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Nanotechnologies — Aerosol generation for air exposure studies of nano-objects and their aggregates and agglomerates (NOAA)

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National foreword

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Nanotechnologies — Aerosol generation for air exposure studies of nano-objects and their aggregates and agglomerates (NOAA)

Nanotechnologies — Génération d'aérosols pour réaliser des études d'exposition à l'air des nano-objets et de leurs aggrégats et agglomérats (NOAA)

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Contents

Page

Foreword ... **v**

Introduction ... **vi**

1 Scope ... **1**

2 Normative references ... **1**

3 Terms and definitions ... **1**

4 Abbreviated terms ... **7**

5 Study design considerations ... **8**
5.1 General ... 8
5.2 Workplace exposure scenario ... 8
5.3 Existing inhalation toxicity testing guidelines ... 9
5.4 Globally harmonized system of classification and labelling of chemicals (GHS) ... 9

6 Considerations in selection of proper generators ... **9**
6.1 Basic scheme ... 9
6.1.1 Flow chart ... 9
6.1.2 Selection of study ... 11
6.1.3 Characterization of physicochemical properties of nanomaterials ... 11
6.1.4 Exposure information on possible use or handling and manufacturing ... 11
6.1.5 Exposure characteristics ... 11
6.1.6 Types of inhalation exposure methods ... 12
6.1.7 Particle characterization method ... 12

7 NOAA aerosol generators ... **12**
7.1 General ... 12
7.2 Dry dissemination ... 15
7.2.1 Wright dust feeder (see Figure 2) ... 15
7.2.2 Brush type aerosol generator (see Figure 3) ... 16
7.2.3 Small scale powder disperser (SSPD; see Figure 4) ... 17
7.2.4 Fluidized bed aerosol generator (FBG; see Figure 5) ... 18
7.2.5 Acoustic dry aerosol generator elutriator (ADAGE; see Figure 6) ... 19
7.2.6 Vilnius aerosol generator (VAG; see Figure 7) ... 20
7.2.7 Rotating drum generator (see Figure 8) ... 21
7.3 Wet dissemination ... 23
7.3.1 Atomizer/nebulizer (see Figure 9 to Figure 11) ... 23
7.3.2 Electro-static assist axial atomizer (see Figure 12) ... 26
7.4 Phase change ... 27
7.4.1 Evaporation/condensation generator (see Figure 13) ... 27
7.4.2 Spark generator ... 28
7.4.3 Condensation nano-aerosols ... 29
7.5 Chemical reaction ... 30
7.5.1 Combustion ... 30
7.6 Liquid phase filtration/dispersion — Critical point drying (tertiary butyl alcohol sublimation) and direct injection system for whole-body inhalation studies ... 32
7.6.1 Principle of operation ... 32
7.6.2 Advantages ... 32
7.6.3 Limitations ... 32

8 Experimental integration ... **36**
8.1 General ... 36
8.2 Exposure characterization ... 37
8.3 Particle properties ... 37
8.4 Considerations for ***in vivo*** exposure systems ... 37

9 Considerations in use of nano-aerosol generator for *in vitro* study ... **38**

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Document Sharing Hub

Full document details: PD ISO/TR 19601:2017

Annex A (informative) **NOAA generators, their particle size distribution and measurement methods** **39**
Annex B (informative) **Aerosol dilution system** **44**
Bibliography **47**

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

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Introduction

Inhalation is a primary route of exposure to aerosolized nano-objects and their aggregates and agglomerates (NOAA). The NOAAs include nano-objects 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 sizes larger than 100 nm. To evaluate the inhalation toxicity of NOAA, it is important to consider certain parameters that make the toxicity testing relevant to human exposure. The three critical aspects to consider when designing and conducting nanomaterial inhalation toxicity study are

a) uniform and reproducible nano-object aerosol generation that is relevant to realistic exposures,

b) thorough characterization of nanomaterials throughout the duration of testing including starting and generated materials, and

c) use of occupational exposure limits (OEL) and reference concentrations (RfC) (as derived from existing studies and/or real-time exposure monitoring data) for dosimetry.

Therefore, to conduct *in vitro* and *in vivo* NOAA, it is important to choose an appropriate NOAA aerosol generator and use online and off-line techniques for nano-object characterization.

