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Workplace exposure — Assessment of dermal exposure to nano-objects and their aggregates and agglomerates (NOAA)

Exposition sur les lieux de travail — Évaluation de l'exposition cutanée aux nano-objets et à leurs agrégats et agglomérats (NOAA)

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Foreword

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ISO/TS 21623 was prepared by the European Committee for Standardization (CEN) Technical Committee CEN/TC 137, *Assessment of workplace exposure to chemical and biological agents*, in collaboration with ISO Technical Committee ISO/TC 146, *Air quality*, Subcommittee SC 2, *Workplaces atmospheres*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

Introduction

Dermal exposure assessment explores the dynamic interaction between environmental contaminants and the skin. In contrast to inhalation exposure assessment, the assessment of dermal exposure requires a different set of exposure considerations. During the last decades, the body of knowledge with regard to dermal exposure has expanded for many types of substances, which amongst others resulted in publications for the evaluation of dermal exposure to chemical substances that can be found, for example, in CEN/TR 15278, CEN/TS 15279, and ISO/TR 14294.

Currently, engineered/manufactured nanomaterials and nano-enabled products are produced and used on a wide scale. Occupational skin exposure to these substances can have biological relevance to human health. Potential adverse effects include local skin effects, systemic toxicity following skin absorption/uptake and inadvertent ingestion through the hand-to-mouth pathway. This document provides guidance for the evaluation of potential dermal exposure to manufactured nano-objects, their agglomerates and aggregates (NOAA).

This document is a compilation of the results of a pre-normative research project, executed under Mandate M/461 for standardization activities regarding nanotechnologies and nanomaterials as issued by the European Commission. This pre-normative research gives an overview of the mechanisms of occupational dermal exposure to nanoparticles or nano-enabled products. This includes potential concomitant for intake or uptake. It is based on relevant evidence of exposure for identified job titles. Part of the pre-normative research comprised experimental work on the skin penetration of nanoparticles, transfer of nanoparticles from a surface to the skin, and exploratory work on the feasibility to quantify dermal exposure to NOAA[4]-[6].

Workplace exposure — Assessment of dermal exposure to nano-objects and their aggregates and agglomerates (NOAA)

1 Scope

This document describes a systematic approach to assess potential occupational risks related to nano-objects and their agglomerates and aggregates (NOAA) arising from the production and use of nanomaterials and/or nano-enabled products. This approach provides guidance to identify exposure routes, exposed body parts and potential consequences of exposure with respect to skin uptake, local effects and inadvertent ingestion.

This document also considers occupational use of products containing NOAA by professionals, e.g. beauticians applying personal care products, cosmetics or pharmaceuticals, but does not apply to deliberate or prescribed exposure to these products by consumers.

This document is aimed at occupational hygienists, researchers and other safety professionals to assist recognition of potential dermal exposure and its potential consequences.

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.

EN 1540, *Workplace exposure — Terminology*

ISO 18158, *Workplace air — Terminology*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in EN 1540, ISO 18158 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 https://www.iso.org/obp

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/TS 80004-2:2015, 3.4]

3.2
aggregate
particle comprising 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.

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

[SOURCE: ISO/TS 80004-2:2015, 3.5]

3.3
dermal contact volume
volume containing the mass of the agent that contacts the *dermal exposure surface* (3.7)

Note 1 to entry: This is equivalent to the volume of the skin contaminant layer and for practical reasons represents the volume of the compartment where the mass of the substance is all contained.

[SOURCE: CEN/TR 15278:2006, 2.2, modified — Note 1 adapted]

3.4
dermal exposure concentration
dermal exposure mass (3.6) divided by the *dermal contact volume* (3.3) or the dermal exposure mass divided by the mass contained in the skin contaminant layer

Note 1 to entry: Dermal exposure concentration is expressed in g/l or g/kg or other appropriate units as necessary.

[SOURCE: CEN/TR 15278:2006, 2.4, modified — Note 1 adapted]

3.5
dermal exposure loading
dermal exposure mass (3.6) divided by the *dermal exposure surface* (3.7) area

Note 1 to entry: For practical reasons, it can be expressed as mass of agent in an exposed part of the skin contaminant layer divided by the surface area of that part.

[SOURCE: CEN/TR 15278:2006, 2.5]

3.6
dermal exposure mass
mass of agent present in the *dermal contact volume* (3.3)

Note 1 to entry: For practical reasons, it is defined by the amount of agent in g present in the skin contaminant layer, or other appropriate units as necessary.

Note 2 to entry: The outcome of the process of dermal exposure, i.e. the contact, can be expressed by different parameters of exposure.

[SOURCE: CEN/TR 15278:2006, 2.6, modified — Note 1 adapted]

3.7
dermal exposure surface
skin surface area where an agent is present

Note 1 to entry: For practical reasons, this is represented by a two-dimensional representation of the skin contaminant layer in cm^2.

[SOURCE: CEN/TR 15278:2006, 2.7]

3.8
nanocomposite
solid comprising a mixture of two or more phase-separated materials, one or more being *nanophase* (3.13)

Note 1 to entry: Gaseous nanophases are excluded.

