Guidance on the Safety Assessment of Nanomaterials in Cosmetics
Revision 2019

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What is legally a nanomaterial?

**EU Cosmetics Legislation (EC) No 1223/2009**

- “Nanomaterial" means an *insoluble or biopersistent and intentionally manufactured* material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm.”

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The European Commission,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (1), and in particular Article 31(1) thereof,
The EC Recommendation (2011/696/EU)

- "Nanomaterial" means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm.

- In specific cases and where warranted by concerns for the environment, health, safety or competitiveness, the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50%.

- The recommendation also considers fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm as nanomaterials.
The EU Recommendation for a definition of a nanomaterial is not yet adopted for cosmetic regulation but should be considered when assessing safety of the materials composed of small particles.
The use of nanomaterials in cosmetic products is specifically covered under the EU Cosmetics Regulation (EC) No 1223/2009 and are subject to a high level of protection of human health.

The Regulation requires:

- Specific regulatory arrangements for nanomaterials.
- Cosmetic products containing nanomaterials to be notified to the European Commission 6 months prior to being placed on the market.
- Nanoscale ingredients to be labeled (name of the ingredient, followed by ‘nano’ in brackets).
- If there are concerns over safety of a nanomaterial, the EC will refer it to SCCS for scientific opinion.
Examples of possible uses of Nanomaterials in Cosmetics

**UV-Filter in sunscreens**
- better dispersibility, better visual clarity,
- effective UV-protection
- e.g. nano-Titanium dioxide, nano-zinc oxide

**Colorants**
- e.g. Carbon Black

**Oral Care**
- (Toothpaste, Mouth wash)
- e.g. Hydroxyapatite

**Antimicrobials**
- e.g. Nanosilver

**Other**
- (Absorbent, Bulking, Anticaking)
- e.g. Silica
Safety concerns on Nanomaterials in Cosmetics

- Nanoparticles may differ from conventional equivalents in terms of:
  - Solubility/dissolution
  - Particle agglomeration/aggregation
  - Surface adsorption/binding of other substances
  - Biological interactions close to molecular level
  - Potential surface catalysed reactions

- Nanoparticles may cross membrane barriers, and reach unintended parts of the body.

- Nanoparticles show altered biokinetics and specific particle behaviour.

- Internal exposure to insoluble and biopersistent particles may lead to adverse effects.
Current Guidance SCCS/1484/12

- SCCS/1484/12:
  Guidance on the Safety Assessment of Nanomaterials in Cosmetics
  Published in 2012
- Determination of Margin of Safety (MoS): preferably $\geq 100$
- Use of animal data
- March 2013: Ban on generation of *in vivo* data for all toxicological endpoints for cosmetic ingredients and cosmetics

Revision needed to consider safety assessment of cosmetic ingredients based on non-animal testing
Important documents for safety assessment of nanomaterials in cosmetics

**The SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation**

10th Revision

SCCS/1602/18

The SCCS adopted this guidance document at its plenary meeting on 24 – 25 October 2018.

**Guidance on the Safety Assessment of Nanomaterials in Cosmetics**

SCCS/1484/12

The SCCS adopted this opinion at its 15th plenary meeting of 26 – 27 June 2012.

**Checklists for Applicants submitting dossiers on Cosmetic Ingredients to be evaluated by the SCCS**

SCCS/1588/17

**Memorandum on**

"Relevance, Adequacy and Quality of Data in Safety Dossiers on Nanomaterials"

SCCS/1524/13
How to tackle safety concerns on Nanomaterials in Cosmetics

Nanomaterial Safety

Classical risk assessment paradigm can be applied

Hazard identification (acute, chronic)
Local/ systemic effects
Dose response characterisation

Exposure assessment
Routes of exposure
Likelihood & extent of exposure

Hazard

Exposure

Risk

Uncertainty factors
Margin of Safety
When is nano-specific risk assessment required?

Simplified from SCCS/1588/17

Exposure Assessment considering uptake routes

- Physicochemical characterisation - Is the material still in the nanoscale?
  - YES

Local effects?

Systemic exposure possible?

