only specific to nanoparticles if used with an appropriate inlet pre-separator.
	Electrical Low Pressure Impactor (ELPI®)	Real-time size-selective (aerodynamic diameter) detection of active surface-area concentration. Active surface area does not scale directly with geometric surface area for particles larger than 100 nm.
	Electron Microscopy	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 might be related to geometric area for some particle shapes.
Surface area by calculation	DMAS	Real-time size-selective (mobility diameter) detection of number concentration. Data might be interpreted in terms of aerosol surface area under certain circumstances. For instance, the mobility diameter of open agglomerates has been shown to correlate well with projected surface area[170].
	DMAS and ELPI® used in parallel	Differences in measured aerodynamic and mobility can be used to infer particle fractal dimension, which can be further used to estimate surface area.

Characteristics of the above mentioned instruments are given in Annex C.

7.3.2 Sampling strategy issues

Until it has been agreed which is(are) the most appropriate metric(s) for assessing exposure to manufactured NOAAs in relation to potential adverse effects, it has been recommended that a range of instrumentation be used to provide full characterization of the aerosols in workplaces where NOAAs are being produced, handled or used to make new materials[172]. This approach currently requires the use of relatively large and expensive "research" instruments, which is not conducive to the sampling procedures and strategies required to assess personal exposure for compliance with any exposure limit or for epidemiological purposes or for identifying major emission sources. A review on exposure related workplace measurements and laboratory studies is given in Kuhlbusch et al.[134].

However, new instruments are being continuously developed and there are small portable instruments for particle number concentrations, particle surface area concentrations and health-related surface area concentrations. While most of instruments are not yet truly personal, they are compact enough to be carried from location to location in the workplace and to be sited close to the worker at each location. Currently however, these instruments do not provide enough information for full characterization of the workplace, so static instruments such as the DMAS, ELPI® and devices for collecting particles for physical and chemical characterization should be included. Care should be taken in setting these static samplers as aerosol characteristics can change with distance from source, leading to spatial and temporal variation of nano-aerosol mass and number concentration. This is especially true for hot processes leading to particle nucleation from vapour that will often lead to variations in emission rate and concentration over time.

To improve the comparability of exposure data, the accepted practice of giving personal exposure as an eight-hour-shift value should also be observed in the case of nano-aerosols. In consequence, wherever possible exposure measurement results concerning shorter measurement intervals should be converted into shift data by time weighted recalculation. In all cases, where short-term exposure itself is the target of investigations, the time base of measurements needs to be documented. A time base of 15 min for short-term exposure measurements is recommended as it is generally used in occupational hygiene.

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Selection of the most appropriate sampling location or locations is a key factor for a reliable interpretation of data in view of personal exposure. This requires analysis of tasks carried out by workers using or handling nanomaterials, identification of all the potential nano-aerosol-emitting sources in the workplace and an understanding of the ventilation system in the workplace to determine the potential for cross contamination. This could be a significant problem for NOAAs as they will remain airborne for considerable periods of time and be easily dispersed by the air currents in the workplace. For single sources, the relationship between aerosol emission and work activities should be clear, enabling the reliable assignment of exposure levels to be made.

However, unless the workplace is operating under clean room conditions or has high efficiency filters on the inlet air through well-defined inlets, outdoor sources of nano-aerosols (e.g. vehicle exhausts, other industrial activities, power stations, etc.) will penetrate indoors and result in overestimation of the levels of NOAAs emitted from the process under investigation. This will inevitably lead to an overestimation of the worker exposure to NOAAs derived from that process. 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. However, it might not be possible to subtract the background particle counts from the exposure level counts since the background counts can fluctuate with time. Another method is to carry out simultaneous measurement of background concentrations using a duplicate set of monitoring equipment to monitor outside the workplace, and to subtract the outdoor levels from those measured inside the workplace. However this can be expensive and assumes that the ambient particles do not change during transport into the workplace[172].

An important component of assessing exposure in the workplace to manufactured NOAAs is the characterization of the background. Recent studies have been carried out whereby a suite of direct-reading instruments (e.g. CPC, SMPS, APS) were used to characterize the variability of the background nano-aerosol levels over time[134][136]. Where possible, measurement strategies should include the use of multiple direct-reading instruments to cover all the relevant measurands (e.g. particle size distribution, particle count, and particle surface areas).