Note 2 to entry: Materials with nanoscale phases formed by precipitation alone are not considered to be nanocomposite materials.

[SOURCE: ISO/TS 80004-4:2011, 3.2]

3.9
nano-enabled
exhibiting function or performance only possible with nanotechnology

Note 1 to entry: Potential release of NOAA from nano-enabled products is considered relevant in view of dermal exposure assessment.

[SOURCE: ISO/TS 80004-1:2015, 2.15, modified — Note 1 added]

3.10
nanomaterial
material with any external dimensions in the nanoscale or having internal structure or surface structure in the *nanoscale* (3.14)

[SOURCE: ISO/TS 80004-1:2015, 2.4, modified — Notes 1 and 2 deleted]

3.11
nano-object
discrete piece of material with one, two or three external dimensions in the *nanoscale* (3.14)

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]

3.12
nanoparticle
nano-object (3.11) with all external dimensions in the *nanoscale* (3.14) 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 three times), terms such as nanofibre or nanoplate may be preferred to the term nanoparticle.

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

3.13
nanophase
physically or chemically distinct region or collective term for physically distinct regions of the same kind in a material with the discrete regions having one, two or three dimensions in the *nanoscale* (3.14)

Note 1 to entry: Nano-objects embedded in another phase constitute a nanophase.

[SOURCE: ISO/TS 80004-4:2011, 2.12]

3.14
nanoscale
length range approximately from 1 nm to 100 nm

Note 1 to entry: Properties that are not extrapolations from larger sizes are predominantly exhibited in this length range.

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

3.15
perioral region
perioral area
area surrounding the mouth

Note 1 to entry: See Reference [10].

3.16
skin contaminant layer compartment
SCL
three-dimensional compartment on top of the stratum corneum (SC) of the human skin where sebum lipids, sweat and additional water from transepidermal water loss (TEWL) are present, including products from cornification and unshed corneocytes

3.17
source domain
SD
generation mechanism that determines particle emission characteristics for a particular life cycle stage

Note 1 to entry: Different mechanisms determine the emission rate, particle size distribution, source location and transport of NOAA during the various life cycle stages (synthesis, downstream use, application or treatment of products and end of life)[11].

4 Dermal exposure to NOAA — Evidence and exposure routes

4.1 General

The mechanisms of occupational dermal exposure and evidence for skin penetration and local skin effects have been defined in this document.

The relevance of dermal exposure to NOAA outlined in this document considers the following outcomes:

a) potential for penetration and systemic effects;

b) absorption by the stratum corneum (SC) and potential for local (skin) effect;

c) inadvertent ingestion.

4.2 Source domains

A conceptual source-receptor framework suitable for nanomaterials and nano-enabled products has been developed. This links the source domains concept, as developed for modelling occupational inhalation exposure to NOAA[11] with the conceptual framework for dermal exposure. The dermal exposure framework describes the various pathways, underlying mechanisms, and potential consequences for NOAA contamination of the skin[12].

The source domains (SD) reflect different mechanisms of release and consequently possible different nature of released aerosols and are thus associated with the life cycle stages of NOAA.

— SD 1: During the production phase (synthesis) prior to harvesting the bulk material, point source or fugitive emission, e.g. emissions from the reactor, leaks through seals and connections, and incidental releases, can take place. In these cases, discrete nanoparticles and homogeneous and inhomogeneous agglomerates will be formed.

— SD 2: During the manufacturing of products, the handling and transfer of bulk manufactured nanomaterial powders with relatively low energy nanoparticles can be released, e.g. during collection, harvesting, bagging/bag dumping/bag-emptying, dumping, scooping, weighing, dispersion/compounding in composites, etc. However, the powders are already in agglomerated stage and high shear forces are needed for deagglomeration. Therefore, the majority of the released particles will be agglomerates.

— SD 3: During further processing or in the use phase of a ready-to-use nano-product, release can be expected during the relatively high-energy dispersion/application of

  — solid, powdery or (liquid) intermediates containing highly concentrated (>25 %) nanoparticles, e.g. pouring/injection moulding, (jet) milling, stirring/mixing. As higher shear forces can occur during high energy dispersion, de-agglomeration can occur, and

  — relatively low concentrated (<5 %) ready-to-use products, e.g. application of coatings or spraying of solutions that can form nano-sized aerosols after evaporation of the liquid phase component, usually of mixed composition.

— SD 4: During the use phase of a product or its end-of-life phase, activities resulting in fracturing and abrasion of manufactured nanoparticles-enabled end products at work sites can result in release of NOAA, e.g. a) low energy abrasion, manual sanding or b) high energy machining (e.g. sanding, grinding, drilling, cutting, shredding, etc.). High temperature processes like burning are included. In case of release, most likely multi-composed aerosols will be emitted, and in case of machining also matrix-bound nanoparticles, whereas during thermal processes nanoparticles can also be formed following nucleation and condensation of vapours.