Aerosol generation techniques are well established and have been used in laboratory studies, inhalation therapy and industry for many years. A number of aerosol generation techniques are routinely used for other materials that can be adapted for nano-object inhalation toxicity studies. In principle, aerosol generation involves application of some form of energy to the material to reduce its size or to form small particles that are dispersed in a gas stream.

This document provides the status of nano-object aerosol generators. This document further discusses the advantages and limitations of the respective nano-object generators, which can aid in choosing the appropriate generator when conducting the nano-object inhalation toxicity study. No matter what generation system is used for toxicity study, the generated atmospheres should be thoroughly characterized in order to allow for comparison to occupational exposure atmospheres so that a valid risk assessment/occupational exposure limit (OEL) can be developed. Therefore, this document will also provide nano-object aerosol size information generated from respective generators along with the proper nano-object characterization methods. This document complements the work of the Organization for Economic Cooperation and Development (OECD) Working Party on Manufactured Nanomaterial (WPMN) and other related framework documents. Recommendations and guidelines to assist investigators in making appropriate choices of an aerosol generator for their target NOAAs to be tested are presented in this document.

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Nanotechnologies — Aerosol generation for air exposure studies of nano-objects and their aggregates and agglomerates (NOAA)

1 Scope

This document describes methods for producing aerosols of nano-objects and their aggregates and agglomerates (NOAA) for *in vivo* and *in vitro* air exposure studies. The purpose of this document is to aid in selecting an appropriate aerosol generator to fulfil a proposed toxicology study design. This document describes characteristics of aerosol generation methods, including their advantages and limitations. This document does not provide guidance for aerosolization of specific nano-objects.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO/TS 80004-1, *Nanotechnologies — Vocabulary — Part 1: Core terms*

ISO/TS 80004-2, *Nanotechnologies — Vocabulary — Part 2: Nano-objects*

ISO/TS 80004-4, *Nanotechnologies — Vocabulary — Part 4: Nanostructured materials*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO/TS 80004-1, ISO/TS 80004-2, and ISO/TS 80004-4 and the following apply.

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

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

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

3.1
aerodynamic diameter
diameter of a spherical particle with a density of 1 000 kg/m^3 that has the same settling velocity as the *particle* (3.29) under consideration

Note 1 to entry: Aerodynamic diameter is related to the inertial properties of aerosol particles and is generally used to describe particles larger than approximately 100 nm.

[SOURCE: ISO/TR 27628:2007, 2.2]

3.2
aerosol
metastable suspension of solid or liquid *particles* (3.29) in a gas

[SOURCE: ISO/TR 27628:2007, 2.3]

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3.3
agglomerate
collection of weakly bound *particles* (3.29) or *aggregates* (3.4) or *mixtures* (3.17) of the two where the resulting external surface area is similar to the sum of the *surface areas* (3.32) 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* (3.31) and the original source particles are termed *primary particles* (3.30).

[SOURCE: ISO/TS 80004-4:2011, 2.8]

3.4
aggregate
particle (3.29) comprising strongly bonded or fused particles where the resulting external surface area may be significantly smaller than the sum of calculated *surface areas* (3.32) of the individual components

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

Note 2 to entry: Aggregates are also termed *secondary particles* (3.31) and the original source particles are termed *primary particles* (3.30).

[SOURCE: ISO/TS 80004-4:2011, 2.7]

3.5
coagulation
formation of larger *particles* (3.29) through the collision and subsequent adhesion of smaller particles

[SOURCE: ISO/TR 27628:2007, 2.6]

3.6
differential electrical mobility classifier
DEMC
classifier that is able to select aerosol particles according to their electrical mobility and pass them to its exit

Note 1 to entry: A DEMC classifies aerosol particles by balancing the electrical force on each particle with its aerodynamic drag force in an electrical field. Classified particles are in a narrow range of electrical mobility determined by the operating conditions and physical dimensions of the DEMC, while they can have sizes due to difference in the number of charges that they have.

