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Review

A Review of the EU's Regulatory Framework for the Production of Nano-Enhanced Cosmetics

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Abstract: Literature has suggested metallic nanomaterials (NMs) for a multitude of applications in cosmetic products, either as active ingredients or excipients. Alike most high-paced industrial sectors, cosmetology continues to capitalize on its unique properties/functions (e.g., as UV-filters, colorants, etc.), adding value to a wide range of products. However, as a result of their nano-scale, NMs do not always conform with the handling guidelines of their bulk counterparts, nor do conventional analytical methods account for their complex physicochemical and biological interactions. Among others, metallic nanoparticles have attracted the interest of many over the years due to their unique features, but possible precautions should be considered because of their bio-persistent nature. As a result, it is prevalent to consider a nano-specific framework, to regulate the use of NMs and the production of nano-enhanced cosmetics. To address this, we provide insight into the NMs that are currently used in the EU market, with a focus on metallic NMs, while analyzing the underlying legislation and relevant Opinions of the Scientific Committee on Consumer Safety (SCCS), from a scientific and commercial perspective. Even though the current Cosmetics Regulation (EU Regulation No 1223/2009) already entails specific provisions on NMs, cosmetic products incorporating unauthorized NMs have been repeatedly commercialized in the European Union. Considering the potential risks of NMs if they are mishandled, we provide an analysis of the risk assessment, as stated in Article 16 of the Cosmetics Regulation, to serve as a guideline for the future growth of nano-enhanced products. Based on the limited integration of metallic NMs along with multiple non-metallic NPs into cosmetic products, the attention of the community is directed towards coordinating efforts on the integration of metallic NMs into cosmetics.

Keywords: nanomaterials; cosmetics; EU regulation; opinions; SCCS; metallic nanomaterials (NMs)

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1. Introduction

Nanotechnology has attracted significant scientific interest due to the highly attractive properties of nanomaterials (NMs) and as a result, the market of nano-enhanced products has concomitantly grown to reach a multi-trillion dollar figure on an annual basis [1,2], with about half of that, dedicated to the field of personnel and health care [3]. The cosmetics industry was an early adopter of nanotechnology, with Christian Dior launching nano-enhanced products as early as 1986 [4]. Likewise, the world's largest cosmetics company, L'Oreal, ranked sixth among USA's nanotechnology patent holders in 2012, with a portfolio exceeding 600 million USD [5] and products featuring up to four NMs [6].

However, there are still concerns about the current legal framework [7] and whether it can adequately account for the complex physico-chemical properties of the manufactured

NMs, their bio-physical interactions, and whether analytical methods are suitable to account for their toxicological profile. During the past years, several opinions were published by EC with respect to the safety and dosage of various metallic nanoparticles in cosmetic products, some of which were approved and are still being used in the cosmetic industry, providing extra benefits to the final product.

The hazard and exposure assessment of any chemical (in the macro-, micro-, or nano-scale) brought to the European market is subject to the REACH regulation [8]. In 1976, the EU began monitoring the use of cosmetics and their ingredients on a more specific basis, through the harmonization of the cosmetics regulations (Directive 76/768/EEC), providing basic safety and quality guidelines for the European cosmetics sector. The directive was revamped with EC Regulation 1223/2009, published by the European Parliament and the Council on the 30th of November 2009, integrating international guidelines to ensure the protection and safety of commercially available cosmetic products. The main purpose of this regulation was to address the technological gaps, present in Directive 76/768/EEC, taking into consideration the latest scientific developments, including the use of nanomaterials [9,10].

NMs have become increasingly prevalent in various sectors and consumer products. In the wake of their rapid adoption, they have been defined in different ways, based on their intended applications and the regulations/legislation these are governed by. A summary of the most common definitions of nanomaterials is provided in Table 1.

Table 1. Classification/definition of nanomaterials based on prevalent regulatory bodies.

Regulation	Definition of Nanomaterial	Ref.
Commission Recommendation	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 1–100 nm.	[11]
Regulation (EU) No 528/2012—Biocidal Products Regulation (BPR)	A natural or manufactured active substance or non-active substance 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 1–100 nm.	[12]
Regulation (EC) No 1223/2009—Cosmetic products	A material that is insoluble or bio-persistent and intentionally manufactured with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm.	[9]

In view of these definitions, the Cosmetics Regulation predominantly provides guidelines for the integration of chemicals, for example, nanomaterials that are intentionally made and insoluble/partially soluble or bio-persistent (e.g., metals, metal oxides, etc.). Materials within the nanoscale, that are soluble, degradable, and/or non-persistent in biological systems (e.g., liposomes, emulsions, plant-derived vesicles, etc.) [13], are not considered nanomaterials under EC Regulation 1223/2009 and as such, are not governed by this Regulation.

As stated in the EC Regulation 1223/2009 (Article 19), cosmetics enhanced with nanomaterials must be labeled accordingly, in order to attain market transparency and inform the consumers and other parties of their presence. The nanomaterial should not only be included in the list of ingredients but also declared in accordance with internationally recognized nomenclatures, such as the INCI (International Nomenclature of Cosmetic Ingredients), followed by the addition of "nano" in brackets. For instance, nano-sized zinc oxide has been approved as a UV-filter and is widely used in sunscreens. In this context, any cosmetic product containing zinc oxide nanoparticles must clearly state "zinc oxide (nano)" in its ingredient list [9].