Process conditions will determine the release process (i.e. mechanism, form, composition and level of release) and together with handling the process of skin contamination (i.e. through direct contact, deposition from the air compartment or transfer from contaminated surfaces). In addition, professional use of personal care products can result in direct contact of the product with the skin. Transformation (e.g. change in particle size distribution, agglomeration, etc. of the nanomaterial on the skin compared to the release) can occur either directly by the exposure process or route (e.g. transfer or direct contact), or during time of residence in the air compartment.

The level of exposure, either dermal exposure concentration, mass or surface area of exposed (body) location(s) will be determined by the underlying processes of release and exposure. In addition, the exposure time, characteristics of the substances and skin physiological conditions need to be considered.

4.3 Exposure routes

Observational studies show that the most highly exposed body parts are the hands, and the predominating exposure pathway is nanoparticle transfer from contaminated surfaces[13]-[15]. However, deposition of airborne aerosols or direct contact with products containing NOAA can also contaminate other body parts (e.g. forearms and forehead). Laboratory experiments carried out as part of the pre-normative research, showed that transfer efficiency for nano-size particles was approximately 30 times higher than that of micron-size particles, and showed for each particle size that the higher the log-transformed loading, the lower the transfer efficiency (after accounting for particle size)[4][6]. Location of the exposure is of particular interest, since both the thickness of the SC and the density of the hair follicles varies substantially over body locations, which is an important parameter with regard to potential penetration and local effects of nanoparticles through the skin[16]-[19]. In addition to skin physiology, skin conditions and time of contact, the actual contact site is also relevant for potential inadvertent oral exposure due to hand-to-mouth contact[20].

Dermal exposure risk by industrial sector and job title are based on reported use of nanomaterials and nano-enabled products (see Annex A). No indication on the level of dermal exposure can be extracted from available information. However, based on the form of NOAA and nano-enabled products present in the work environment and the type of activities performed by the worker, it is possible to have a first indication of the potential for dermal exposure occurring at the workplace and the accompanying potential risk.

Nanoparticles on the skin can penetrate SC reaching viable epidermis using different pathways:

a) through sweat glands and hair follicles, which is probably the most efficient way for penetration and permeation of NOAA;

b) the intercellular route, which is only possible for very small NOAA (<4 nm) or in damaged skin condition;

c) the intracellular pathway is unlikely to be relevant for NOAA, but might be relevant for released (metal) ions.

Present evidence suggests that only very small particles (<4 nm) can penetrate intact skin, whereas insoluble, nonreactive particles with sizes >45 nm will not be absorbed by the intact skin. Penetration in the intermediate size ranges was only observed in the case of a disrupted skin where the barrier function of the skin was affected. Flexible/non-rigid NOAA, e.g. liposomes and micelles, especially spherical lipid structures, can deviate from this categorization since ultra-deformable liposomes, despite their nominal size of normally around 100 nm to 200 nm, can squeeze through the much narrower SC lipid bilayers due to their flexibility[21].

When handling liquid products at the workplace (e.g. by means of stirring, spraying, etc.) or due to vapour condensation, nanoscale droplets containing NOAA can be formed. Depending on the volatility of the substance, these droplets can easily evaporate or stay in the air for a longer period, and can even increase in volume over time due to condensation processes[22]. When these droplets come into contact with the skin (resulting in moistening of the skin), the chemical composition of the liquid, its skin-damaging properties and percutaneous absorption characteristics have to be taken into account, regardless of the droplets' original dimensions. Particular attention shall be given to nanoscale droplets consisting of liquid dispersions, that can release solid NOAA (e.g. metal salts) after evaporation of the solvent.

In case of exposure to metal (oxide) nanoparticles (Ni, Cr, Co, etc.) or carbon-based nanoparticles with metal catalytic residues, the potential release of ions can induce local skin effects (e.g. irritation and contact dermatitis), which can be enhanced by a relatively long time of residence in case of penetration of NOAA into the hair follicles. Allergic contact dermatitis is expected for certain types of nanoparticles, yet not much data exists in the peer-reviewed literature[23].

The integrity of SC and its damage due to pre-existing disease and other work-related conditions (e.g. wet work and abrasion) can be assessed relatively easily with subjective assessment methods, including questionnaires (see Annex B). Biophysical measurements of skin barrier, for instance measuring transepidermal water loss (TEWL), can have some utility in the workplace but methods are not well established. Currently, no data are available to evaluate the potential for oral intake of NOAA due to hand-mouth contact. It is assumed that determinants of inadvertent ingestion of NOAA do not differentiate from those for conventional chemicals, which means that inadvertent ingestion exposure by indirect contact depends on

— the mass loading of substance on hand or object,

— the transfer efficiency from hand or object to the perioral area (proportion),

— transfer efficiency from the perioral area to the oral cavity (proportion),

— the surface area of the hand or object involved in contact (proportion), and

— the frequency of hand- or object-to-perioral contacts.

5 Stepwise approach for assessment of dermal exposure to NOAA

5.1 General

The assessment of dermal exposure to NOAA shall begin with an initial screening assessment considering the following:

— identification of hazards;

— identification of who is involved and how;