[SOURCE: ISO 15900:2009, 2.7]

3.7
differential mobility analysing system
DMAS
system to measure the size distribution of submicrometre aerosol particles consisting of a *DEMC* (3.6), flow meters, a particle detector, interconnecting plumbing, a computer and suitable software

[SOURCE: ISO 15900:2009, 2.8]

3.8
dustiness
propensity of a material to generate airborne dust during its handling

[SOURCE: EN 1540:2011]

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3.9
engineered nanomaterial
nanomaterial (3.21) that is rationally designed manufactured

[SOURCE: ISO/TS 80004-1:2015, 2.8, modified]

3.10
hazard category
division of criteria within each *hazard class* (3.11) as used in Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

3.11
hazard class
nature of the physical, health or environmental hazard as used in Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

[SOURCE: GHS, 2015]

3.12
geometric mean diameter
GMD
measure of central tendency of particle size distribution using the logarithm of particle diameters

Note 1 to entry: The GMD is normally computed from particle counts and when noted may be based on *surface area* (3.32) or particle volume with appropriate weighting, as:

$$\ln(\mathrm{GMD}) = \frac{\sum_{i=m}^{n} \Delta N_i \ln(d_i)}{N}$$

where

d_i is the midpoint diameter for the size channel, i;

N is the total concentration;

ΔN_i is the concentration within the size channel, i;

m is the first channel;

n is the last channel.

[SOURCE: ISO 10808:2010, 3.5, modified]

3.13
geometric standard deviation
GSD
measure of width or spread of particle sizes, computed for the *DMAS* (3.7) by

$$\ln(\mathrm{GSD}) = \sqrt{\frac{\sum_{i=m}^{n} N_i \left[\ln d_i - \ln(\mathrm{GMD})\right]^2}{N-1}}$$

[SOURCE: ISO 10808:2010, 3.6]

3.14
count median diameter
CMD
diameter equal to *GMD* (3.12) for particle counts assuming a logarithmic normal distribution

[SOURCE: ISO 10808:2010, 3.7, modified]

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3.15
mass median aerodynamic diameter
MMAD
calculated *aerodynamic diameter* (3.1) which divides the *particles* (3.29) of an *aerosol* (3.2) in half based on mass of the particles

Note 1 to entry: 50 % of the particles by mass will be larger than the median diameter and 50 % of the particles will be smaller than the median.

[SOURCE: EPA IRIS Glossary]

3.16
manufactured nanomaterial
nanomaterial (3.21) intentionally produced to have specific properties or composition

[SOURCE: ISO/TS 80004-1:2015, 2.9, modified]

3.17
mixture
solution composed of two or more *substances* (3.33) in which they do not react

Note 1 to entry: A solution is also a mixture.

[SOURCE: GHS, 2015]

3.18
mobility
<aerosols> propensity for an aerosol particle to move in response to an external influence, such as an electrostatic field, thermal field or by diffusion

[SOURCE: ISO/TR 27628:2007, 2.9]

3.19
nano-aerosol
fluid nanodispersion with gaseous matrix and at least one or more liquid or solid nanophase (including *nano-objects* (3.22))

[SOURCE: ISO/TS 80004-4:2015, 3.5.4]

3.20
nanofibre
nano-object (3.22) with two similar external dimensions in the *nanoscale* (3.25) and the third dimension significantly larger

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

Note 2 to entry: The terms nanofibril and nanofilament can also be used.

[SOURCE: ISO/TS 80004-2:2015, 4.5, modified]

3.21
nanomaterial
material with any external dimension in the *nanoscale* (3.25) or having internal or surface structure in the nanoscale

Note 1 to entry: Generic term covering both *nano-object* (3.22) and *nanostructured material* (3.27).

EXAMPLE Nanocrystalline materials, nanoparticle powder, materials with nanoscale precipitates, nanoscale films, nano-porous material, nanoscale emulsions and materials with nanoscale textures on the surface. End products containing nanomaterials (e.g. tires, electronic equipment, coated DVDs) are not themselves nanomaterials.

[SOURCE: ISO/TS 80004-1:2015, 2.4, modified]

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3.22
nano-object
discrete piece of material with one, two or three external dimensions in the *nanoscale* (3.25)

Note 1 to entry: The second and third external dimensions are orthogonal to the first dimension and to each other.

[SOURCE: ISO/TS 80004-1:2015, 2.5]

3.23
nanoparticle
nano-object (3.22) with all external dimensions in the *nanoscale* (3.25) where the lengths of the longest and the shortest axes of the nano-object do not differ significantly

Note 1 to entry: If the dimensions differ significantly (typically by more than 3 times), terms such as *nanofibre* (3.20) or *nanoplate* (3.24) may be preferred to the term nanoparticle.

