Scientific Committee on Consumer Safety

SCCS

OPINION ON

Styrene/Acrylates copolymer (nano) and Sodium styrene/Acrylates copolymer (nano)

The SCCS adopted this document
at its plenary meeting on 21/22 June 2018

ACKNOWLEDGMENTS

Working group on nanomaterials in cosmetics

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This Opinion has been subject to a commenting period of 10 weeks after its initial publication (from 2 March until 11 May 2018). There were no comments received and the final version of the opinion remained unchanged compared to the preliminary one.

All Declarations of Working Group members are available on the following webpage:
http://ec.europa.eu/health/scientific_committees/experts/declarations/sccs_en.htm

1. ABSTRACT

The SCCS concludes the following:

1. In view of above, and taking into account the scientific data provided, the SCCS is requested to give its opinion on the safety of the nanomaterial Styrene/acrylates copolymer and Sodium styrene/Acrylates copolymer when used in leave-on cosmetics products with a maximum concentration limit of 0.06%, taking into account the reasonably foreseeable exposure conditions.

The SCCS cannot conclude on the safety of any of the three styrene/acrylate copolymer nano-entities submitted by the Applicants. The data submitted are insufficient to evaluate possible toxicity. Regarding use it was reported that the nano-entities as present in Nanospheres 100 Theophyllisilane C (SA), were used for encapsulation of a slimming agent Theophyllisilane C. According to the information provided by the Applicants, the formulation might be used in health products like milks, emulsions, creams, lotions and solutions. However, no data on the use frequency was provided, so, the potential exposure could not be estimated based on a use scenario. In addition, the submitted information was based on a (nearly) finished product consisting of a nanomaterial shell (Nanosphere 100) and encapsulated active ingredients (Theophyllisilane C and Algisium C2 (SA) methylsilanol mannuronate). For the formulation Nanospheres 100 D.S.H. C.N (SA), no information on composition was submitted.
Data should be provided separately for all of the three styrene/acrylate nanospheres, including any encapsulated substances.

2. SCCS is requested to address any further scientific concerns with regard to the use of Styrene/ acrylates copolymer and Sodium styrene/Acrylates copolymer in nano form in cosmetic products.

For applications as evaluated in this Opinion, it is imperative that the safety assessment not only considers safety of the individual components (e.g. the encapsulating material and the encapsulated contents), but also the safety of all the components when put together in the form of a nano-sized entity.

Keywords: SCCS, scientific opinion, Styrene/Acrylates copolymer (nano) CAS No 9010-92-8, EC No 927-710-1, Sodium styrene/Acrylates copolymer (nano) CAS No 9010-92-8, Regulation 1223/2009

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In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease Prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS
The Committee shall provide Opinions on questions concerning all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example: cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Article 2(1)(k) of Regulation (EC) No 1223/2009 establishes that "nanomaterial" means an insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on a scale from 1 to 100 nm.

That definition covers only materials in the nano-scale that are intentionally made, and are insoluble/partially-soluble or biopersistent (e.g. metals, metal oxides, carbon materials, etc), and it does not cover those that are soluble or degradable/non-persistent in biological systems (e.g. liposomes, emulsions, etc). Article 16 of the Cosmetics Regulation requires any cosmetic product containing nanomaterials to be notified to the Commission six months prior to being placed on the market, and Article 19 requires nano ingredients to be labelled (name of the ingredient, followed by 'nano' in brackets). If there are concerns over the safety of a nanomaterial, the Commission shall refer it to the Scientific Committee on Consumer Safety (SCCS) for a full risk assessment.

The Commission received 8 notifications of cosmetic products containing Styrene/Acrylates copolymer CAS No 9010-92-8, EC No 927-710-1 and Sodium styrene/Acrylates copolymer CAS No 9010-92-8 in nano forms. These ingredients are reported in the CosIng database without any reference to the nano form with the function of film forming and opacifying, but they are not regulated under Cosmetic Regulation (EC) No 1223/2009. According to the applicants, the ingredients are used in nano-coated form in leave-on cosmetic products with maximum reported concentration limit of 0.06%.

The Commission has concerns over safety of the use of Sodium styrene/Acrylates copolymer (nano) and Styrene/ acrylates copolymer (nano) in cosmetic products.