Although relatively simple particle number and surface area measurements can be used for identifying the sources of leaks and major emission sources, at some point it becomes necessary to confirm that the measurements being made are related to the NOAA's of concern. Sampling strategies such at NEAT 1.0[173] and NEAT 2.0[174] have made provision for the sampling and off-line analytical TEM analysis and chemical characterization of the particles collected. This information informs what percentage and in what size ranges the NOAA's of concern contribute to the real-time measurement of particles. This ratio can then be used to calculate the surface area concentration of the manufactured NOAAs in the total surface area concentration values for all airborne NOAAs detected. The accuracy of this approach will obviously depend upon the manufactured NOAAs having at least one detectable element that is not present in outdoor aerosols. Application of this method to CNTs is described in C.6.

If there is no reliable characterization of the NOAA of interest, the real-time measurands have to be compared to determine whether a significant exposure or release might have occurred and the background is exceeded. Several decision rules can be used. Such decision rules, and even one combined decision rule, have been tested for a variety of exposure situations[175][176]. However, it was acknowledged that the sampling and analysis of additional aerosol samples to determine the occurrence of nano-objects will be a more reliable decision process.

— previously, many measurement strategies identify the need for:

  — tiered approach to facilitate exposure assessments;

  — tiered approach that is be easy to implement and cost effective;

  — approach based on established measurement methods;

  — approach capable of discriminating and quantifying manufactured NOAAs from background particles.

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An example of an early tiered approach is described below and in Figure 6[124]:

— Tier 1 — Information Gathering. Tier 1 is focused on the gathering of information prior to a workplace exposure assessment. This is done to determine if additional assessment is needed in regard to potential occupational exposures to manufactured NOAAs.

— Tier 2 — Basic Assessment: If occupational exposure cannot be excluded following the Tier 1 analysis, a Tier 2 investigation will occur. Tier 2 involves detecting, monitoring and measuring possible release and detection of elevated particulate and NOAA concentrations by cost effective targeted monitoring. Assessment includes measuring nano-aerosol concentrations vs. background concentration levels to determine a realistic value for occupational exposures to manufactured NOAAs.

— Tier 3 — Comprehensive Assessment: Tier 3 becomes necessary if significant exposure can still not be excluded. In Tier 3, extended measurements are required for a more detailed assessment. This would include monitoring to identify the level of manufactured NOAAs, and would require the implementation of a control strategy to minimize occupational exposures.

This is just one example of several available tiered approaches to exposure assessment for nanomaterials. More recently, a "harmonized tiered approach" has been adopted by OECD[127]. Recommendations on how to perform an assessment of inhalation exposure to nano-objects and their agglomerates and aggregates (NOAA), including which measurement strategy to adopt, will be also provided in EN 17058[177].

Exposure data generated through the use of these approaches will be collected in suitable databases in order to reach a comprehensive description of exposure situations and use these data in control banding tools and for the derivation of future exposure limit values. Databases like NECID[178] or eNanoMapper are existing tools towards this aim. Calibration and the correct operation of the monitoring instruments is required to ensure data quality and enable such use of collected data (e.g. NanoGem[124] and Nanoindex[179]).

