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Nanotechnologies — Lung burden mass measurement of nanomaterials for inhalation toxicity tests

Nanotechnologies — Mesure de la masse de la charge pulmonaire des nanomatériaux pour les études de toxicité par inhalation

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Contents

Foreword iv
Introduction v
1 Scope 1
2 Normative references 1
3 Terms and definitions 1
4 Abbreviated terms 7
5 Use of lung burden measurements for risk assessment of nanomaterials 7
6 Inhalation exposure and tissue sampling to determine lung burden 8
6.1 Inhalation exposure 8
6.2 Lung Burden Evaluation in Single or Multiple Lobes 8
6.3 Post-exposure Observation Points 9
7 Available methods for lung burden measurements 10
7.1 General 10
7.2 Carbon nanomaterials 10
7.3 Metal-based nanomaterials 11
7.4 Polymeric nanomaterials and others 12
8 Application of lung burden data to toxicokinetics of nanomaterials 12
8.1 General 12
8.2 Sampling points 12
8.3 Particle lung clearance and retention kinetics 12
8.3.1 General 12
8.3.2 One-compartment first-order clearance model 13
8.3.3 Two-compartment first-order model 14
Annex A (informative) Test scheme for 28-d study (TG 412) 17
Annex B (informative) Test scheme for 90-d study (TG 413) 18
Annex C (informative) Lung burden measurement methods 21
Bibliography 27

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~~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*.

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

Inhalation is a primary route of exposure to aerosolized nanomaterials and therefore appropriate inhalation toxicity tests are required to address risk assessment needs for these materials. For this reason, the Organisation for Economic Cooperation and Development (OECD) recently updated its inhalation toxicity test guidelines 412 (subacute) and 413 (subchronic) to make them applicable to nanomaterials~~[,][1][2][.]~~. These revised test guidelines require post-exposure lung burden measurements to be undertaken when a range-finding study or other relevant information suggests that inhaled test nanomaterials are poorly soluble with low dissolution rate and likely to be retained in the lung. The measurements of lung burden inform on pulmonary deposition and retention of nanomaterials in the lung. At least three lung burden measurements are needed ~~for evaluating clearance kinetics. The present document therefore lists number of observations and makes suggestions for consideration by the OECD~~to evaluate clearance kinetics.

This document gives information on how to derive clearance kinetic parameter values using lung burden measurement data. ~~Information provided within this document should therefore be a basis for dialogue with the OECD as this work complements the work of the OECD Working Party on Manufactured Nanomaterials (WPMN). As the OECD inhalation toxicity test guidelines TG412 and TG413 and the associated guidance document GD 39~~This document complements OECD TG 412[1] and OECD TG 413[2]. As References [1], [2] and [3] only provide limited information on methods for lung burden measurement for nanomaterials or the derivation of lung clearance kinetics, this document ~~will provide~~provides useful supporting information for conducting inhalation studies based on these test guidelines.

Nanotechnologies —— Lung burden mass measurement of nanomaterials for inhalation toxicity tests

1 Scope

The document provides information on the measurement of nanomaterial mass in tissue after inhalation exposure, which can inform on lung clearance behaviour and translocation.

2 Normative references

~~There are no normative references in this document.~~

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 80004 (all parts), *Nanotechnologies — Vocabulary*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in the ISO 80004 series and the following 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
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 under consideration

Note 1 to entry: Aerodynamic diameter is related to the inertial properties of *aerosol* (3.2) particles and is generally used to describe particles larger than approximately 100 nm.

[SOURCE: ISO/TR 27628:2007, ~~definition 2.~~2~~]~~.2[4]~~]~~]

3.2
aerosol
metastable suspension of solid or liquid particles in a gas

[SOURCE: ISO/TR 27628:2007, ~~definition~~ 2.3~~]~~[4]~~]~~]

3.3

agglomerate
collection of weakly or moderately 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/TS 26824:2013, definition 1.2] [5]

3.4
aggregate
particle comprising strongly bonded or fused particles where the resulting external surface area is significantly smaller than the sum of calculated surface areas 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, or otherwise combined former primary particles.

NOTE 2 to entry: The forces holding an aggregate together are strong forces, for example, covalent bonds, or those resulting from sintering or complex physical entanglement, or otherwise combined former primary particles.