2. Identification of Nano-Enhanced Products and Specifications Thereof

Article 13 of the Cosmetics Directive clearly states that all cosmetic products marketed in Europe must be indexed at the Cosmetic Products Notification Portal (CPNP) by a responsible person (RP) such as the manufacturer and/or distributor. This ensures the online availability of the cosmetic information to competent authorities, that is, poison centers (or similar EU bodies), for purposes of market surveillance and direct treatment of unexpected complications [14].

The RP must declare on the CPNP whether the cosmetic product contains any nanomaterials, excluding colorants, preservatives, UV-filters, or other restricted ingredients [9]. Nano-enhanced products are however subject to safety requirements exceeding those of conventional cosmetics [15], demanding among others, a six-month evaluation period of their CPNP dossier prior to their commercialization. During this period, if concerns are raised, the Scientific Committee on Consumer Safety (SCCS), an authority responsible for the publication of Opinions on health and safety risks of non-food consumer products and services, is called to review the available toxicological data and/or perform a risk assessment [15].

Correspondingly, any ingredient satisfying the Cosmetics' Regulation definition for nanomaterials (Article 2) [9], is subject to the identification of the respective safety data, including the risk assessment [13].

For nanomaterials that are not yet included in Annexes III, IV V, or VI of the Cosmetics Regulation (i.e., have not yet undergone a full risk assessment by the SCCS), the RP should provide the Commission with at least the following information:

1. The identification of the NM (chemical name according to the International Union of Pure and Applied Chemistry (IUPAC) etc.).
2. The physicochemical characteristics of the NM (e.g., size, surface charge).
3. An estimation of the annual quantity of NM, intended to be placed on the market through the cosmetic product.
4. The toxicological profile of the NM.
5. The reasonably foreseeable exposure conditions.
6. The safety data of the NM and its respective risk assessment.

2.1. NM Identification

Prior to the notification of a new nanomaterial on CPNP, the RP (or a Delegate) is required to classify the final product, for which the NM is intended. There are three classification levels, structured as to fully categorize each product and the available choices of each subsequent level are determined by the prior selected one. For instance, if a product is categorized at Level 1 as a "Skin product", then Level 2 will provide—among others —its classification as a "Make-up product". Once the RP opts for this choice at Level 2, he can assort the product within one of the corresponding sub-categories of Level 3, for example, "Eyeliner" or "Lipstick".

The next step is to identify the nanomaterial by either entering data manually or by retrieving data from the Cosmetic Ingredient Database (CosIng) [15]. This database includes information on cosmetic ingredients, as recorded in Cosmetics Regulation (EC) No 1223/2009, in Directive 76/768/EEC, and in a list of SCCS Opinions on cosmetic substances. However, CosIng has no legal value and can be used for informative purposes only, suggesting that the presence of a given substance in the database does not necessarily imply that it is also legally accepted for use in cosmetics [16].

The final step of the identification section is to specify nanomaterial's IUPAC name and other descriptors, such as the International Nomenclature of Cosmetic Ingredients (INCI), Chemical Abstracts Service (CAS) number, etc. as well as the contact details of the RP (or Delegate) [15].

2.2. NM Specification

Extensive characterization of the NM has to be provided, sourcing data from different stages of the manufacturing process, as stated in Opinion SCCS/1484/12. The minimum physicochemical characteristics, mandatory for the assessment of the NM, are summarized in Table 2 [13,15].

Table 2. Checklist of required physicochemical characteristics of NM intended for use in cosmetic products [13,17,18].