The Commission performed a 12-week call for data with the deadline of June 2015, where interested parties were invited to submit any relevant scientific information on the safety of Styrene/Acrylates copolymer (nano) (CAS No 9010-92-8, EC No 927-710-1) and Sodium styrene/Acrylates copolymer (nano) (CAS No 9010-92-8) used in cosmetic products and in particular data regarding all toxicological end-points and an indication on the suggested concentration safe limits for these ingredients. The documentation received by the Commission is in the annex to this mandate.

Therefore, the Commission is requesting the SCCS a safety assessment of the nano form of Styrene/ acrylates copolymer and Sodium styrene/Acrylates copolymer covered in the notifications listed in the annex to this mandate, in the above-mentioned categories of products, taking into account the reasonably foreseeable exposure conditions.

Terms of reference

1. *In view of above, and taken into account the scientific data provided, the SCCS is requested to give its opinion on the safety of the nanomaterial Styrene/ acrylates copolymer and Sodium styrene/Acrylates copolymer when used in leave-on cosmetics products with a maximum concentration limit of 0.06%, taking into account the reasonably foreseeable exposure conditions.*

2. *SCCS is requested to address any further scientific concerns with regard to the use of Styrene/ acrylates copolymer and Sodium styrene/Acrylates copolymer in nano form in cosmetic products.*

3. OPINION

Preamble:

The current mandated questions relate to the safety of styrene/acrylate copolymer and sodium styrene/acrylates copolymer when used in leave-on cosmetics products up to a concentration of 0.06%. However, the information submitted as part of the dossier shows that the styrene/acrylate copolymer is used as an encapsulating material to form nano-entities (indicated by the applicants as nanospheres) that also contain theophyllisilane C (methylsilanol carboxymethyl theophylline alginate) or methylsilanol mannuronate (the ester of monomethylsilanol and oligomeric mannuronic acid). The information provided therefore deals with a final product theophyllisilane or methylsilanol mannuronate encapsulated in nano-entities consisting of styrene/acrylic copolymer. Also a third product is indicated, namely Nanospheres 100 D.S.H. C.N. (SA).

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

3.1.1 Chemical identity

3.1.1.1 Primary name and/or INCI name

INCI (International Nomenclature Cosmetic Ingredients) name:

Styrene/Acrylates copolymer

Ref.: 1, 3, 4

SCCS comment:
Category of chemical composition cannot be determined due to missing information.

3.1.1.2 Chemical names

Nanospheres 100 Theophyllisilane C (SA),
(Theophyllisilane C = methylsilanol carboxymethyl theophylline alginate)

Nanospheres 100 Algisium C2 (SA)
(Algisium C2 = methylsilanol mannuronate)

Ref.: 6

Nanospheres 100 D.S.H. C.N. (SA)
(D.S.H. = dimethylsilanol hyaluronate)

Ref.: 4

SCCS comment:
Insufficient information was submitted on the chemical identity of both the encapsulating material and the encapsulated chemical compounds.

3.1.1.3 Trade names and abbreviations

1. Nanospheres 100 Theophyllisilane C (SA), Product code 105 Nanospheres 100 loaded with Theophyllisilane C (=Methylsilanol carboxymethyl theophylline alginate).

Ref.: 1

2. Nanospheres 100 Algisium C2 (SA), Product number 000, Nanospheres 100 loaded with Algisium C2 (= methylsilanol mannuronate).

Ref.: 3

3. Nanospheres 100 D.S.H. C.N. (SA).

Ref.: 4

3.1.1.4 CAS / EC number

1. Nanospheres 100 Theophyllisilane C (SA), (nano) CAS No 9010-92-8, EC No 927-710-1

2. Sodium styrene/Acrylates copolymer (nano) CAS No 9010-92-8

SCCS comment:
Insufficient information was submitted on the chemical identity of the composing substances. The CAS number provided is for the encapsulating material forming the nano-entities (i.e. the sodium styrene/acrylates copolymer), whereas the CAS number for the encapsulated ingredients is not provided. CAS numbers for all ingredients should be provided.

3.1.1.5 Structural formula

No information provided.

SCCS comment:
No information was submitted. Information on the structural formulas of all ingredients should be provided.

3.1.1.6 Empirical formula

No information provided.

SCCS comment:
No information was submitted. Information on the empirical formulas of all ingredients should be provided.