[SOURCE: ISO/TS 26824:2013, definition 1.3] [5]

3.5
coagulation
formation of larger particles through the collision and subsequent adhesion of smaller particles

[SOURCE: ISO TR 27628:2007, definition 2.6] [4]

3.6
differential electrical mobility classifier
DEMC
classifier that is able to select aerosol particle sizes from a distribution that enters it and pass only selected sizes to the exit

Note to Entry: A DEMC is sometimes called a Differential Electrical Mobility Spectrometer (DEMS). A DEMC classifies aerosol particle sizes by balancing the electrical force on each particle in an electrical field with its aerodynamic drag force. Classified particles have different sizes due to their number of electrical charges and a narrow range of electrical mobility determined by the operating conditions and physical dimensions of the DEMC [6].

3.7
differential mobility analyzing system
DMAS
system to measure the size distribution of submicrometer aerosol particles consisting of a DEMC, a particle charge conditioner, flow meters, a particle detector, interconnecting plumbing, a computer, and suitable software

[SOURCE: ISO 15900: 2009][6]

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

[SOURCE: EN 15051:2006] [7]

3.9
engineered nanomaterial
nanomaterial designed for a specific purpose or function

[SOURCE: ISO/TS 80004-1, definition 2.8] [8]

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

3.11
hazard class
nature of the physical, health or environmental hazard as used in GHS

[SOURCE: GHS: 2011][9]

3.12
hazard statement
statement assigned to a hazard class and category as used in GHS that describes the nature of the hazards of a hazardous substance or mixture, including, where appropriate, the degree of hazard

[SOURCE: ISO 11014:2009, definition 3.6][10]

3.13
inhalation exposure chamber system
system designed to expose experimental animals to an inhaled test substance of predetermined duration and dose by either the nose-only or whole-body method

NOTE 1 to entry: The term "nose-only" is synonymous with "head-only" or "snout-only".

NOTE 2 to entry: Adapted from OECD TG 403, 412, 413, 1995.

3.14
nanomaterial generation system
device to generate nanomaterial aerosol with controlled size distribution and concentration

3.15
geometric mean diameter
GMD
measure of the central tendency of particle size distribution using the logarithm of particle diameters

NOTE to entry: The GMD is normally computed from particle counts and when noted may be based on surface area or particle volume with appropriate weighting, as:

d_i = midpoint diameter for the size channel, i

N = total Number

ΔN_i = Number within the size channel, i

~~m = first channel~~

~~n = last channel~~

~~[SOURCE: ISO 10808:2010b(E), definition 3.5][11]~~

~~**3.16**~~
~~**geometric standard deviation**~~
~~**GSD**~~
~~measure of width or spread of particle sizes, computed for the DMAS by~~

~~[SOURCE: ISO 10808:2010b(E), definition 3.6][11]~~

~~**3.17**~~
~~**count median diameter**~~
~~**CMD**~~
~~CMD is equal to CMD for particle counts assuming a logarithmic normal distribution. The general form of the relationship as described in ISO 9276-5 is~~

~~e = 2,71828…base of natural logarithms~~

~~p = dimensionality (type of quantity) of a distribution~~

~~r = dimensionality (type of quantity) of a distribution~~

~~s = standard deviation of the density distribution~~

~~$x_{50,r}$ = median particle size of a cumulative distribution of dimensionality, r~~

~~[SOURCE: ISO 10808:2010b(E), definition 3.7][11]~~

~~**3.18**~~
mass median aerodynamic diameter
MMAD
calculated *aerodynamic diameter* (3.1) which divides the particles of a measured *aerosol* (3.2) distribution in half based on the mass of the particles where fifty percent of the particles by mass will be larger than the median diameter and fifty per cent of the particles will be smaller than the median

[SOURCE: EPA IRIS Glossary~~]~~ [12]~~]~~]

3.~~19~~4
manufactured nanomaterial
nanomaterial (3.8) intentionally produced for commercial purposes to have specific properties or specific composition

[SOURCE: ISO/TS 80004-1~~, definition 2.9] [8]~~:2015, 2.9[8], modified — "for commercial purposes" has been added to the definition.]

3.~~20~~5
mixture

mixture composed of two or more substances in which they do not react

Note 1 to entry: A solution is a mixture as well.

[SOURCE: GHS, 2011] [9]]

3.216
mobility
propensity for an *aerosol* (3.2) particle to move in response to an external influence, such as an electrostatic field, thermal field or by diffusion

[SOURCE: ISO TR 27628, definition 2.9][4]

3.22
nanoaerosol
aerosol comprised of, or consisting of, nanoparticles or nano-objects

NOTE to entry: Aerosols may contain Nano-objects and their aggregates and agglomerates (NOAAs), which may include aggregates and agglomerates larger than 100 nm

Adapted from [ISO/TR 27628:2007][4], 2.9[4], modified — the domain "<aerosols>" has been removed.]