Information	Description	Methods [1]
Chemical identity	Refers to information on the formula (e)/molecular structure(s) of the NM's constituents, along with chemical/common names, and CAS/EINECS numbers (where available).	MS, AAS, ICP-MS, FTIR, NMR, etc.
Chemical composition	Contains information on the chemical composition of the NM, including purity, nature of impurities, coatings or surface moieties, doping material, encapsulating materials, processing chemicals, dispersing agents, and other additives or formulants, for example, stabilizers.	UV-Vis, HPLC, GC/LC-MS, AAS, ICP-MS, FTIR, NMR, XRD, etc.
Production process-derived particles	Description of the process used for production/modification of the NM, due to their significant effect on the properties of the NM, for example, pyrogenic or precipitated silica, sulfate, chloride, or argex process for TiO_2.	-
Particle size [2] and distribution, including the presence of agglomerates or aggregates	Provides information/data on particle size (mean, median, and ±SD in nm), size distribution in terms of relative number versus size, as well as number weighted sum function (cumulative numbers). Graphical distribution diagrams must be provided for primary and secondary populations (e.g., agglomerates, aggregates), along with particle number and mass distribution. Particle size specifications should include any batch-to-batch variation, while information on the employed characterization techniques must be listed. The use of more than one characterization method has been recommended [19–23], with the default one, being electron microscopy-based imaging.	FFF, HDC, HPLC, AUC, disc-CLS, TEM, SEM, AFM, DLS, DMA
Morphology/Shape	Contains information on the NM's preparation state/physical form (powder, solution, suspension, or dispersion), shape (spherical, tube, rod, etc.), and potential aggregation (primary particulates or agglomerates). Aspect ratio (for fiber/tube-like materials), especially for bio-persistent materials with aspect ratio >3. All data should be supported, for example, by appropriate TEM images.	AFM, TEM, SEM, NMR, XRD
Structure	Requires information on the NM structure, including 1D, 2D, and or 3D spatial distribution of the components (e.g., homogeneous mixture, core-shell, surface coating) [22]. Information should be supported by high-quality electron microscopy images of non-homogeneous particles.	AFM, TEM, SEM
Crystallographic structure	Contains information on the NM's crystalline form (amorphous, polycrystalline, crystalline including specification of phase and volume fraction, as well as spatial distribution).	XRD, TEM
Surface characteristics	Requires detailed information on the NM's surface. This should include surface charge (zeta potential), morphology/topography, interfacial tension, reactive sites, as well as any chemical/biochemical modifications or coatings that could change the surface reactivity or add a new functionality, as well as any surface contaminants.	LDE, SPM, XPS, MS, RS, FTIR, NMR, AUC, GE, SPM, LDE, PALS, Nano SIMS, SERS
Solubility	Contains information on solubility of the nanomaterial in relevant solvents and partitioning between the aqueous and organic phase (e.g., log Kow for organic NMs, and surface-modified inorganic nanomaterials). This includes dissolution rates for soluble and partially soluble NMs, along with information on the hygroscopicity of powders should also be provided.	Solubility/dissolution rate in water and other solvents
Surface area [3]	Requires BET-specific surface area information of the NM along with volume-specific surface area (VSSA). VSSA should, ideally, be calculated based on the density of the NM, rather than its bulk counterpart.	BET

Table 2. *Cont.*

Information	Description	Methods [1]
Dispersibility	The dispersibility (insoluble NMs) in terms of a relative amount of the particles that can be dispersed in a suspending medium, must be provided. This should include information on the stability of the dispersion in the given media and the conditions applied [22].	-
Catalytic activity [4]	Contains information on the chemical reactivity of the NM's core material and/or surface coating, including photocatalytic activity and radical formation potential of relevant materials.	Kinetic data on the chemical, biochemical & catalyzed reactions
Concentration	Requires information on concentration in terms of particle mass and particle number per volume must be provided, both for dispersions and per mass for dry powders.	UV-Vis, HPLC, GC/LC-MS, AAS, ICP-MS, etc.
Dustiness [3]	Contains information on the dustiness of dry powder products.	EN 15051:2006, DIN 33897-2
Density and pour density [5]	Includes information on density/porosity of granular materials and pour density.	DIN ISO 697, EN/ISO 60
Redox potential	Contains information on the oxidation state and redox potential (for inorganic materials), including the conditions under which redox potential was measured.	Potentiometric methods, X-ray absorption spectroscopy
pH [6]	pH of aqueous suspension must be provided.	pH in aqueous media
Viscosity [7]	Provides information on the viscosity of liquid dispersions.	OECD TG 114
Stability	Contains stability/dissociation constant data for the NM in the relevant formulation/media.	MS, HPLC, DLS, FTIR, NMR
Other aspects	Among others, UV absorption (extinction coefficient), light reflection.	UV-Vis

[1] Indicative analytical methods used for the physicochemical characterization; [2] For spray products, the size distribution of the droplets after spraying and of the dried residual particles should be provided; [3] For dry powder products only; [4] For the final product; [5] For granular materials only; [6] For aqueous solutions; [7] For liquid dispersions.

The SCCS recommends that nanomaterials intended for use in a cosmetic product should at least be characterized at three stages: (A) the raw material form (as manufactured), (B) after addition to final cosmetic formulation, and (C) during toxicological investigations. If the characterization of the NM at any of these stages is not feasible, for example, due to the lack of methods, or degradation, then this should be clearly justified and documented [13,17].

2.3. Toxicological Profile

The challenges in risk assessing the use of NMs, which essentially aids in discerning them from conventional cosmetic ingredients, have been pointed out since the harmonization phase of the new Cosmetics Regulation [7]. However, several regulatory bodies have come to a consensus, that NMs should be evaluated through the adoption of existing approaches [24,25].

Based on the above, the toxicological profile of the nanomaterial should be determined, using in silico, in vitro, and in vivo studies to evaluate the hazard potential of the cosmetic ingredient. Even though there are various in vitro studies available for the assessment of certain hazards, in vivo techniques are considered more reliable in the current risk assessment scheme, especially considering dose-response evaluation studies. Nevertheless, a ban on animal testing of cosmetic products was enforced by the Commission since 2009 [13], somewhat complicating the toxicological assessment of new NMs.

To accommodate this, the RP should record the key toxicological endpoints of the nanomaterial and submit a dossier for evaluation to the CPNP, including, as a minimum,

the summary of the toxicological studies, the relevant toxicological studies as recommended by the SCCS (SCCS/1484/12) (see Table 2) and any relevant scientific literature [13,15].

