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Nanotechnologies — Occupational risk management applied to engineered nanomaterials

Part 1: Principles and approaches

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National foreword

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Part 1: Principles and approaches

Nanotechnologies — Gestion du risque professionnel appliquée aux nanomatériaux manufacturés —

Partie 1: Principes et approches

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Foreword

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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 document 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).

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

This second edition cancels and replaces the first edition (ISO/TS 12901-1:2012), which has been technically revised.

The main changes are as follows:

— clauses have been updated and new references have been added to reflect recent research findings;

— a new subclause dedicated to graphene has been introduced in Clause 5;

— Clause 6 has been reorganized and eye exposure and accidental injection risks have been added for potential risk considerations from other potential routes of exposure;

— subclause 6.3 has been expanded and reorganized into two subclauses;

— Figure 1 has been added to Clause 7;

— text related to protection from ocular exposure has been added in 11.2 and substantial changes have been made to the personal protective equipment subclause;

— a new subclause, 11.3.4, has been introduced, focusing on safety by design;

— In 11.3.5 concerning state-of-the-art approaches, the reference to Clause A.1 has been removed and replaced with references to ISO/TR 12885 and other relevant documents;

— in 11.4, which discusses the evaluation of control measures, Clauses A.2 to A.4 have been removed and references to ISO/TR 18637:2016 and other relevant documents have been incorporated;

— Tables 1, 2 and 3 have been added;

— significant changes have been implemented in Clause 15;

— Annexes A, B and C have been added.

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Introduction

The field of nanotechnologies continues to advance rapidly through the development of new materials, products and applications. At the same time, many questions have been raised relating to the potential risks to human health and to the environment of some of these new nanomaterials. Several research programs have been launched at the international level to better understand and quantify these risks. Although some research is already published, this effort will need to continue for some time, as those involved in the development and use of nanomaterials need to assess the risks of nanotechnologies and to implement effective risk management approaches based on the best available evidence. International standardization on nanotechnologies should contribute to realizing the potential of this technology for the betterment and sustainability of our world through economic development, improving the quality of life, and also for improving and protecting public health and the environment.

This document supports this aim by describing the principles of an occupational risk management framework for nano-objects, and their aggregates and agglomerates (NOAA) greater than 100 nm and gives practical advice on its implementation based on the best current emerging evidence concerning the potential risks of nanomaterials. ISO/TS 12901-2 describes a specific approach based on control banding to further support the implementation of good practice in this area[1].

This document applies to such components, whether in their original form or incorporated in materials or preparations from which they can be released during their life cycle. However, as for many other industrial processes, nanotechnological processes can generate by-products in the form of unintentionally produced NOAAs, that can be linked to health and safety issues that need to be addressed as well.

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Nanotechnologies — Occupational risk management applied to engineered nanomaterials —

Part 1: Principles and approaches

1 Scope

This document provides guidance on occupational health and safety measures relating to materials that contain and release engineered or manufactured NOAA during their life cycle, including the use of engineering controls and appropriate personal protective equipment, guidance on dealing with spills and accidental releases and guidance on appropriate handling of these materials during disposal.

This document is intended to be used by competent personnel, such as health and safety managers, production managers, environmental managers, industrial/occupational hygienists and others with responsibility for the safe operation of facilities engaged in production, handling, processing and disposal of these materials.

2 Normative references

There are no normative references in this document.

3 Terms and definitions

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

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

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

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

3.1
agglomerate
collection of weakly or medium strongly bound particles where the resulting external surface area is similar to the sum of the surface areas of the individual components

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

Note 2 to entry: Agglomerates are also termed secondary particles and the original source particles are termed primary particles.

[SOURCE: ISO 26824:2022, 3.1.2]

3.2
aggregate
particle comprising of strongly bonded or fused particles where the resulting external surface area is significantly smaller than the sum of surface areas of the individual components

Note 1 to entry: The forces holding an aggregate together are strong forces, for example covalent or ionic bonds, or those resulting from sintering or complex physical entanglement, or otherwise combined former primary particles.

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Note 2 to entry: Aggregates are also termed secondary particles and the original source particles are termed primary particles.

[SOURCE: ISO 26824:2022, 3.1.3, modified —"or ionic" has been added to Note 1 to entry.]