[SOURCE: ISO/TS 80004-2:2015, 4.4]

3.24
nanoplate
nano-object (3.22) with one external dimension in the *nanoscale* (3.25) and the other two external dimensions significantly larger

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

[SOURCE: ISO/TS 80004-2, 4.6, modified]

3.25
nanoscale
size range from approximately 1 nm to 100 nm

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

Note 2 to entry: The lower limit in this definition (approximately 1 nm) is introduced to avoid single and small groups of atoms from being designated as *nano-objects* (3.22) or elements of *nanostructures* (3.26), which might be implied by the absence of a lower limit.

[SOURCE: ISO/TS 80004-1:2015, 2.1, modified]

3.26
nanostructure
interrelation of the constituent parts of a material in which one or more of those constituent parts belong to the *nanoscale* (3.25)

[SOURCE: ISO/TS 80004-1:2015, 2.6, modified]

3.27
nanostructured material
material having internal or surface structure in the *nanoscale* (3.25)

Note 1 to entry: If external dimension(s) are in the nanoscale, the term *nano-object* (3.22) is recommended.

[SOURCE: ISO/TS 80004-1:2015, 2.7, modified]

3.28
nanotube
hollow nanofibre

[SOURCE: ISO/TS 80004-2:2015, 4.8]

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3.29
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 definition applies to particle *nano-objects* (3.22).

[SOURCE: ISO/TS 26824:2013, 1.1]

3.30
primary particle
original source particle of *agglomerates* (3.3) or *aggregates* (3.4) or *mixtures* (3.17) of the two

Note 1 to entry: Constituent particles of agglomerates or aggregates at a certain actual state may be primary particles, but often the constituents are aggregates.

Note 2 to entry: Agglomerates and aggregates are also termed *secondary particles* (3.31).

[SOURCE: ISO 26824:2013, 1.4]

3.31
secondary particle
particle (3.29) formed through chemical reactions in the gas phase (gas to particle conversion)

[SOURCE: ISO/TR 27628:2007, 2.17]

3.32
surface area
area of external surface plus the internal surface of its accessible macro- and mesopore

Note 1 to entry: Includes mass-specific surface area or volume-specific surface area.

[SOURCE: ISO/TR 13014:2012, 2.28]

3.33
substance
chemical elements and their compounds in the natural state or obtained by any production process, including any additive necessary to preserve the stability of the product and any impurities deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition

[SOURCE: GHS, 2015]

3.34
ultrafine particle
particle (3.29) with a nominal diameter (such as geometric, aerodynamic, *mobility* (3.18), projected-area or otherwise) of 100 nm or less

Note 1 to entry: The term is often used in the context of particles produced as a by-product of a process (incidental particles), such as welding fume and combustion fume.

[SOURCE: ISO/TR 27628:2007, 2.21]

3.35
reference concentration
benchmark estimates of the quantitative dose–response assessment of chronic non-cancer toxicity for individual inhaled chemicals

[SOURCE: EPA, 1994]

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4 Abbreviated terms

ADS	aerosol dilution system
ADAGE	acoustic dry aerosol generator elutriator
AERCON	aerosol control unit
ALI	air–liquid interface
APS	aerodynamic particle sizer
CMD	count median diameter
CNT	carbon nanotube
DEHS	diethylhexyl sebacate
DEMC	differential electrical mobility classifier
DI	deionized
DMAS	differential mobility analysing system
DOP	dioctyl phthalate
EDX	energy dispersive X-ray analyser
ELPI	electrical low pressure impactor
EM	electron microscopy
EPA	Environmental Protection Agency
EU	European Union
FBG	fluidized bed aerosol generator
GD	guidance document
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GLP	good laboratory practice
GMD	geometric mean diameter
GSD	geometric standard deviation
MAD	mutual acceptance of data
MFC	mass flow controller
MMAD	mass median aerodynamic diameter
MOUDI	micro-orifice uniform deposit impactor
MWCNT	multi-walled carbon nanotube
NOAA	nano-objects and their aggregates and agglomerates
NM	nanomaterial

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OECD	Organization for Economic Cooperation and Development
OEL	occupational exposure limit
OPC	optical particle counter
OPPTS	office of pollution prevention and toxic substances
PSL	polystyrene latex
RfC	reference concentration
RPM	revolutions per minutes
SEM	scanning electron microscope
SNPS	scanning nanoparticle sizer
SPSF	standard project submission form
SSPD	small scale powder disperser
SWCNT	single-walled carbon nanotube
TEM	transmission electron microscope
TEOM	tapered element oscillating microbalance
TG	test guideline
TGA	thermogravimetric analysis
VAG	vilnius aerosol generator
WPMN	working party on manufactured nanomaterials

5 Study design considerations

5.1 General

Inhalation toxicity studies are important for evaluating the health risk of workers and the general population exposed to aerosolized NOAA. In designing an inhalation study for NOAA and selecting the proper generator, it is important to consider possible workplace exposure scenarios and existing inhalation toxicity testing guidelines.