An animal ban has been enforced since Directive 76/768/EEC and the same provisions have been included in Regulation (EC) No 1223/2009. As a result, any animal testing of cosmetic ingredients or finished formulations/products is restricted according to European legislation and a marketing ban is imposed on any product in violation of this provision. Some exceptions on animal testing, included assessment of reproductive toxicity, repeated dose toxicity, and toxicokinetics until 11 May 2013, irrespective of the availability of alternative in vitro tests [10,13].

To this end, and in order to comply with the current restriction on animal testing, many efforts have been made to find alternatives to in vitro and in silico evaluation of cosmetic ingredients and final products. This is rather challenging since the European Commission only accepts toxicological data from validated approaches and there are currently only a few approved methods suited for toxicological hazard identification [13].

Table 3 provides an overview of the toxicological data that are required during the hazard assessment of cosmetic ingredients or finished products.

Table 3. Checklist of toxicological data [13,17,26].

Type of Test	Intent/Purpose
1. Dermal/percutaneous absorption 2. Toxicokinetics	Next to the uptake of nanomaterials (e.g., oral, inhalation, or dermal/percutaneous absorption), the toxicological assessment should focus on the distribution, metabolism, and elimination parameters relevant to the nanoparticles, especially in cases, where evidence of systematic absorption exists. These aspects combined, may provide insight into the fate and behavior of the NM and identify likely target organs. To eliminate possible biophysical interactions, the integrity of the NMs' structure (e.g., agglomerates or aggregation behavior) and physicochemical characteristics should be examined, in terms of surface binding of proteins or other moieties.
3. Acute toxicity (if available) 4. Irritation and corrosivity 5. Skin sensitization 6. Mutagenicity/genotoxicity 7. Repeated dose toxicity [1]	Evaluated together with type 1 testing, points 3 to 7, are considered as the base data for the toxicological assessment of any cosmetic ingredient, whether in micro- or nano-form.Based on the latest legislation, testing protocols associated with mutagenicity and genotoxicity are restricted to in vitro assays. The evaluation may progress to in vivo experiments only to demonstrate non-mutagenicity when positive results are noted in vitro.
8. Carcinogenicity 9. Reproductive toxicity	In cases where type 1 testing indicates significant oral intake or considerable skin penetration during dermal/percutaneous absorption, these additional toxicological investigations may become necessary based on the toxicological profile of the NM and its chemical structure. Additional data on genotoxicity and/or mutagenicity may also be required.
10. Photo-induced toxicity	If the cosmetic product is intended for dermal use and exposure to sunlight, with the NM absorbing certain wavelengths, then photo-induced toxicity should be evaluated. As the energy potential of these wavelengths, may elicit transformations in the NM's configuration, its chemical reactivity may be affected. Among the phototoxic effects that require further investigation are: photoirritancy, photosensitization, and photomutagenicity. All additional data on the NM's phototoxic potential must be provided for the relevant UV light wavelengths derived from the absorption spectrum of the NM [27], along with photostability data under the intended conditions of use of the final cosmetic product.
11. Human data (where available)	In general, the SCCS considers human data as extremely useful and should be included whenever available. Nevertheless, volunteer studies involving nanomaterials should be approached with caution as there is still a lack of information on the severity of potential adverse effects. As a result, human data concerning the evaluation of nanomaterials are widely considered to be subject to ethical restrictions [27].

[1] Considering the various routes of exposure (oral, dermal, inhalation).

3. Exposure Assessment

One of the most crucial decision points during risk assessment of an ingredient or product is the identification of the possible exposure routes, termed: exposure assessment. This is mandatory for any cosmetic ingredient, including nanomaterials [13].

In order to estimate the systemic exposure through in vitro or in vivo studies, it is compulsory to determine the likelihood and the extent of NM's delivery through skin, lung, or gastrointestinal tract, while also taking into account considerations applicable on nano-aspects. Accordingly, the exposure dose of nanomaterial must be carefully addressed, especially if a non-physiological administration is possible (e.g., intratracheal instillation as a surrogate for inhalation).

Towards this end, the RP shall provide data about the exposure conditions, by indicating, as a minimum, the type of cosmetic (rinse-off or leave-on), the possible exposure routes (e.g., dermal, oral, and/or inhalation (for sprayable products)) and the concentration of the nanomaterial in the cosmetic product (%w/w). The RP has to provide information related to foreseeable exposure conditions as presented in Table 4 [13,15].

Table 4. Checklist for information on exposure [13,17,26].

A/A	Exposure Related Information
1	Category of cosmetic products in which the ingredient is intended for use
2	Concentration of the ingredient in the finished cosmetic product
3	Quantity of the product used at each application
4	Frequency of use [1]
5	Total area of skin contact [1]
6	Duration of exposure
7	Foreseeable uses which may increase exposure
8	Consumer target groups (e.g., children, people with sensitive, damaged, or compromised skin)
9	Quantity likely to enter the body (fraction absorbed), for each target group
10	Application on skin areas exposed to sunlight
11	Estimated dermal exposure, based on the intended use of the product
12	Estimated oral exposure, based on the intended use of the product
13	Estimated inhalation exposure, based on the intended use of the product
14	Exposure calculation for each target group
15	Other relevant information

[1] In the absence of information, default values for some of the parameters may be used (SCCS Notes of Guidance SCCS/1564/15).