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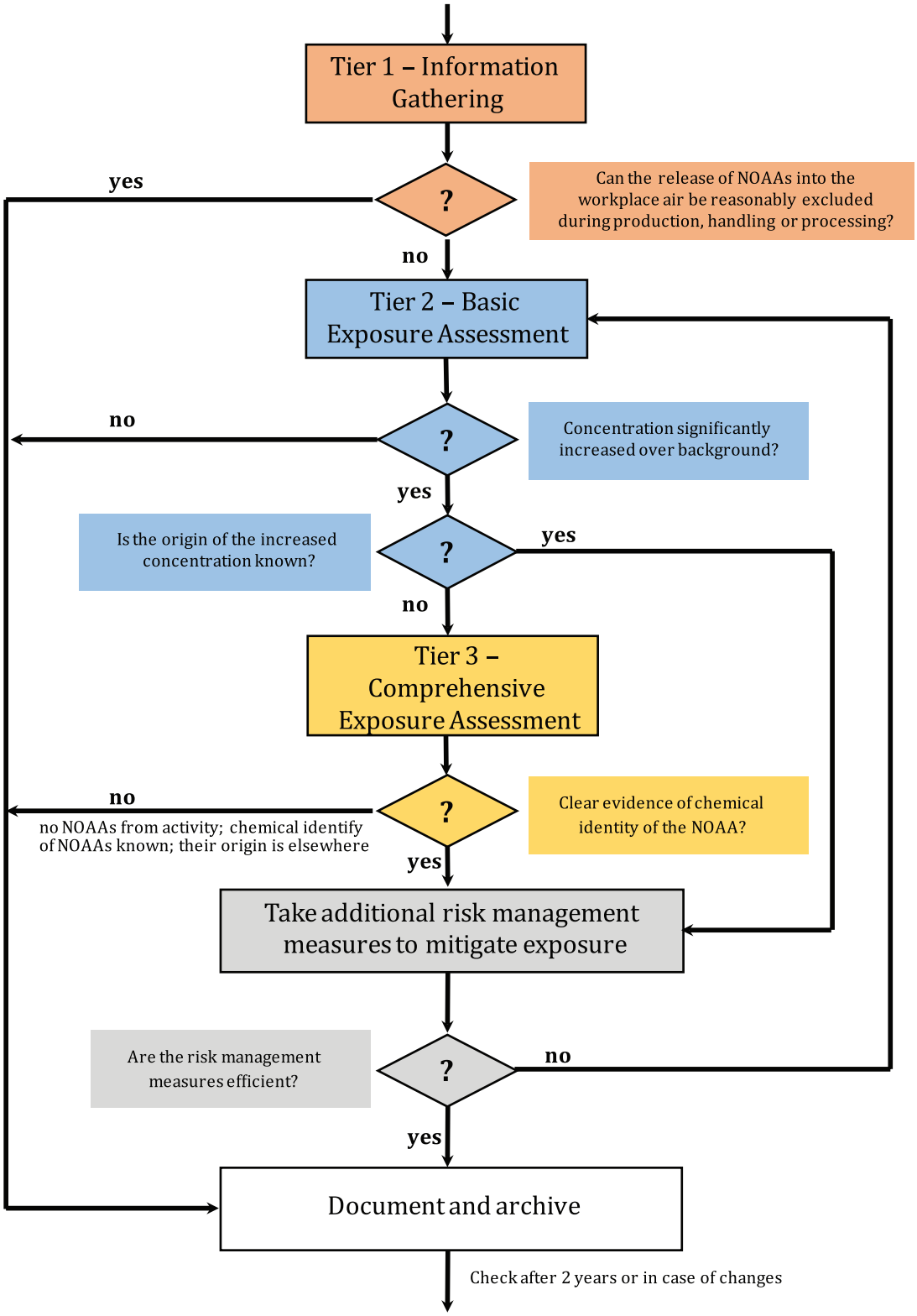

Figure 6 — Flow chart of a tiered approach (based on Figure 1 of Reference [124])

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7.4 Dustiness assessment

7.4.1 General

The control of the emitted and released airborne nano-objects and particles during the handling and transportation of bulk materials is an important consideration for workers' exposure and the design and operation of many industrial or research processes. It is therefore important to obtain information about the propensity of bulk materials to release nano-objects and respirable particles and thus assist in assessing the risk for exposure to a hazardous material.

Dustiness data have been recommended for nanomaterials exposure assessment by the Organization for Economic Co-operation and Development[180] and are also already in use as an input parameter in some control banding tools for nanomaterials or to predict the likelihood of exposure by modelling. Finally, dustiness data can provide the manufacturers of nanomaterials with information that can help to improve their products (e.g. by selecting less dusty nanomaterials) or the users to improve their processes or their technical prevention approaches.

Dustiness depends on a number of factors including the physical state of the bulk material (e.g. powder, granules, pellets and moisture content), the physicochemical properties of the particles contained in the bulk material (e.g. size and shape, relevant density, type of coating, hydrophobicity and hydrophilicity properties, aggregation of particles), the environment (e.g. moisture, temperature), the condition of the bulk material, the type of aerosol generation (activation energy or energy input, time characteristics of the energy input) and the interaction between particles during agitation (e.g. friction shearing, van der Wall forces). Dustiness testing should simulate typical powder processing and handling. It should enable a comparison of the relative dust release potential of different bulk materials and data derived from dustiness testing could be used as input for qualitative or quantitative exposure assessment. Dustiness involves the application of a given type and amount of activation energy or energy input, to a stipulated amount of test material during a stipulated time, whereby particles are dispersed into the air and are described quantitatively.

7.4.2 Measurement methods

No single dustiness method is likely to represent and reproduce all the various types of processing and handling used in workplaces. Therefore, there are a number of methods for the design of dustiness devices and different values will be obtained by different test methods. However, the test and the variables including the sampling and measurement configuration need to be closely specified to ensure reproducibility. The results of pre-normative research[181] led to the development of four test methods: the rotating drum, the continuous drop, the small rotating drum and the vortex shaker.