5.2 Workplace exposure scenario

When designing an inhalation toxicity study for NOAA exposure, the actual workplace exposure scenario should be considered. Generation of NOAA aerosol should simulate actual workplace NOAA emissions and exposure in terms of concentration (mass or number based if known), shape, size and distribution size of NOAA, frequency of exposure, and handling and manufacturing conditions. For inhalation experiments, the starting NOAA could be in powder form, well or poorly suspended in liquid media or solid-state material as generated by condensation/evaporation or spark generation. Various methods of NOAA generation could be adopted to generate NOAA aerosols to simulate an actual exposure situation.

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5.3 Existing inhalation toxicity testing guidelines

Generation of aerosols should be adapted to the needs described in existing inhalation testing guidelines, such as OECD Test Guideline (TG) 412, 413, 436 or Guidance Document (GD) 39[6][7][8][14][15] or equivalent or relevant national or international guidelines. The OECD is currently (2016) adapting the inhalation toxicity TGs to nanomaterials, adding investigations of effects in the lung after exposure to nanoparticles. The particle sizes described also for nanoparticles have an unchanged mass median aerodynamic diameter (MMAD) of up to 2 µm with a geometric standard deviation (GSD) up to 3.

5.4 Globally harmonized system of classification and labelling of chemicals (GHS)

The outcomes of the inhalation toxicity study may be used for hazard evaluation, classification and labelling according to GHS. In GHS, concentration ranges are used to describe the severity of toxicity, and this include ranges for inhalation toxicity, also valid for NOAA in a GHS context. The concentration units used are milligram per litre (mg/l) per time unit, which can be hour, 4 h or day, and the values triggering classification are from 0,05 to 5. See Table 1 to Table 3. For further information on GHS, consult the United Nations website at https://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev04/English/ST-SG-AC10-30-Rev4e.pdf.

Table 1 — Inhalation toxicity hazard category

Exposure route	Category 1	Category 2	Category 3	Category 4
Dust and mist (mg/l)	0,05	0,5	1,0	5

Table 2 — Guidance values for specific target organ toxicity (single exposure)

Route of exposure	Units	Category 1	Category 2
Inhalation (rat) dust/mist/fume	mg/l/4 h	$C \leq 1,0$	$5,0 \geq C \geq 1,0$

Table 3 — Guidance values for specific target organ toxicity (repeated exposure)

Route of exposure	Units	Category 1	Category 2
Inhalation (rat) dust/mist/fume	mg/l/6 h/day	$C \leq 0,02$	$0,02 < C \leq 0,2$

6 Considerations in selection of proper generators

6.1 Basic scheme

6.1.1 Flow chart

The basic scheme is described in Figure 1.