4. Overall Assessment

Finally, the overall risk assessment of any NM should be provided in terms of Margins of Safety (MoS), as applied on conventional ingredients. This is assessed based on the data collected with respect to the category of the cosmetic product, its toxicological profile, any local/systemic exposure, and the NM's physicochemical characterization (process flow as illustrated in Figure 1).

Even though the use of nanomaterials in cosmetics may provide multiple benefits to the final consumer, these materials can also pose a significant health risk, if not processed appropriately. Manufacturers of cosmetic products should consider that NMs differ significantly from conventional ingredients since their negligible dimensions can render them more permeable to biological membranes, thus adding a further dimension to their toxicological profile and exposure conditions. NMs can easily reach certain organs that are otherwise difficult to approach by conventional substances, due to their unique properties (e.g., surface characteristics) and small dimensions.

The SCCS requires a comprehensive safety assessment on the systemic exposure to NMs, especially for those that are insoluble/partially soluble and bio-persistent. The SCCS has advised the consideration of nano-aspects during these procedures, as they might otherwise lead to substantial health risks [13].

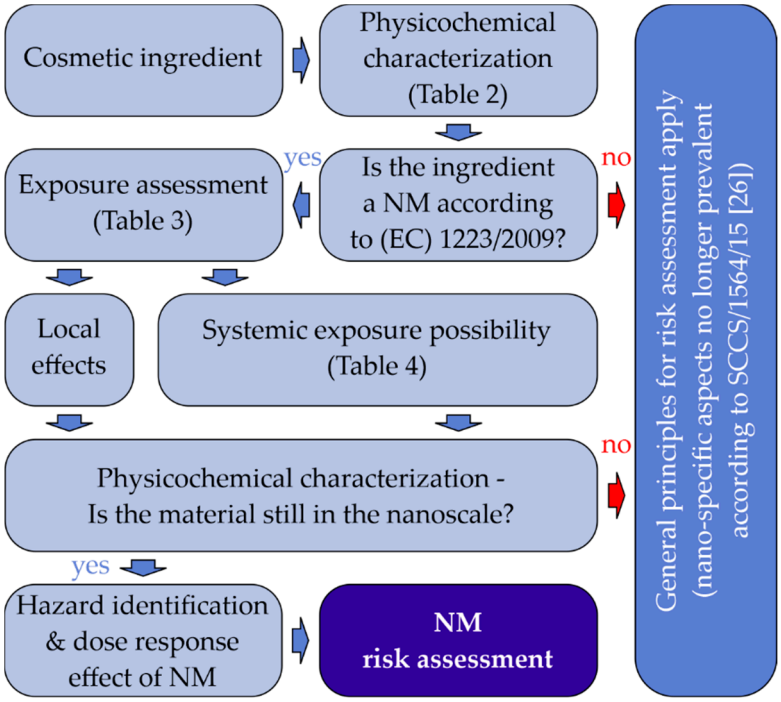

Figure 1. Schematic outline for the safety assessment of nanomaterials in cosmetics [17].

5. Nanocatalogue by European Commission

As stated in Article 16 of Regulation (EC) No 1223/2009, the European Committee has published a catalogue (Table 5), listing all the nanomaterials used in cosmetics that are already placed on the market. This list includes, among others, nanomaterials used as colorants, UV-filters, and preservatives while also indicates the categories of cosmetic products and the exposure conditions.

Table 5. Nanomaterials presented in nanocatalogue by European Commission [28].

INCI [1] or Other Name	Exposure Route	Product Category [2]	Function
Carbon black [3]	Dermal, oral	leave on/rinse off	colorant
Titanium dioxide [4]	Dermal, oral, Inhalation	leave on/rinse off	colorant, UV-filter
Zinc oxide [5]	Dermal, oral, Inhalation	leave on/rinse off	colorant, UV-filter
Methylene bisbenzotriazolyl tetramethylbutylphenol	Dermal, oral	leave on/rinse off	UV-filter
Tris-biphenyl triazine	Dermal, inhalation	leave on	UV-filter
Alumina	Dermal	leave on/rinse off	other functions
Copper/Colloidal copper	Dermal, oral	leave on/rinse off	other functions
Gold/Colloidal gold	Dermal, oral, inhalation	leave on/rinse off	other functions
Platinum/Colloidal platinum	Dermal	leave on/rinse off	other functions
Silver/Colloidal silver	Dermal, oral	leave on/rinse off	other functions
Fullerenes	Dermal	rinse off	other functions
Gold thioethylamino Hyaluronic acid	Dermal	leave on/rinse off	other functions
Hydrated silica	Dermal, oral	leave on/rinse off	other functions
Hydroxyapatite	Dermal, oral	leave on/rinse off	other functions
Lithium magnesium Sodium silicate	Dermal	leave on/rinse off	other functions
Silica	Dermal, oral Inhalation	leave on/rinse off	other functions
Silica dimethicone silylate	Dermal	leave on	other functions
Silica dimethyl silylate	Dermal, oral	leave on/rinse off	other functions
Silica silylate	Dermal	leave on/rinse off	other functions
Sodium magnesium fluorosilicate	Dermal, oral	leave on/rinse off	other functions
Sodium magnesium silicate	Dermal	leave on	other functions
Sodium propoxyhydroxypropyl thiosulfate silica	Dermal	leave on	other functions
Styrene/acrylates copolymer	Dermal	leave on	other functions

[1] In principle (EU) International Nomenclature of Cosmetic Ingredients; [2] Depending on the cosmetic category, for example, face products; [3] CI 77266; [4] CI 77891; [5] CI 77947.