Conventional dustiness methods for micrometre size particles estimate the airborne dust generated in terms of dustiness mass fraction (e.g. respirable, thoracic, inhable) expressed in mg/kg. The current European standard EN 15051-1-3[182][183][184] for conventional dustiness provides two methods: the rotating drum method and the continuous drop method. Although these methods are accepted standards for micrometer size particles, the biological behaviour of nano-objects because of their small size and surface area has raised the question whether the dustiness can be adequately characterized by their mass fraction only. Therefore, particle number concentration and size distribution are other important measurands for measuring and characterizing the dustiness of bulk material containing nano-objects. ISO/TS 12025[185] provides general methodology for the quantification of nano-object release from powders as a result of treatment, ranging from handling to high energy dispersion, by measuring aerosols liberated after a defined aerosolization procedure. Further work to establish test methods that measure the dustiness of bulk materials containing nano-objects in terms of health-related index mass fraction, index number and emission rate, is taking place[186][187][188][189]. In addition, the new standards will also establish test methods that characterize the aerosol from its particle size distribution and the morphology and chemical composition of its particles.

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7.5 Dermal exposure assessment

7.5.1 Sampling

7.5.1.1 General

Sampling of manufactured NOAAs deposited on skin in the workplace can be accomplished by adapting well established sampling methods developed for chemicals[190][191][192].

The direct assessment of dermal exposure to manufactured NOAAs can be accomplished by measuring the amount of the manufactured NOAAs in contact with the skin over a period of time. The methods developed for such purposes entail either the removal of accumulated contaminants from the skin[193] or interception of the material as contact occurs. The removal methods include uncertainties in the removal efficiency and require that the duration of contact be evaluated through independent means. Uncertainty is introduced by the interception methods through the use of materials that usually do not mimic the adherence characteristics of the skin accurately. These methods are summarized in the following subclauses.

7.5.1.2 Removal procedures

Rinse method. Various solvents (for example, solutions of surface active compounds) can be used to rinse the exposed skin and remove accumulated NOAAs. These solutions can then be analysed for the presence of NOAAs, followed by chemical, particle size and shape analyses.

Wipe method. Solvent impregnated materials can be used to wipe the skin and remove residues. The wipe material is then analysed for the NOAAs of concern. For example, metal concentrations might be measured using ICP-MS; other analytical methods would likely be required for most nanomaterials.

Tape stripping method. Adhesive tape can be applied to the skin for purposes of removing contaminant NOAAs both from the surface of the skin and from within the skin. ICP-MS or other analytical techniques can be used to estimate the amount of residue including NOAAs removed with the tape.

In all these methods, skin should be cleaned before potential NOAA exposure might occur. This confirms NOAA exposure if NOAA are identified after removal procedures.

7.5.1.3 Interception procedures

Patch method. Patches made from various materials such as cotton or polyester gauze, alpha-cellulose paper, polyurethane foam, or polypropylene film can be placed on the body to collect NOAAs as contact occurs. The method requires some fairly extensive assumptions, and in the occupational setting, it has been proven to be useful for screening purposes but is limited as a quantitative method. It is generally believed that amounts of contaminant recovered by either removal or interception methods do not accurately correspond to amounts of contaminant deposited on the skin. Collection efficiency is considerably lower via removal[194] than interception methods[195]. Results of these methods are more a reflection of skin loading than actual exposure; thus, measurement results at best provide indices of relative exposure.

Glove method. Absorbent gloves can be used to collect NOAAs contacting the hands[195][196][197].

Whole body dosimetry. This method involves the use of clothing covering the whole body (usually cotton, long underwear tops and bottoms and socks) to trap NOAAs. A problem with this method is the difficulty in extracting NOAAs from such a large collector. An advantage of this method over the patch method is that it is less likely to miss areas where exposure might occur. Another approach that can be used to estimate exposure is by using patches that are placed on multiple anatomical regions of the body[198].

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7.5.1.4 Other procedures

Fluorescent tracers. This procedure involves modifying the NOAAs of concern with a nontoxic fluorescent tracer and then using video imaging to identify and quantify the points where the NOAAs contact the skin[199].

Contaminated surfaces. Contaminated surfaces, such as tools and equipment, represent another category of sampling. According to Fenske[200], surface sampling can be considered a first approximation of personal dermal exposure. This observation supports the value of controlling the migration of NOAAs in the workplace.

7.5.2 Sample characterization

Electron microscopy can be used to characterize size distribution, number concentration and shape of NOAAs collected on samplers. In wipe methods, use of mixed-cellulose ester filters as wipes could facilitate such analysis.

Light scattering, laser diffraction, size exclusion chromatography, acoustic techniques and field flow fractionation could be used to characterize size distribution and number concentration[201], while spectroscopic techniques can be useful in obtaining information about chemical composition and structure of NOAAs. These techniques can work with rinse sampling methods.