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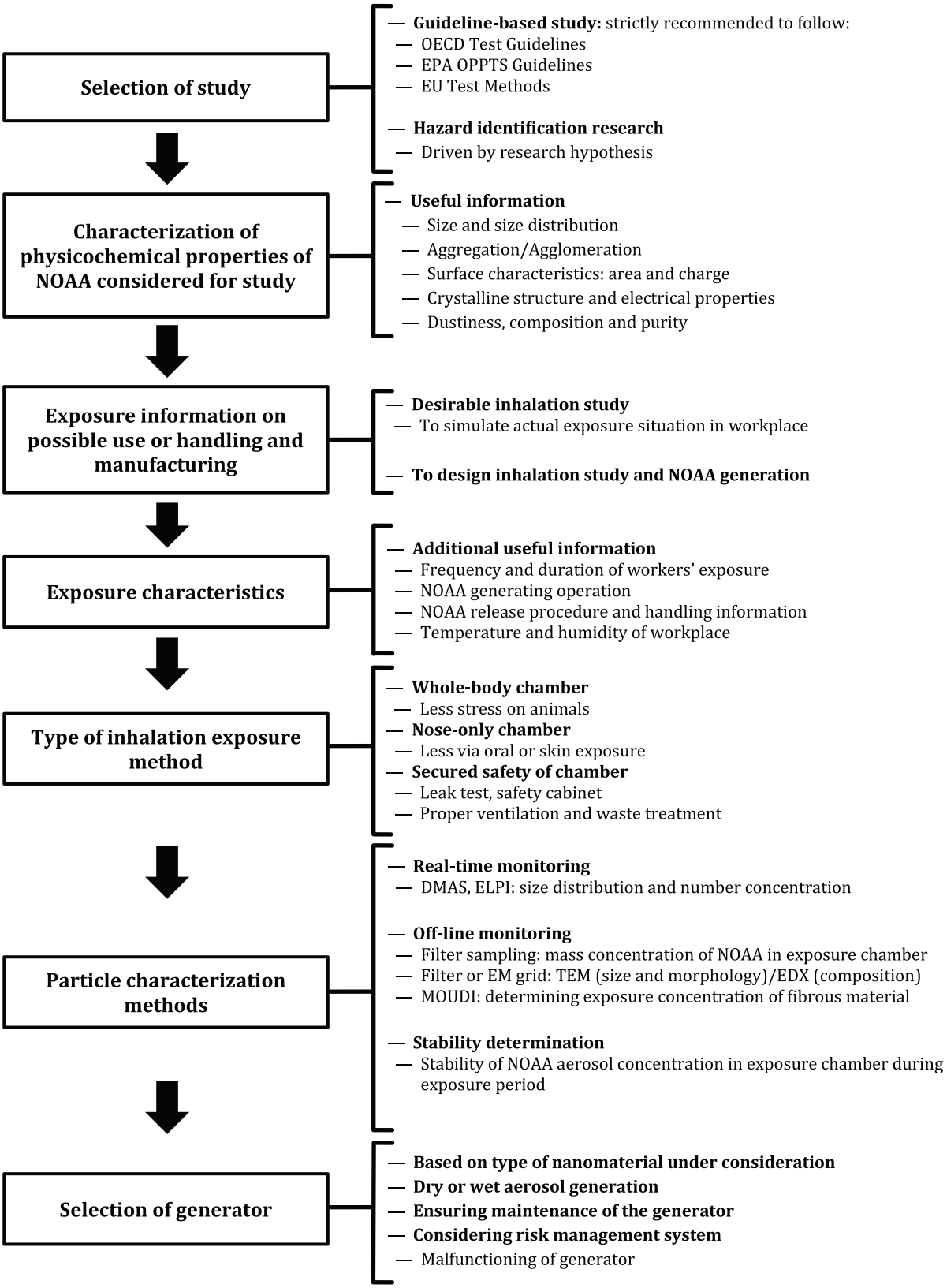

Figure 1 — Basic scheme in selection of proper generators

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6.1.2 Selection of study

Studies should be conducted based on the standardized testing guidelines such as the ones put forth by OECD (TG 403, 412, 413 and 436)[6][7][8][14], EPA OPPTS (870.1300, 870.3465 and 870.4100[16][17][18]) or the EU. It is recommended to strictly follow relevant test guidelines to determine the number of animals in the study, duration of exposure and the observation period and test material characterization (including concentration and particle size measurement and frequency of measurements). A study can be conducted according to good laboratory practice (GLP), which is regulatory requirement for new studies in some regions, (preferred) or non-GLP.

Also, studies from scientific research sources can be used for hazard identification of NOAA and the study design is usually more flexible than a test guideline based study. Of note here is that such studies are usually performed to prove a research hypothesis and are not recognized by the OECD mutual acceptance of data (MAD) principle. The study results can be published in a scientific journal or retained for in-house use.