This nanocatalog presents 29 nanomaterials (3 as colorants, 4 as UV-filters, and 18 as other functions), listing along with their names, their intended function, and other information (e.g., exposure route), as provided by the RPs or the CosIng database [28].

6. Opinions on Nanomaterials by SCCS

Over the years, the SCCS has provided Opinions on health and safety risks (e.g., chemical, biological, mechanical, physical risks, etc.) of non-food consumer products (e.g., cosmetic products, cosmetic ingredients, toys, textiles, clothing, etc.) and services (e.g., artificial sun tanning) to ensure the protection of human health [29].

Key Opinions on nanomaterials, including metallic NMs of high cosmetic interest, that the SCCS has provided throughout the years are presented hereinafter and are summarized in Table 6. As mentioned, cosmetic products containing nanomaterials, on which no opinion has been published by the SCCS, should be notified to the CPNP six months prior to being placed on the market. This allows the SCCS to timely review the risk assessment provided by the RP in order to publish an Opinion for the submitted nanomaterial.

Tris-biphenyl triazine has attracted the interest of the cosmetic industry due to its UV-absorbing capabilities, thus acting as a UV-filter. According to SCCS/1429/11, nano-sized tris-biphenyl triazine has been found to be safe for dermal applications at concentrations as high as 10%. However, spray products containing this ingredient could not yet be recommended by SCCS due to a lack of information on their safety after repeated inhalation [30].

Zinc oxide (ZnO) is one of the most promising nanomaterials used in cosmetics due to its bi-fold function as a UV-filter and colorant. After a relevant risk assessment, the SCCS has concluded that ZnO with specific characteristics can safely be used for dermal applications without the risk of adverse effects at concentrations of up to 25% [31,32].

Table 6. Conclusions of the SCCS on opinions published for nanomaterials.

Ingredient	Opinion	Conclusions of SCCS	Adoption On	Reference
Tris-biphenyl triazine	SCCS/1429/11	10% of tris-biphenyl triazine can be considered safe for dermal application.	20/09/2011	[30]
Zinc Oxide [1]	SCCS/1489/12	Up to 25% of ZnO can be used without posing a risk of adverse effects in humans, after dermal application.	18/09/2012	[31]
Carbon Black [2]	SCCS/1515/13	Maximum allowed concentration as a colorant is 10%.	12/12/2013	[33]
TitaniumDioxide [3]	SCCS/1516/13 SCCS/1580/16 SCCS/1583/17	Maximum allowed concentration as a UV-filter in sunscreen cosmetics is 25%. TiO2 with different coatings can be considered safe for application on healthy, intact, or sunburnt skin. No conclusions for spray applications.	22/06/2013 07/03/2017 19/01/2018	[34–36]
Silica [4] & its derivatives	SCCS/1545/15	No firm conclusion either for or against the safety of SAS due to inadequate submitted data.	20/03/2015	[37]
MBBT [5]	SCCS/1546/15	The use of MBBT, in nano-structured form as a UV-filter at a concentration up to 10% in dermally applied cosmetic products, is considered safe.	25/03/2015	[38]
Styrene/acrylates copolymer & sodium styrene/acrylates copolymer	SCCS/1595/18	Due to lack of information available at that time, the SCCS could not draw any conclusions on the safety of these nano-entities.	21/06/2018	[39]
Colloidal Silver	SCCS/1596/18	The SCCS was not in the position to draw a conclusion on the safety of colloidal silver in nano form when used in oral and dermal cosmetic products.	24/10/2018	[40]
Hydroxyapatite	SCCS/1624/20	SCCS draw no conclusion on the safety of rod-shaped hydroxyapatite NMs, while reported potential toxicity of needle-shaped hydroxyapatite NMs.	27–28/10/2020	[41]

[1] CI 77947; [2] CI 77266; [3] Titanium dioxide coated with Cetyl Phosphate, Manganese Dioxide or Triethoxycaprylylsilane as UV-filter in dermally applied cosmetic according to SCCS/1580/16; CI 77891; [4] Silica (nano) CAS 12945-52-5; Hydrated Silica (nano) CAS 112926-00-8; Silica Silylate (nano) CAS 68909-20-6; Silica Dimethyl silylate (nano) CAS 68611-44-9; [5] Methylene bis-benzotriazolyl tetramethylbutylphenol.