7.6 Dose (internal exposure) assessment

Internal exposure is more directly linked to adverse health effects. However, dose assessment involves analysis of tissues, body fluids, and exhaled air. In occupational settings, less invasive methods such as collection of hair, urine and exhaled air are used most commonly.

Dose can be determined by measuring amount of manufactured NOAAs of interest and/or their metabolites. The term “biomarker” is often used to describe a range of biological effects resulting from interactions between human biological systems and a toxicant. Biomarkers can provide direct evidence for the exposure to a particular toxicant if there is a unique correlation between a particular biomarker and a toxicant. One of the advantages of measuring biomarkers of exposure is that it provides information about combined exposure through multiple routes, including non-occupational. Measurements of biomarkers of exposure are used for screening and monitoring of workers.

Biomarkers of exposure to manufactured NOAAs are being developed and is complicated by great variety of chemical and physical properties resulting in a wide range of biological responses[202][203][204].

7.7 Discussion

As with all new and emerging technologies, the development of harmonized and validated measurement techniques for assessing and controlling exposure to manufactured NOAAs in the workplace will always be working from a position of insufficient knowledge until the suitability of current controls are assessed, the emission rates of manufactured NOAAs from those processes are determined and the exposures of the workforce to those NOAAs are characterized. Together with information on the toxicity of the NOAAs to human health, these parameters form the basis of the risk assessment process (see Clause 8. Risk Assessment of Nanomaterials) that informs legislation on its production, sale and use, allows the setting of appropriate occupational exposure limits and leads to guidance on the choice of suitable control procedures.

The area is moving fast and instrument manufacturers are currently developing new devices that they hope will become the mainstay of future manufactured NOAAs exposure assessments. Besides recently-introduced health-related and small portable diffusion charger surface area monitors, there are a number of developments in the pipeline, including: personal CPCs; small, portable instruments that provide particle number size distributions (similar to the information provided by the DMAS) and small, portable NOAA mass monitors. In addition, there are many other long-term developments including a possible portable device that should be able to discriminate between manufactured and incidental nanomaterials. So, assuming that international agreement can be obtained about which

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metric or metrics is the most appropriate to use as the basis of exposure assessment for inhalation of airborne nanomaterials, then the future looks promising that a wider range of personal monitors with improved functionality will be available. The choice of sampler or monitor depends upon the role for which it is to be used and a device for exposure assessment might be different from that used to determine sources and to assess the efficiency of control systems.

7.8 Summary

A possible approach to conducting exposure assessments and sampling for manufactured NOAAs in the workplace is to follow one of the recently proposed methodologies. Effective methodologies include the "nanomaterial emission assessment approach" and the "harmonized tiered approach". These two methods build on an initial assessment with possible subsequent sampling and monitoring. The initial (Tier 1) assessment begins with an observational walk through survey of the workplace to gain a better understanding of each work process and to determine potential emission sources of manufactured NOAAs. This can be supplemented by cost-effective targeted measurements with personal or hand-held monitoring instruments to assess or to help determine whether significant airborne releases of manufactured NOAAs occur (e.g. comparing particle concentrations at the emission source to background particle concentrations or taking samples for electron microscopy particle characterization). For more complex situations a wider range of monitoring instruments and measurands (Tier 3) which requires the use of larger "research" instruments will provide more detailed measurements and insights into the nature of workplace exposure to NOAAs. Such approaches can provide a means for determining whether existing measures are adequate for controlling manufactured NOAAs emissions or if additional controls are needed. Finally, experience with the existing measurement strategies is under way and should be used to refine the currently used strategies.

See the Bibliography for further guidance for health and safety professional, specifically for industrial or occupational hygienists on exposure assessment strategies.

8 Risk assessment in occupational settings

8.1 Introduction and scope

The present clause describes the current state of the art of risk assessment for production and processing of nanomaterials. Thus, only occupational settings, e.g. production plants, pilot plants or laboratories, as well as, the professional use and manipulation (e.g. cutting, abrasion) of NOAA-containing products (e.g. coatings, paints), but not consumer product safety or environmental safety, are considered.

A sub-class of nanomaterials, free or unbound NOAAs, is of particular concern from an occupational safety and health perspective. Nanostructured materials, nanolayers or solids containing embedded NOAAs, e.g. polymer composites, coatings or finishings can also result in exposures. For example, in field studies it was shown that destructive processing (even using wet-saw) of polymer composites containing NOAAs generates substantial aerosol release, which includes some aggregated nanofibre material, but there was no evidence of release of unagglomerated nano-objects[205][206]. Such aerosols can contain both incidental and manufactured NOAAs. Therefore, it is important to properly characterize generated aerosols.