6.1.3 Characterization of physicochemical properties of nanomaterials

The physicochemical characterization of the nanomaterial (NM) as manufactured is important before generation of a NOAA aerosol or *in situ* generation. NMs are manufactured using diverse synthesis procedures that impart those unique properties designed for specific applications. As a result, the materials might have a complex structure, include impurities and have different surface properties (coatings or other modifications). Such physicochemical properties dictate the toxicological output of NMs and should therefore be thoroughly characterized. Useful information on physicochemical properties includes, but is not limited to, particle size, size distribution, shape, aggregation/agglomeration, surface characteristics such as area and charge, crystalline structure, dustiness, composition and purity. Trace impurities such as presence of endotoxin, metal catalyst residue or impurities from the raw materials might affect the toxicity outcome[12][19]to[25]. Therefore, characterization of NM is critical to ascertain that the NM properties match the claims made by the manufacturer before any study initiation. Several international standards are currently available to characterize NMs. For instance, for characterization of single-wall carbon nanotubes (SWCNT), there are standards for using transmission electron microscopy (TEM)[26], scanning electron microscopes with energy dispersive X-ray spectroscopy (SEM-EDX)[27], near infrared (NIR)[28], thermogravimetric analysis (TGA)[29], characterization of volatile components in SWCNT samples using evolved gas analysis/gas chromatograph-mass spectrometry[30] and characterization of multi-wall carbon nanotubes (MWCNT) — mesoscopic factors[31]. Some other methods, such as Raman spectroscopy, that are not internationally standardized can be found in ISO/TR 13014. However, experimentation with the test NOAA is required before any study initiation to ascertain that the particle size distribution is representative of the size distribution observed during typical handling and use. Agglomerates of primary particles are present in most workplace exposures.

6.1.4 Exposure information on possible use or handling and manufacturing

A desirable inhalation study should simulate an actual exposure situation. Exposure information on NOAA in terms of particle mass, concentration, number, size, dispersion (dispersed or aggregated/agglomerated) or shape is very useful in designing the inhalation study. Depending upon this information, particle shape and concentration similar to realistic exposures could be determined.

6.1.5 Exposure characteristics

In addition to the exposure information described above, information on exposure characteristics such as frequency and duration of workers' exposure, worker activities, NOAA manufacturing operation, NOAA source release scenarios and handling information would be very useful in designing an inhalation study. Additional information on workplace temperature and humidity is also useful information.

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6.1.6 Types of inhalation exposure methods

Two types of exposure chambers are currently widely used for *in vivo* inhalation studies: whole-body chamber and nose-only chamber. The preferred method is whole-body exposure as it is more relevant to human exposure and causes the least pain, suffering and distress to animals. Nose-only exposure reduces oral and skin exposure potential and requires lesser quantity of test materials as compared with whole-body exposure. The choice of the exposure chamber should be based on the study design. The chambers should be secured with safety measures, such as leak-proof construction and leak testing, use of a safety cabinet, proper ventilation with exhaust emissions control and waste treatment.

6.1.7 Particle characterization method

6.1.7.1 Real-time monitoring

Use of real-time particle size and number monitoring devices are desirable. Such real-time monitors, including differential mobility analysing system (DMAZ) and electrical low pressure impactor (ELPI) will give particle size distribution information, as well as particle number concentration in real-time. From these instruments, the concentration stability of test atmospheres can be monitored in real time.

6.1.7.2 Off-line monitoring

Off-line filter sampling can also be used to determine mass concentration of NOAA in the inhalation chamber. For instance, the micro-orifice uniform deposit impactor (MOUDI) could be used to determine time-resolved aerosol particle size exposure concentration by mass including fibrous materials. In addition, off-line filter or EM grid sampling can be processed for TEM observation for size and morphology of NOAA and analysed further for composition by energy dispersive X-ray analyser (EDX). Furthermore, filter samples can be analysed for chemical composition.

6.1.7.3 Stability determination

Nanomaterial concentration should be determined according to test guidelines or test protocols. The stability of NOAA aerosol concentration in the inhalation chamber during the exposure period should be monitored regularly, desirably in real-time. If the concentration deviates more than 20 % during exposure period, stability needs to be improved[8].

6.1.7.4 Selection of generator

The selection of an aerosol generator should consider the following 5.1 to 5.4, electrical charge neutralization and production of undesirable by-products during the generating process requiring dilution or removal. After selecting the generator for NOAA, the maintenance of the generator should be ensured. In prevention of situations of unacceptable risk, such as malfunctioning of the generator, dust explosions and fire, a risk management approach should be considered and risky situations avoided. The description of the types and characteristics of the generators in Clause 6 should be used to select an appropriate generator for the study. It is important to assess the generator's performance for the proposed study and NOAA to be generated with regard to time of generation required, ease of maintenance and refilling.

7 NOAA aerosol generators

7.1 General

Advantages and limitations of generation techniques are listed in Table 4.

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