3.1.2 Physical form

Nanospheres 100 Theophyllisilane C (SA)
Morphology:

Nanospheres characteristics: positive
Physical form: dispersion, opaque white fluid
Crystalline shape: spherical
Agglomeration/aggregation: dispersed free particulates
Aspect ratio: /

Ref.: 1

Nanospheres 100 Algisium C2 (SA)
Morphology:
Nanospheres characteristics: positive
Physical form: opaque liquid, white to pale yellow
Crystalline shape:
Agglomeration/aggregation:
Aspect ratio:

Ref.: 3

Nanospheres 100 D.S.H. C.N. (SA)
Morphology:
Physical form: dispersion
Crystalline shape: spherical
Agglomeration/aggregation: dispersed free particulates
Aspect ratio: /

Ref.: 4

SCCS comment:
Insufficient information was submitted. Regarding physical form, only a statement was presented, without supporting data. Data should be provided regarding the material having nano-size dimensions. Information should be provided for all three nano-entities (designated as nanospheres by the applicants).

3.1.3 Molecular weight

No information provided.

SCCS comment:
No information was submitted. Information on molecular weight of all the nano-entities and the encapsulated substances should be provided.

3.1.4 Purity, composition and substance codes

Nanospheres 100 Theophyllisilane C (SA)
Product 105
Theophyllisilane C: 90 %
Monoethylsilanetriol: 0.3 %
Theophyllin acetic acid: 0.78 %
Alginic acid: 0.09 %
Nanospheres: 10^{16} per kg

Additional information on composition stated:
Silicon content: 0.08 – 0.1 % (SED-I09-070)
Theophylline acetic acid content: 0.67 – 0.87 % (SED-I09-022)
Sodium methyl parahydroxybenzoate: 0.100 – 0.140 % (0.115%) (SED-I09-004)

Propyl parahydroxybenzoate: 0.015 – 0.035 % (0.029%) (SED-I09-004)

Nanospheres 100 Theophyllisilane C (SA) consists of approximately 1% nanomaterials as INCI Styrene/acrylates copolymer.

Ref.: 1

Nanospheres 100 Algisium C2 (SA)

Silicon content:	0.07 – 0.09 % (SED-I09-070)
Mannuronic acid:	positive (SED-I09-096)
Phenoxyethanol:	0.6 – 0.8% (SED-I09-186)
Sorbic acid:	0.068 – 0.113% (SED-I09-004)

Ref.: 3

Nanospheres 100 D.S.H. C.N. (SA)

Ref.: 4

No information was submitted.

SCCS comment:
The composition of 1 kg Nanospheres 100 Theophyllisilane C (SA) in formulation was presented. No information was submitted on the nano-entities themselves. Information should be provided for both the nano-entities and the encapsulated compounds.
The composition and impurities in the nanomaterial (complete nano-entity) itself should be provided. Approximately 6-10 % of the product composition was not accounted for. Detailed composition should be provided.

For Nanospheres 100 Algisium C2 (SA), no information on composition was provided. Approximately 98% of the composition was not accounted for.

For Nanospheres 100 D.S.H. C.N. no information was submitted.

For all three products the composition should be provided.

3.1.5 Impurities / accompanying contaminants

No information was submitted.

SCCS comment:
No information was submitted. Information on the presence of possible impurities should be provided for all three nano-entities (Nanospheres 100 Theophylisilane C, Nanospheres 100 Algisium C2, Nanospheres 100 D.S.H. C.N.) including encapsulated substances.

3.1.6 Solubility

Nanospheres 100 Theophyllisilane C (SA)
Nanospheres 100 D.S.H. C.N. (SA)

Solubility aqueous media:	below 0.01
N-octanol:	not relevant

Ref.: 1, 4

SCCS comment:
Insufficient information was submitted. Nanomaterial information (and if applicable, information about the encapsulated compounds) should be provided including the supporting data of measurements for all three nano-entities (Nanospheres 100 Theophylisilane C, Nanospheres 100 Algisium C2, Nanospheres 100 D.S.H. C.N.).

3.1.7 Partition coefficient (Log P_{ow})

Nanospheres 100 Theophyllisane C (SA)
Nanospheres 100 D.S.H. C.N. (SA)

Log P_{ow}: not applicable

Ref.: 1, 4

SCCS comment:
No information was submitted. A statement that determination of the partition coefficient is not applicable is not sufficient. Rationale should be provided for why the Partition coefficient is not applicable for all three nano-entities. Partition coefficients for encapsulated ingredients should also be provided.