Carbon black (CI 77266) was also evaluated by the SCCS, based on available evidence provided by the RPs for its use as a colorant in its nanoform. CI 77266 was considered for use as a nonentity at a concentration up to 10% without posing any risks of adverse effects in humans after dermal application on healthy, intact skin [32,33].

Titanium dioxide (TiO_2) is another NM that attracted significant interest for its potential application in cosmetic products. The SCCS has published opinions on the safety of TiO_2 for dermal and inhalation exposure. The use of TiO_2 as a UV-filter was recommended at a concentration of up to 25% after application on healthy, intact skin [34]. Another opinion, for dermal applications, approved the use of three different TiO_2 nanomaterials coated with either silica and cetyl phosphate (up to 16% and 6% respectively); alumina and manganese dioxide (up to 7% and 0.7% respectively); or alumina and triethoxycaprylylsilane (up to 3% and 9% respectively) [35]. The SCCS has also analyzed a dossier of TiO_2 nanomaterials submitted for sprayable applications, indicating that, due to the lack of information, no conclusions can be safely driven for repeated lung exposure [32,36].

Various applicants have provided evidence in favor of the use of silica and its derivatives (SAS) in nanoform for their application in cosmetics. However, the SCCS could not draw any firm conclusion over their safety, since the submitted evidence was considered insufficient and inadequate [37].

According to SCCS/1546/15, the SCCS has concluded that the use of MBBT [2,2′-methylene-bis-(6(2*H*-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol)] in nanoform, intended as a UV-filter at concentrations up to 10% in dermally applied cosmetic products, is safe for human use after application on healthy, intact skin [38].

The safety of three styrene/acrylate copolymer nano-entities was also evaluated by SCCS. However, the SCCS could not determine whether these materials, in their nanoform, can be safely used in cosmetics due to insufficient data [39].

A nanomaterial that has attracted great interest in the cosmetic industry, due to its unique properties, is colloidal silver. With SCCS 1596/18, the Committee has concluded that it could not draw any firm decision, despite the abundance of open literature on nanosilver toxicity. The applicants provided a limited amount of data with major gaps, rendering it difficult to draw a conclusion on the safety of colloidal silver. [40].

Finally, the SCCS could not draw any conclusion on the safety of rod-shaped hydroxyapatite NMs for use in oral-care products due to the insufficient available data. On the other hand, needle-shaped hydroxyapatite NMs raised concerns and were restricted from being used in cosmetic products [41].

Based on the above, the European Commission has provided authorization to four UV-filters and to one colorant for their use as nanomaterials in cosmetic products, two of which are metallic nanoparticles of significant consumer interest. The approved nanomaterials are: carbon black (Annex IV, entry 126a), methylene bis-benzotriazolyl tetramethylbutylphenol (Annex VI, entry 23a), titanium dioxide (Annex VI, entry 27a), tris-biphenyl triazine (Annex VI, entry 29), and zinc oxide (Annex VI, entry 30a) [42].

The SCCS continues to publish mandates (call for data) and requests scientific information for the risk assessment of various nanomaterials, such as copper/colloidal copper, hydroxyapatite, gold/colloidal gold, gold thioethylamino hyaluronic acid, platinum/colloidal platinum, zinc oxide, and titanium dioxide (with various coatings), in order to draw a conclusion for their safety as nanomaterials in cosmetics.

7. Cosmetics and Nanotechnology Products Database

The Nanotechnology Products Database (NPD) is a database that provides reliable data about nano-enhanced products, used in various industrial sectors. Over 9000 products have been registered in the NPD, including 2440 companies throughout 61 countries.

The NPD also features data about 829 nano-enhanced cosmetics representing about 100 different types of products. These nano-cosmetics have been marketed globally by 230 companies, the headquarters of which are located in 29 different countries. The products are classified into skincare, personal care, make-up, haircare, sanitizing/sexual well-being,

and shaving preparations in sub-industrial sectors [43]. According to the NPD, 330 of these nano-cosmetic products have found their way to the European market as illustrated in Table 7.

Table 7. Nano-cosmetics commercially available in European countries.

Country	Number of Nano-Cosmetics
Austria	10
Belgium	5
France	69
Germany	82
Italy	1
New Zealand	2
Poland	18
Spain	4
Sweden	3
Switzerland	19
UK	117

Table 8 provides an overview of the type of nanomaterials used in cosmetics in Europe. When these data are compared to Table 6, it becomes evident that several nano-cosmetics are already on the market despite the lack of information about the safety of the nanomaterials they may feature (e.g., gold or silicon dioxide). This has not gone unnoticed by the SCCS, which during October 2019 requested the submission of additional scientific data on gold nanomaterials when used in leave-on/rinse off skin cosmetic products, taking into account reasonably foreseeable exposure conditions. A specific opinion about colloidal gold has not yet been published (research on progress) and therefore no conclusions on the safety of these nano-entities can yet be drawn [43,44].

Table 8. Nanomaterials featured in cosmetic products available in Europe [43].