- YES

Physicochemical characterisation - Is the material still in the nanoscale?
  - YES

Nano-specific Risk Assessment

Hazard identification and dose-response-characterisation considering nano-aspects

- YES

Where a nanomaterial loses the nano-structure – e.g. in a formulation, a test medium, or biological surface/environment, due to solubilisation, breakdown or degradation, or interactions with other substances, it will no longer be expected to behave differently from its non-nano equivalent ➔ conventional Risk Assessment
Physico-chemical characterisation

- Detailed characterisation should include:
  - pristine nanoparticles as produced
  - as present during toxicological investigations
  - as added to the cosmetic product
- Physicochemical parameters to be measured should include:
  - chemical identity, chemical composition, concentration, particle size distribution, morphology and surface characteristics, solubility and dissolution constant, surface area, catalytic activity, dustiness, density and pour density, redox potential, pH, viscosity, stability in formulation and biological media
- Measurements should be carried out using mainstream methods - preferably more than one method – one of which being electron microscopy, with due consideration of the nano-aspects.

Data presented in a safety dossier on nanomaterials need to be relevant to the types of nanomaterials under evaluation.
Example nanodossier evaluation by SCCS  

**Nano-TiO\textsubscript{2} as UV filter in sunscreens**

**Mandate:**
Does the SCCS consider that use of titanium dioxide in its nanoform as a UV-filter in cosmetic products in a concentration up to maximum 25.0 % is safe for the consumers taken into account the scientific data provided?

**Information provided**

15 different nanomaterials  
Coated and uncoated  
Different organic and inorganic coating materials  
Different crystal structures (rutile and anatase)  
Different shapes (spherical and needle-shaped)

**Further information from literature used by the SCCS**
Example: Nano-TiO₂ as UV filter in sunscreens

Outcome of the SCCS Opinion (SCCS/1516/13):

The use of titanium dioxide (nano) as a UV-filter in sunscreens, with the characteristics as indicated in the opinion, and at a concentration up to 25% w/w, can be considered to not pose any risk of adverse effects in humans after application on healthy, intact or sunburnt skin.

The use of titanium dioxide (nano) in spray products that might lead to exposure of the consumer's lungs to titanium dioxide (nano) by inhalation cannot be considered safe.
Rationale for the Opinion:

Based on the provided information and the available literature, it was concluded that skin applications were unlikely to lead to:

- Skin penetration and thus systemic exposure
- Acute toxicity via dermal application or oral ingestion
- Skin irritation, eye irritation or skin sensitisation when applied on healthy skin
- Reproductive effects when applied on healthy skin

However

- Inconclusive genotoxicity as both positive and negative results were reported in literature
- Inhalation toxicity reported (therefore inhalation exposure to be avoided)
- Some penetration in the outer layers of stratum corneum (therefore limitation on the acceptable photo-catalytic activity)

SCCS Conclusions on dermal penetration confirmed by further experimental studies (Danish EPA, 2015)
Inclusion of Titanium dioxide (nano) in Cosmetics Regulation (14th July 2016):
Amendment of Annex VI to Cosmetic Regulation
List of UV filters allowed in Cosmetic Products, Entry 27 a

Important: details on specifications (column h):
Not to be used in applications that may lead to exposure of the end-users lungs by inhalation
Only nanomaterials having the following characteristics are allowed:

- purity ≥ 99 %,
- rutile form, or rutile with up to 5 % anatase, with crystalline structure and physical appearance as clusters of spherical, needle, or lanceolate shapes
- median particle size based on number size distribution ≥ 30 nm,
- aspect ratio from 1 to 4.5, and volume specific surface area ≤ 460 m²/cm³,
- coated with Silica, Hydrated Silica, Alumina, Aluminium Hydroxide, Aluminium Stearate, Stearic Acid, Trimethoxycaprylylsilane, Glycerin, Dimethicone, Hydrogen Dimethicone, Simethicone
- photocatalytic activity ≤ 10 % compared to corresponding non-coated or non-doped reference,
- nanoparticles are photostable in the final formulation

Example: Nano-TiO₂ as UV filter in sunscreens
Challenges for risk assessment cosmetic nano-ingredients

- Uncertainties and knowledge gaps in regard to properties, behaviour and toxicological effects (scientific development ongoing)
- Limitations in regard to validated methods for:
  - Detection/characterisation of nanomaterials
  - Exposure assessment via dermal, inhalation, ingestion routes
  - Alternative testing methods for nanomaterials

Issues emanating from the ban on animal testing of cosmetic ingredients in the EU
Information for risk assessment as needed according to Guidance

- Characterisation/identification data
- Evaluation of all relevant published literature
- Epidemiological and/or observational experiences (e.g. cosmeticovigilance data)
- *In vivo* studies (including performance date)
  - Exposure
  - Hazard identification
- *In vitro* studies according to the Guidance
  - Exposure
  - Hazard identification
Revision SCCS/1484/12
Guidance on the safety assessment of nanomaterials in cosmetics