3.3
engineered nanomaterial
nanomaterial designed for a specific purpose or function

[SOURCE: ISO 80004-1:2023, 3.1.8]

3.4
exposure
contact with a chemical, physical or biological agent by swallowing, breathing, or touching the skin or eyes

Note 1 to entry: Exposure can be short-term (acute exposure), of intermediate duration or long-term (chronic exposure).

3.5
harm
injury or damage to the health of people, or damage to property or the environment

[SOURCE: ISO/IEC Guide 51:2014, 3.1]

3.6
hazard
potential source of harm

[SOURCE: ISO/IEC Guide 51:2014, 3.2]

3.7
health hazard
potential source of harm to health

3.8
nanofibre
nano-object with two external dimensions in the nanoscale and the third dimension significantly larger

Note 1 to entry: The largest external dimension is not necessarily in the nanoscale.

[SOURCE: ISO 80004-1:2023, 3.3.5]

3.9
nano-object
discrete piece of material with one, two or three external dimensions in the nanoscale

[SOURCE: ISO 80004-1:2023, 3.1.5]

3.10
nanoparticle
nano-object (3.9) with all external dimensions in the *nanoscale* (3.12)

Note 1 to entry: If the dimensions differ significantly (typically by more than three times), terms such as *nanofibre* (3.8) or *nanoplate* (3.11) are preferred to the term nanoparticle.

[SOURCE: ISO 80004-1:2023, 3.3.4]

3.11
nanoplate
nano-object with one external dimension in the nanoscale and the other two external dimensions significantly larger

Note 1 to entry: The larger external dimensions are not necessarily in the nanoscale.

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[SOURCE: ISO 80004-1:2023, 3.3.6]

3.12
nanoscale
length range approximately 1 nm to 100 nm

[SOURCE: ISO 80004-1:2023, 3.1.1]

3.13
NOAA
nano-objects, and their agglomerates and aggregates
material comprising *nano-object* (3.9), and their aggregates and agglomerates

Note 1 to entry: NOAAs include structures with one, two or three external dimensions in the nanoscale, 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.

[SOURCE: ISO 80004-1:2023, 3.2.6]

3.14
particle
minute piece of matter with defined physical boundaries

Note 1 to entry: A physical boundary can also be described as an interface.

Note 2 to entry: A particle can move as a unit.

Note 3 to entry: This general particle definition applies to nano-objects.

[SOURCE: ISO 26824:2022, 3.1.1]

3.15
risk
combination of the probability of occurrence of harm and the severity of that harm

Note 1 to entry: The probability of occurrence includes the exposure to a hazardous situation, the occurrence of a hazardous event and the possibility to avoid or limit the harm.

[SOURCE: ISO/IEC Guide 51:2014, 3.9]

4 Abbreviated terms

CB	control banding
CIB	Current Intelligence Bulletin
CNT	carbon nanotube
COPD	chronic obstructive pulmonary disease
COSHH	Control of Substances Hazardous to Health Regulations
CPC	condensation particle counter
CPI	Consumer Products Inventory
DMAS	differential mobility analysing system
DW	double-walled
EC	elemental carbon

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ECHA	European Chemicals Agency
EDX	energy dispersive X-ray
eLCOSH	Electronic Library of Construction Occupational Health and Safety
ENM	engineered nanomaterial
GHS	Globally Harmonized System
HARN	high aspect ratio nanomaterial
HEPA	high-efficiency particulate matter
ICS	International Classification for Standards
ICP-AES	inductively coupled plasma atomic emission spectroscopy
ICP-MS	inductively coupled plasma mass spectrometry
LDSA	lung deposited surface area
LEL	lower explosion limit
LEV	local exhaust ventilation
MIE	minimum ignition energy
MIT	minimum ignition temperature
MNM	manufactured nanomaterial
MWCNT	multi-walled carbon nanotube
NEAT	nanoparticles exposure assessment technique
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
NOAA	nano-objects, and their agglomerates and aggregates
OECD	Organization for Economic Cooperative Development
OEL	occupational exposure limit
OPC	optical particle counter
OSHA	Occupational Safety and Health Administration
PLGA	poly(lactic-co-glycolic) acid
PPE	personal protective equipment
R&D	research and development
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
RPE	respiratory protective equipment
SbD	safety-by-design

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SDS	safety data sheet
SEM	scanning electron microscopy
SW	single-walled
SWCNT	single-walled carbon nanotube
TDS	technical data sheet
TEM	transmission electron microscopy
TEOM	tapered element oscillating microbalance
TGA	thermal gravimetric analysis
UK	United Kingdom
WHO	World Health Organization
XRF	X-ray fluorescence

5 Nanomaterial types and characteristics

5.1 General

Clause 5 describes some of the more common types of engineered nanomaterials to which this document can be applied; a few of these also have naturally occurring forms. This document is not intended to provide a full and comprehensive guide of all nanomaterial types.