While physical hazards posed by the specific process, e.g. high temperatures, high voltage, etc. can be present in occupational settings dealing with NOAAs, this clause focuses more on toxicological hazards and less on fire and explosion hazards. Generally, acute effects should be avoided using typical principles and minimum requirements of occupational health and safety[207][208] provided that acute toxicity information is available for handled NOAAs. However, health risks due to chronic low level of exposures are more difficult to evaluate and therefore it can be more challenging to establish appropriate exposure mitigation programs[172].

Risk assessment is typically conducted by safety experts working in close contact with decision makers establishing risk management requirements. Risk assessment analysis requires detailed information both on products and processes. For example, European legislation requires risk assessments specific to individual substances and individual occupational settings[208][209]. Likewise, presently in many

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countries risk assessment for NOAAs is conducted according to existing regulations for individual materials and settings.

8.2 Risk assessment for NOAAs

8.2.1 General

Risk assessment is an analysis of the potential adverse health effects (current or future) caused by a hazardous agent in the absence of any additional actions to control or mitigate exposure to that agent. Risk assessment in occupational settings includes several elements: hazard identification, hazard assessment, exposure assessment, and risk characterization[210][211][212]. The goal of risk assessment is to evaluate whether existing risk in a specific workplace environment is above organization-specific acceptable level of risk and, therefore, to provide information to decision makers about the need to further strengthen risk management approaches.

Risk assessment can be quantitative or qualitative. However, components of the risk assessment process remain the same and include:

— Hazard Identification-identifies those hazards that make a significant contribution to risk.

— Exposure-Response Assessment-identifies the potential adverse health effects associated with the hazards of concern identified at the workplace.

— Exposure Assessment-evaluates the pathways by which individuals could be exposed to hazards present in a workplace.

— Risk Characterization-incorporates information from the three previous clauses to evaluate the potential risk to exposed individuals at the workplace.

Risk assessment in a specific workplace commonly starts with collection of information on hazard assessment. The process then continues in a logical process whereby hazard and exposure are assessed. Thus the step of risk characterization is the synthesis of hazard and exposure. The existing structure of risk assessment framework is flexible enough to be adapted to NOAAs.

8.2.2 Quantitative and qualitative risk assessment

Quantitative risk assessment. Quantitative risk assessment relies on the availability of quantitative exposure data expressed as the probability of exposure or exposure levels and quantitative exposure limits. Exposure limits are developed using dose-response relationships and signify exposure levels at which risk of adverse health effects or risk of an event leading to adverse health effects is below an acceptable level. Examples of exposure limits are Occupational Exposure Limits (OELs) for specific substances, Minimum Explosible Concentration for explosive dust clouds, and limits of power density for electro-magnetic fields. Another integral component of quantitative risk assessment is measuring and/or estimating actual exposures or probabilities of exposure in the workplace. In addition, good quality hazard (toxicity) data are necessary for a quantitative risk assessment.

In the absence of regulatory binding OELs, a good starting point for the exposure assessment might be the use of provisional NRVs or other proposed indicative OELs. Current challenges in establishing and implementing specific OELs for manufactured NOAAs include[123][125]:

— a lack of adequate *in vitro* and *in vivo* toxicity data, as well as epidemiology studies for many manufactured NOAAs (as such data are traditionally used to develop OELs).

— a lack of harmonized, validated and standardized methods for measuring airborne concentrations of manufactured NOAAs in the workplace. This is also confounded by uncertainties about the most relevant exposure metrics to use for exposure assessments and for number and surface area metrics how to distinguish manufactured NOAAs of interest vs. other airborne particles and contaminants in the workplace.

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— the availability of portable and personal, simple-to-use, real-time instruments to measure airborne manufactured NOAAs have been limited.

Qualitative risk assessment. In the absence of data to utilize traditional quantitative risk assessment methods to evaluate risk, missing information can be obtained using various combinations of expert judgments and extrapolations from existing data for similar materials. In such qualitative risk assessment methods, safety professionals can be required to use their expert opinions in evaluating site-specific risk and in recommending implementation of exposure mitigation options. For example, in "Approaches to Safe Nanotechnology"[172] U.S. NIOSH recommends that "the decision to use respiratory protection should be based on professional judgment that takes into account toxicity information, exposure measurement data, and the frequency and likelihood of the worker's exposure.".

More formalized techniques such as "expert elicitation" utilizing a systematic process of formalizing and quantifying experts' judgments about uncertain quantities[213][214] can be used in grouping nanomaterials according to their hazard properties and exposure potential. Such hazard groupings could facilitate the development of techniques utilizing banding to assess risks and recommend appropriate risk management techniques, such as Control Banding[215]. One example of such a risk assessment scheme groups nanomaterials according to their biopersistence, chemical activity and toxicity[216] (ISO/TS 12901-2:2014)[132]. Expert opinions can be also systematically utilized within decision analytical frameworks for nanomaterial risk assessment and management, such as Multi-criteria Decision Analysis (MCDA)[217].