Important to note: use of *in vivo* data for risk assessment is possible if:
- Data are generated before March 2013
- Data are generated because of other regulations (e.g. chemical (REACH), Pharmaceutical products)

Focus of current revision of SCCS Guidance on nanomaterials in cosmetics
- Safety concerns relate to the nanomaterials that are *insoluble, poorly-soluble, and bio-persistent*
- High quality of nanomaterial characterisation
- Risk assessment mainly based on evaluation of exposure
  - Possibilities for systemic exposure
- Use of *validated* or *scientifically sound* *in vitro* procedures
- Weight of evidence approach
Important issues in 2019 revision Guidance

- **High quality characterisation** including **unambiguous identification** of NM
  - Including surface characteristics
  - As produced (pristine), as used in toxicological testing and as used in final cosmetic product
- **Important characterisation parameters**
  - Chemical identity, chemical composition, production process, particle size and size distribution, morphology/shape, (crystallographic) structure, surface area, surface characteristics, solubility, dispersibility, catalytic activity, concentration, redox potential, pH, dustiness, viscosity, stability, other nanorelated aspects.
- **For toxicological testing**
  - Agglomeration/aggregation, degration, dissolution (particle behaviour)
  - Dose metrics (mass/volume, surface area, number of particles)
Important issues in 2019 revision Guidance
Exposure considerations

- Function and uses
- Relevant exposure scenarios
- Calculation external exposure
  - Dermal, inhalation, oral
- Possibility for systemic exposure
  - Translocation over biological barriers (skin, GI-tract, lung)
  - Possible translocation of degradation or dissolution fractions/products
- Toxicokinetics of nanomaterials
Default parameters for systemic exposure

- When no data are provided default factors will be used for the risk assessment
  - Dermal absorption
    - If no experimental data are provided, the SCCS will apply the default value of 50% of the administered dose as determined for conventional substances, or higher if warranted by the composition of a specific NM.”
  - Inhalation
    - Calculation of lung deposition by modelling.
    - For the absorption of NPs from the lung, a similar default absorption percentage of 100% of the calculated deposition of NPs in the lung will be used, if data on inhalation absorption are not available.
  - Oral
    - In the absence of data, 50% of the administered dose is used as the default oral absorption. If there is information to suggest poor oral bioavailability, a default value of 10% oral absorption could be considered (similar to cosmetic ingredients NoG).
Hazard identification

- Information from literature
- *In vivo* data (before March 2013, other regulations)
- *In vitro* non animal methods
  - Overt toxicity and local effects
- Local effects
- Systemic effects
Additional specific considerations

- Solubility and dispersion
- Surface interactions
- Surface coatings
  - Composition of surface coating materials
  - (No) change in physchem characteristics due to coating (exception for intended changes)
  - Data dermal penetration/stability coating
- Nano-carriers, nano-encapsulated materials
- Immunotoxicity (systemic exposure uptake by MPS organs)
- Genotoxicity (Ames test not suitable)
- Carcinogenicity
- Developmental and reproductive toxicity
Risk assessment

In view of lack of *in vivo* toxicological data Margin of Safety (MoS) using uncertainty factors can not be applied

Weight of evidence approach to support demonstration of safety of the cosmetic ingredient
Dossier requirements on nanomaterials as cosmetic ingredients

- SCCS/1588/17
  - Checklists for nanomaterials as cosmetic ingredients
    - Checklist for material characterisation
    - Checklist for information on exposure
    - Checklist for hazard identification (toxicological data)

- Revised SCCS/1484/12 Nano-Guidance
  - Checklist for hazard identification (toxicological data)
  - List of replacement methods for *in vivo* testing
Revision SCCS/1484/12 Annex 2. Checklist for hazard identification (toxicological data) to be provided for the safety evaluation of nanomaterials intended to be used as cosmetic ingredient

- Likelihood and extent internal exposure
- Dermal absorption
- Biokinetic behaviour (agglomeration/aggregation)
- Acute toxicity
- Irritation and corrosivity
- Skin sensitisation
- Mutagenicity/genotoxicity
- Repeated dose toxicity
- Photo-induced toxicity (sun exposed products)
- Reproductive toxicity (if significant systemic uptake)
- Carcinogenicity (if significant systemic uptake)
- Human data (where available)
- Other information
New nano guidance just has been published!


SCCS/1611/19

GUIDANCE ON THE SAFETY ASSESSMENT OF NANOMATERIALS IN COSMETICS

The SCCS adopted this document on 30-31 October 2019
Thank you for your attention