5.2 Fullerenes

Fullerenes comprise one of four types of naturally-occurring forms of carbon, first discovered in the 1980s.[2],[3] Their molecules are composed entirely of carbon and take the form of a hollow sphere. Fullerenes are similar in structure to graphite which comprises sheets of hexagonal carbon rings, but can also contain pentagonal or heptagonal rings which enable 3D structures to be formed. One of the most commonly described fullerenes is C60, known as a Buckminster fullerene or a buckyball. Fullerenes are chemically stable materials and insoluble in aqueous solutions. Potential applications include drug delivery, coatings and hydrogen storage.

5.3 Carbon nanotubes

Carbon nanotubes are allotropes of carbon with cylindrical structure, high-aspect ratio different tube diameters and lengths as well as tube structures principally consisting of one to many layers of tubular graphene-like sheets[4].The principal types are usually grouped into single-walled (SW), double-walled (DW), and multi-walled (MW) carbon nanotube (CNT). Diameters can vary from around 1 nm for SWCNT to more than 100 nm for MWCNT. Their lengths can exceed several hundred micrometres. Commercial CNT can contain a significant amount of other carbon allotropes and inorganic nanoparticle catalysts.

5.4 Graphene

Graphene is a two-dimensional carbon-based material up to 10 layers thick for electrical measurements, beyond which the electrical properties of the material are not distinct from those for the bulk (also known as graphite). Graphene nanoplates can have a high aspect ratio with lateral sizes ranging from sub-micrometre to a 100 micrometres[5].

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5.5 Nanowires

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

5.6 Quantum dots

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

5.7 Metals and metal oxides, ceramics

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

5.8 Carbon black

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

5.9 Organic nanoparticles

Examples of organic nanoparticles are chitosan, silk fibroin or other biodegradable polymers, including poly(lactic-co-glycolic) acid (PLGA) for biomedical applications.

5.10 Dendrimers

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

5.11 Nanoclays

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

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6 Nanomaterial hazard, exposure and risk

6.1 General

A hazardous material can be identified as follows.

— It can be listed as a substance with an assigned an OEL in national publications.

— It can have a hazard classification in the United Nations Globally Harmonized System[6].

— It can have a hazard classification in national regulations.

— It can be identified as a hazardous material in a safety data sheet, with information about the specific hazards it represents.

— It can be identified in national or international publications which list hazardous chemicals.

Occupational exposure limits for categories of NOAA have been proposed by different organizations and are summarized in References [7] and [8]. Guidance on the categorization of NOAA have been suggested and are summarized in Annex A. However, with the limited knowledge about the toxicity of some NOAA and the concern that current safety data sheets do not adequately reflect the hazardous nature of such NOAA, nanomaterials in a particulate form, or in a form where nano-objects potentially can be released, should be considered potentially hazardous unless sufficient information to the contrary is obtained.

It is well-established that inhalation exposure to many types of particles, including nanoparticles, can negatively impact the health of individuals or exposed populations. These data are from studies of workers, animals and the general population exposed to particulate air pollution[9],[10],[11]. The lung effects depend on the particle dose, physicochemical properties and susceptibility of the individuals. Animal studies have shown that nano-objects can be more potent at causing adverse lung effects on a mass basis than larger respirable particles due to their greater surface area per unit mass[12]. Based on adverse lung effects observed with ultrafine particles of similar size, form factor and/or chemical composition as NOAA, concerns exist that lung diseases such as pneumoconiosis and chronic obstructive pulmonary disease (COPD) associated with exposure to coal dust and pulmonary fibrosis and lung cancer associated with exposure to asbestos can occur in the case of NOAA exposure[13],[14]. In fact, pleuropulmonary symptoms in young workers have potentially been associated with exposure to silica nanoparticles used in polyacrylate spray paint[15]. In a study of workers exposed to TiO_2 nanoparticles, various markers of cardiopulmonary effects were observed to be at least in part due to the nano-object exposure [16]. In another study, workers showed changes in lung function and inflammatory markers in exhaled breath condensates when machining nanomaterial composites [17].