Both quantitative and qualitative risk assessment models require regular re-assessment of available hazard and exposure information.

8.2.3 Hazard identification

Hazard identification calls for identifying and monitoring hazards that make a significant contribution to risk. In this case the focus is on developing a list of pertinent toxic hazards (chemicals or NOAAs) and physical hazards (strong electro-magnetic fields, high intensity light sources, high level of noise, flammable and explosive materials, high pressures and vacuum, etc.). Regardless of engineering controls, low potential of exposures, or low hazard, this step is to identify all hazards that are relevant to potential occupational exposures.

For the identification of the hazard, information can be obtained from typical sources such as speciality literature, Safety Data Sheets (SDS) and International Chemical Safety Cards (ICSC), vendor information beyond that supplied in the SDS/ICSC, government and trade association publications and proprietary information or test data. However, there is often a lack of nano-specific data or exposure limits. Thus, the information from these sources might not adequately characterize the hazard of specific NOAAs. When this information is not available from third parties, testing to generate data can be conducted.

8.2.4 Exposure-response assessment

Toxicological hazards. In occupational settings, protection from toxic effects is achieved by reducing exposures to the toxic substance below established "safe" levels resulting in an acceptable level of risk. 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. For threshold toxicological effects, quantitative determination of "safe" levels includes the following steps:

1) determination of a No-Observed-Adverse-Effect Level (NOAEL) or a "Benchmark Dose" (BMD) using animal or human exposure-response data;

2) extrapolation of animal levels to human levels (recognizing the significant uncertainties introduced by such extrapolations): models translating environmental exposures to dose, such as a human lung dosimetry model, are used to calculate working lifetime exposure concentration;

3) derivation of occupational exposure limits upon consideration of technical feasibility, variability and uncertainties of models and approximations used and acceptable level of risk.

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Toxicological properties of nanomaterials might arise from the intrinsic chemical composition of a material, such as those that would originate from bulk material. 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[218]. Toxicological studies are also conducted on novel NOAAs such as carbon nanotubes, which do not have bulk analogues.

The definition, design and standardization of adequate toxicological test protocols for NOAAs are in various stages of development including actual published standards. It is advised that the guidance document, ISO/TR 13014:2012[219], be consulted prior to undertaking any toxicological study. Available international accepted test guidelines (e.g. OECD) should be checked first concerning applicability to NOAAs and if necessary improvement and adaptation of these guidelines should be performed. Apart from the obvious toxicological issues, other major challenges being faced during experimental testing would be the representative formation of nano-object dispersions as well as their explicit characterization. At relatively high number concentration of particulate matter either in gas or liquid phase, nano-objects tend to form larger agglomerates very rapidly due to Brownian motion and relatively strong attractive interactions between nano-objects. For example, this can occur during unloading of nano-objects from a production line and packaging and in such circumstances exposure to agglomerates rather than individual nano-objects are likely.

Multiple toxicological findings have been reported and the number of studies being conducted is steadily increasing. The early toxicity studies were sometimes conducted with test materials which were not well characterized, mostly due to the technological limitations. In addition, scientists have proposed occupational exposure limits for certain NOAAs such as ultrafine titanium dioxide, carbon nanotubes and carbon nanofibres[130][220][221], while for other NOAAs a threshold could be derived using ISO/TR 18637:2016[222].

Hazards based on toxicological properties of nanomaterials are currently evolving as the volume of toxicological studies increases. However it is currently considered that:

— the toxicological properties of NOAAs cannot always be predicted from the known toxicity of the substance in bulk form alone; and

— for some nanomaterials, mass is not an appropriate metric for characterizing exposure and surface area (e.g. some poorly soluble low toxicity NOAAs), and particle number (e.g. fibrous NOAAs) have been proposed as better alternatives.

It should be noted that generally mass is used in the various studies as a convenient dose metric. However, one should also know the surface area and number concentration per mass for the NOAA in order to be able to convert the doses to these metrics for possible dose response relationship and clarification of toxic mechanisms.

Occupational exposure limits based on mass concentration, which are applied for bulk materials, might not be sufficiently adequate for nanomaterials of the same chemical composition[223][31]. For certain nanomaterials, occupational exposure limits based on other metrics, such as surface area or particle number, might be more suitable. However, until methods and exposure limits based on these metrics are sufficiently developed and accessible, the current, proposed mass-based limits, where they exist, must serve as guidance to assess exposure risk.