Ingredient	Number of Nano-Cosmetics
Titanium dioxide (nanoparticle/nanopowder)	73
Silver (nanoparticle/nanopowder)	42
Q10 (Vitamin C and E) (nanoliposomes)	36
Carbon (nanoparticle/nanopowder)	28
Gold (nanoparticle/nanopowder)	15
Silicon dioxide (nanoparticle/nanopowder)	11
Argan (nanoliposome)	9
Silver (nanoporous)	6
Snail (nanoliposome)	5
Zinc oxide (nanoparticle/nanopowder)	3
Hyaluronic acid (nanoliposomes)	3
Retinol (nanoliposome)	2
Organoclay (nanoparticle/nanopowder)	2
Methylene bis-benzotriazolyl tetramethylbutylphenol (nanoliposome)	2
Peptide (nanoliposome)	1
Triethoxycaptylylsilane (nanoliposome)	1
Hydroxystearic acid (nanoliposome)	1

However, most manufacturers comply with EU legislation, commercializing nanomaterials that are already authorized and a full risk assessment has been completed by SCCS. For example, titanium dioxide can be used for specific applications (not sprayable) as clearly mentioned in respective opinions [34–36]. To avoid regulatory aspects altogether, several industries have lately directed their interest towards materials in the nano-spectrum, that are soluble, degradable, and/or non-persistent in biological systems. As a result of their origin, these materials (e.g., nanoliposomes) are not considered as nanomaterials [13]

and can be used freely in cosmetics without being registered in CPNP, yet maintaining an attractive set of properties for the cosmetic sector.

8. Conclusions

According to data provided by the Nanotechnology Products Database (NPD), the number of nano-enhanced cosmetic products available on the European market is increasing, with almost 2% of all cosmetic products notified in the CPNP containing some type of NMs in 2018 [41].

The Cosmetics Regulation and existing opinions of SCCS provide sufficient details on all the necessary data that must be included for a comprehensive risk assessment of a new nanomaterial, including its physicochemical characterization, the toxicological profile, and the foreseeable exposure conditions. After the submission of new material on CPNP, the SCCS evaluates the risk assessment of the NM and publishes an Opinion, recommending the use or stating the hazards that repeated use of this NM may have. Despite this, several of these nano-enhanced cosmetics include NMs, that were (during their launch) not authorized by the EC's Regulation on cosmetics [9]. Until now only five insoluble/partially soluble or bio-persistent nanomaterials, two of which are metallic NMs of zinc oxide and titanium dioxide, have been authorized by the SCCS for safe use in cosmetics, with clear indications as to the required characteristics (e.g., size, concentration) and intended applications (e.g., dermal applications). This results in an evident gap considering product demand and technology readiness level, with respect to the available safety data for the use of nano-enhanced cosmetics, rendering this an opportune time for the registration of new NMs on CPNP. Based on the limited integration of metallic NMs, despite their attractive properties, along with the use of multiple non-metallic NPs in cosmetic products, the attention of the community is directed towards coordinating efforts on the integration of metallic NMs into cosmetics.

The regulatory framework, governing nano-enhanced products with respect to the above, has to be further developed and its requirements monitored and reinforced by the authorities. Despite legislation calling for an EC approval of nano-ingredients prior to their use in a cosmetic product, this is not always the case. As a result, nano-enhanced cosmetics have been often subject to recall, exposing their producers to legal consequences.

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Abbreviations

AAS	Atomic Absorption Spectroscopy
AFM	Atomic Force Microscopy
AUC	Analytical Ultracentrifugation
BET	Brunauer–Emmett and Teller method
CAS	Chemical Abstracts Service
CI 77266	Carbon black
CosIng	Cosmetic Ingredient Database
CPNP	Cosmetic Products Notification Portal
DLS	Dynamic Light Scattering
disc-CLS	disc-Centrifugal Liquid Sedimentation
DMA	Dynamic Mobility Analyzer
EFSA	European Food Safety Authority
FFF	Field Flow Fractionation
FTIR	Fourier Transform Infrared Spectroscopy
GC/LC-MS	Gas Chromatography/Liquid Chromatography coupled with Mass Spectrometry
GE	Gel Electrophoresis
HDC	Hydrodynamic Chromatography
HPLC	High Performance Liquid Chromatography
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
INCI	International Nomenclature of Cosmetic Ingredients
LDE	Laser Doppler Electrophoresis
MBBT	2,2′-methylene-bis-(6(2*H*-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol)
MoS	Margins of Safety
MS	Mass Spectrometry
Nano SIMS	Nanoscale Secondary Ion Mass Spectrometry
NM	Nanomaterial
NMR	Nuclear Magnetic Resonance
NPD	Nanotechnology Products Database
OECD	Organization for Economic Co-operation and Development
PALS	Phase Analysis Scattering
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
RP	Responsible Person
RS	Raman Spectroscopy
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCCNFP	Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers
SCCS	Scientific Committee on Consumer Safety
SEM	Scanning Electron Microscopy
SERS	Surface-enhanced Raman Spectroscopy
SPM	Scanning Probe Microscope
TEM	Transmission Electron Microscopy
TiO2	Titanium dioxide
UV	Ultraviolet
UV-Vis	Ultraviolet-Visible Spectrophotometry
XPS	X-Ray Photoelectron Spectroscopy
XRD	X-ray Diffraction
ZnO	Zinc Oxide

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