Toxicity, specifically for relatively insoluble particles, appears to relate to the total surface area and the displaced volume of the nano-objects[18],[19],[20]. However, there are other physicochemical factors that can influence the toxicity of nanomaterials, such as shape, crystalline state, elemental composition and surface chemistry[21]. In addition to inhalation, risks to health associated with NOAA can result from dermal exposure, exposure through the eye, ingestion, and intravenous/intramuscular exposure[22]. NOAA can also generate risks to safety, in particular resulting from fire, explosion and chemical reactions[23].

6.2 Risk to health

6.2.1 Hazard information

For some nanomaterials, various health effects have been observed in animal studies. These include cardiovascular and respiratory diseases, as well as carcinogenicity[24],[25],[26],[27]. As research continues, it is understood that pulmonary exposure can lead to adverse outcomes in a number of organ systems beyond the lung and heart. For example, the silver Current Intelligence Bulletin (CIB) uses hepatic toxicity (biliary hyperplasia) as the adverse outcome for risk assessment[28]. Health effects depend on various physico-chemical properties of the material itself and other pollutants that can be absorbed in the nanomaterial. Considering the lack of information on specific materials, it has been suggested to apply read-across in order to extrapolate from known airborne particle exposures and predict potential health effects for an unknown material. Read-across is defined as the grouping of materials in categories with similar physico-chemical

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properties as they can have similar toxicological properties[29]. Various approach to grouping are used, some based on the chemical composition of the material, while others are based more on the physico-chemical properties (size, shape, solubility). A detailed review on approaches can be found in Reference [29].

6.2.2 Exposure

6.2.2.1 Routes of exposure

Routes of exposure for nanomaterials are similar to general chemicals: inhalation, ingestion, dermal and injection.[22] Inhalation and dermal exposure are the main routes of exposure. Oral exposure is less likely at the workplace although it can mainly occur through hand to mouth transfer after dermal exposure. At high concentrations, ocular exposure should be considered since NOAA can penetrate the cornea.

6.2.2.2 Potential risk considerations to health from inhalation of NOAA

More than 30 major reviews and position papers have discussed the potential risks to health and to the environment from exposure to NOAA.[30] The potential risks to health from inhalation of NOAA, specifically bio-persistent NOAA[1)], are summarized as follows.

a) An important rationale for developing nanomaterials is that they will have new, improved or enhanced properties compared to larger particles of the same material. Altered chemical and/or physical properties can be expected to be accompanied by altered biological properties, some of which can imply alterations in toxicity.

b) Due to their small size, nano-objects can reach parts of biological systems that are not normally accessible by larger particles. This includes the increased possibility of crossing cell boundaries or moving from the lungs into the blood stream and so on to all of the organs in the body, or even through deposition in the nose, from which they can then be directly transported to the brain. This process is known as translocation, which can be active or passive and, in general, nano-objects can translocate much more easily than larger structures.

c) NOAA have a much higher surface area than the same mass of larger particles to the extent that surface area is a driver for toxicity, which clearly implies potentially increased toxic effects.

d) In addition, for some NOAA, reduction in size has been shown to relate to increased solubility. This effect can lead to increased bioavailability of materials which are considered to be insoluble or poorly soluble at larger particle sizes[2)].

e) A specific issue relates to comparisons between biopersistent high aspect ratio (ratio of length to diameter) NOAA (e.g. some forms of carbon nanotubes or nanowires) and asbestos.[2] Some biopersistent fibrous particles cause disease because they can be inhaled and enter the alveolar region of the lung and are not easily removed because

   1) their physical dimensions mean they cannot be removed by lung clearance mechanisms, and

   2) they are highly durable and do not dissolve in the lung lining fluids.

   Hence, they remain in the lung for a long period of time, causing inflammation and ultimately disease. Asbestos is an example of such a biopersistent fibre. High aspect ratio NOAA of similar morphology (shape and rigidity) and durability are therefore likely to persist in the lungs, if inhaled.

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

---

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

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

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