Physical hazards. Nanomaterial-specific fire and explosion hazards have been described[224][225]. Fire and explosion hazards posed by NOAAs could be more pronounced than those for larger particles or bulk materials, particularly if the larger particle congeners are combustible dusts. Therefore, additional tests are necessary to evaluate flammability, explosivity and reactivity of nanomaterials. Test protocols for these hazards are in place for bulk materials in dry powder form and are applicable to nanomaterials as well. These protocols include measurement of burning rate, self-ignition temperature and the characterization of the explosive properties such as minimum ignition energy, and explosion severity test (K_{st} and P_{max}). Flammability of nanomaterials can be also evaluated using tests developed for chemicals, for example, using ASTM E-918-83 Standard Practice for Determining Limits of Flammability of Chemicals at Elevated Temperature and Pressure[226]. The explosive properties are analysed through utilizing the results of the Fallhammer test (mechanical sensitivity, shock) and Koenen test (thermal

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sensitivity)[227]. Therefore, once the physical hazard data are available, risk assessment for fire and explosion hazards could be conducted using existing techniques.

Hazard assessment. Where there is a lack of applicable hazard data for nanomaterials, hazard grouping of nanomaterials based on expert opinions could be implemented. For example, in the ISO Control Banding approach for nanomaterials (ISO/TS 12901-2:2014)[132] five hazard groups are identified.

Given the great variety of possible nanomaterials and high costs of experiments assessing hazardous properties, computational models (such as Quantitative Structure Activity Relationship like models) predicting hazard properties of novel nanomaterials are expected to play an increasingly important role in risk assessment.

Further information about hazard characterization can be found in Clause 6 and Annex B.

8.2.5 Exposure assessment

Emission scenarios. The next step includes characterization of the quantity of hazard material or physical agent. The quantity of material handled or physical agent present in the workplace is an important factor affecting exposure potential. Naturally, workplace sites where only small amounts of material are being handled or processed would be expected to have lower exposure potential compared to sites handling larger amounts. Such an analysis of work places facilitates assessment of exposure potential among workers' populations with distinct work duties related to or within exposure-relevant distance to the work process of interest, thus leading to identification of populations of concern.

Emission identification also includes a survey of individual workplaces, worker procedures, manufacturing processes and the safety measures in place, including use of engineering controls and personal protective equipment. These will help in the description of the exposure and identification of potential for exposure among workers' populations with distinct work duties related to or within exposure-relevant distance to the work process of interest. If such a preliminary survey indicates potential for exposure, further collection and analysis of data to assess workplace exposure can be warranted. As the discussion about relevant metrics is ongoing, multiple tools to characterize exposure to nano-objects could be employed[172]. Such tools include traditional techniques to characterize mass concentration and airborne particle number concentration. This information might be supplemented by particle size distribution, surface area, chemical characterization data and/or electron microscopy (for further details please see Clause 7 and Annex C).

Exposure routes. Exposure to NOAAs can occur as a result of direct contact. In the case of nano-objects, the discussion of potential exposure scenarios should consider the liberation potential of the nano-objects. Liberation potential can be defined as the ability of individual nano-objects to be available for direct contact with human skin or other organs such as lungs. The following factors are to be considered for the release of airborne NOAAs: physicochemical properties and process characteristics. Physico-chemical properties of NOAAs might include: size, surface coating, charge, dustiness, etc. In considering process characteristics, the conditions of the material should be observed — that is, whether the material is contained in a liquid or solid matrix. Mechanical processing such as stirring, drilling, sawing, milling, grating and cutting can result in release of nano-objects and particles of nanostructured materials. Other processes which can result in exposures include spraying liquid formulations containing NOAAs and high-energy treatment of nanomaterials or nano-enabled materials, such as laser drilling or plasma welding resulting in vaporization of treated materials. Additionally, engineering processes, which range from closed contained systems to open air handling, can have a wide range of potential for exposure. Risk of exposure can be also affected by other factors such as incorrect use of and malfunctioning equipment — both manufacturing and exposure mitigating equipment (engineering controls and personal protective equipment); inadequate workplace practices; poor personal hygiene and unsafe individual worker's behaviour.

Realistic exposure scenarios need to be identified for exposure assessment. Inhalation and dermal exposure are typically the most common routes of exposure in the workplace. Oral exposure at the workplace is considered less likely (although ingestion is a component of inhalation exposure through mucocilliary clearance and swallowing of inhaled particles). Ingestion might also occur from unintentional hand to mouth transfer after dermal exposure[207][208]. Parenteral exposure could occur

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