3.237
nanofibre
nano-object with two similar external dimensions in the nanoscale and the third dimension significantly larger

Note 1 to entry: A nanofibre can be flexible or rigid.

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

Note 3 to entry: The largest external dimension is not necessarily in the nanoscale.

[SOURCE: ISO/TS 80004-2] [ISO/TS 27687:2008, definition:2015, 4.5[13], modified — Notes 1 and 2 to entry have been replaced.]

3] [.8]
3.24
nanomaterial
nm
material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale

Note 1 to entry: This generic term is inclusive of *nano-object* and nanostructured material.

Note 2 to entry: See also engineered nanomaterial, manufactured nanomaterial and incidental nanomaterial.

[SOURCE: ISO/TS 80004-1, definition:2015, 2.4] [8]]

3.259
nano-object
discrete piece of material with one, two or three external dimensions in the nanoscale

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

~~[ISO/TS 80004-2, definition 2.2] [8]~~

~~3.26~~
nanoparticle
nano-object with all external dimensions in the nanoscale 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* (3.7) or *nanoplate* may be preferred to the term nanoparticle.

Note 2 to entry: Ultrafine particles may be nanoparticles.

[SOURCE: ISO/TS 80004-2~~, definition~~:2015, 4.4~~] [8]~~[13]]

3.~~27~~10
nanotube
hollow *nanofibre*

~~[ISO/TS 27687:2008, definition 4.4] [13]~~

(3.~~28~~7)

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

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

~~3.29~~
~~**nanoscale**~~
~~length range from approximately 1 nm to 100 nm~~

~~NOTE 1 to entry Properties that are not extrapolations from a larger size are predominantly exhibited in this length range~~

~~[~~[SOURCE: ISO/TS 80004-2~~, definition 2.1] [~~:2015 4.8~~]~~[13]]

3.~~30~~11
~~**nanostructure**~~
~~composition of inter-related constituent parts, in which one or more of those parts is a nanoscale region~~

~~NOTE to entry: A region is defined by a boundary representing a discontinuity in properties.~~

~~[ISO/TS 80004-1, definition 2.6] [8]~~

~~3.31~~
~~**nanostructured material**~~
~~material having internal nanostructure or surface nanostructure~~

~~NOTE to entry: This definition does not exclude the possibility for a nano-object to have internal structure or surface structure. If external dimension(s) are in the nanoscale, the term nano-object is recommended.~~

~~[ISO/TS 80004-1, definition 2.7] [8]~~

~~3.32~~

single-walled carbon nanotube
SWCNT
SWCNT single-walled carbon nanotube consisting of a single cylindrical graphene layer

Note 1 to entry: The structure can be visualized as a graphene sheet rolled into a cylindrical honeycomb structure.

[SOURCE: ISO/TS 80004-1, ~~definition;~~ 2015, 4.4~~]~~ ~~[8]]~~]

3.~~3~~312
multi-wall carbon nanotube
MWCNT
MWCNT multi-walled carbon nanotube ~~(4.3)~~ composed of nested, concentric or near-concentric graphene ~~(2.11)~~ sheets with interlayer distances similar to those of graphite ~~(2.12)~~

Note 1 to entry: The structure is normally considered to be many *single-walled carbon nanotubes* (~~4.4~~3.11) nesting each other, and would be cylindrical for small diameters but tends to have a polygonal cross-section as the diameter increases.

[SOURCE: ISO/TS 80004-1, ~~definition;~~ 2015, 4.6~~]~~ ~~[8]]~~]

3.~~3~~413
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*.

[SOURCE: ISO/TS 26824:2013, ~~definition~~ 1.4~~]~~ ~~[5]]~~]

3.~~3~~514
poorly soluble particle
inhaled test particles that are likely to be retained in the lung ~~(~~

[SOURCE: OECD TG 412, paragraph 2~~)~~ ~~[11]~~]

3.~~3~~615
primary particle
original source particle of *agglomerates* or *aggregates* or mixtures of the two

Note 1 to entry: Constituent particles ~~(3.3)~~ 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.

[SOURCE: ISO 26824:2013, ~~definition~~ 1.4~~]~~ ~~[5]]~~]

3.~~3~~716
secondary particle
particle formed through chemical reactions in the gas phase (gas to particle conversion)

[SOURCE: ISO/TR 27628:2007, ~~definition~~ 2.17~~]~~[~~[4]]~~]