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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

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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 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).

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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.

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

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.

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

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

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.

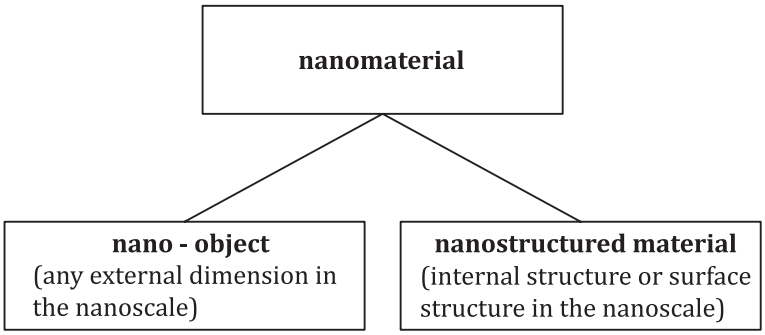


Figure 1 — Nanomaterials framework (Based on ISO/TS 80004-1:2015)[1]

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.

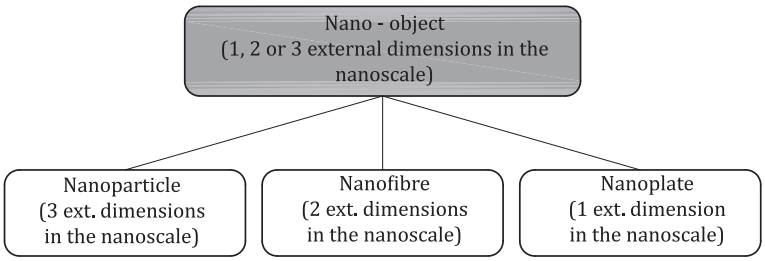
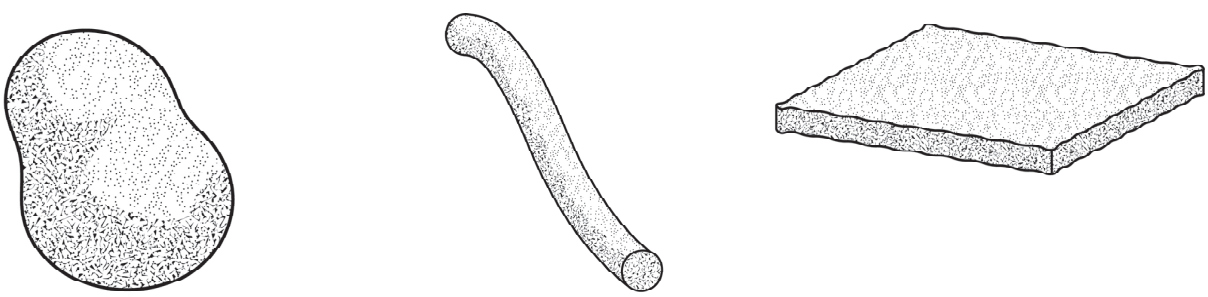


Figure 2 — Fragment of hierarchy of terms related to nano-objects (ISO/TS 80004-2:2015)[2]



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]

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].

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

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.