3.1.8 Additional physical and chemical specifications

Nanospheres 100 Theophyllisane C (SA)
Nanospheres 100 Algisium C2 (SA)

Melting point:	
Boiling point:	
Flash point:	
Vapour pressure:	/
Density:	/
Viscosity:	/
pKa:	/
Refractive index:	/
pH:	5.0 – 7.0 (SED-I09-103)
UV_Vis spectrum (….. nm):	/

Ref.:1, 3

SCCS comment:
Insufficient information was submitted. Information for all three nano-entities including encapsulated substances should be provided. Alternatively, rationale for why certain parameters are not considered relevant should be provided.

3.1.9 Particle size

Nanospheres 100 Theophyllisane C (SA)
Primary particle size:
Lowest cut-off level = 20 nm
Volume weighted median: Min = 70 nm and Max = 130 nm
Number weighted median: Min = 60 nm and Max =115 nm

Ref.: 1

Nanospheres 100 D.S.H. C.N. (SA)
Primary particle size:
Lowest cut-off level = 20 nm
Volume weighted median: Min = 27 nm and Max = 310 nm
Number weighted median: Min = 27 nm and Max =160 nm
Method Dynamic Light Scatter equipment Malvern ZETA SIZER 1000HS.

Ref.: 4

SCCS comment:
DLS might be an inappropriate method as it might not take smaller particles into account. The method is sub-optimal, since particles in the lower nanometer scale can be underestimated (or missed). Information for Nanospheres 100 Algisium C2 should be provided as well.

3.1.10 Microscopy

No information provided.

SCCS comment:
Information for all three nano-entities should be provided.

3.1.11 Crystal structure

No information provided.

SCCS comment:
Information for all three nano-entities should be provided.

3.1.12 UV absorption

No information provided.

SCCS comment:
Information for all three nano-entities should be provided.

3.1.13 Surface characteristics

Nanospheres 100 Theophyllisane C (SA)
Nanospheres 100 D.S.H. C.N. (SA)

Surface charge:	not measurable
Surface modification/functionalisation:	none
Coating:	yes

Ref.: 1, 4

Information on composition of coating was not provided. Only information of two nano-entities was provided.

SCCS comment:
Insufficient information was submitted. Information for all three nano-entities, including composition of coating, should be provided.

3.1.14 Droplet size in formulations

No information provided.

SCCS comment:
No information was submitted. Information or rationale should be provided on why this parameter it is not applicable/relevant for all three nano-entities.

3.1.15 Homogeneity and stability

No information provided.

SCCS comment:
Information for all three nano-entities and encapsulated substances should be provided.

3.1.16 Other parameters of characterisation

Nanospheres 100 Theophyllisane C (SA)
Catalytic activity
Chemical reactive surface: no
Photocatalytic activity: no
Core material doped: no

Microbiology
Mesophilic aerobic germs: < 100/mL (SED-I09-250&251)
Yeasts: < 1 /mL (SED-I09-205)
Moulds: < 1 /mL (SED-I09-205)

Not to be submitted to temperatures below 0°C.

Ref.: 1

Nanospheres 100 Algisium C2 (SA)

Microbiology
Mesophilic aerobic germs: < 100/mL (SED-I09-250&251)
Yeasts: <1 /mL (SED-I09-205)
Moulds: <1 /mL (SED-I09-205)

Ref.: 3

Nanospheres 100 D.S.H. C.N. (SA)
Catalytic activity
Chemical reactive surface: no
Photocatalytic activity: no
Core material doped: no

Ref.: 4

3.1.17 Summary on supplementary physicochemical characterisation

SCCS comments to physicochemical characterisation:
The physicochemical characterisation is insufficient to identify the nanomaterials presented in the dossier. Data need to be provided for both the encapsulated substances and the nanomaterial used as shell material for the nano-entities.

3.2 FUNCTION AND USES

The following information was provided by the Applicant:

Nanospheres 100 Theophyllisilane C (SA).
NANOSPHERES 100 microreservoirs slowly liberate THEOPHYLLISILANE C at cutaneous level which ensures a better biodisponibility for THEOPHYLLISILANE C. This diffusion or controlled release avoids useless punctual overloads. Thus, response to cosmetic treatment becomes harmonious, avoiding multi-daily applications and the repartition of the active principle becomes homogeneous at the cutaneous surface, for a better efficacy.

THEOPHYLLISILANE C has a slimming activity due to methylsilanetriol potentialised by a theophylline derivative. Monomethylsilanetriol activates lipolysis, which opposes unsaturated fatty acid stockage and avoids a formation of free radicals and cytotoxic peroxide.

Use as a slimming formulation.
Anti-aging cosmetics.

Designed to manufacture cosmetic and health products such as milks, emulsions, creams, lotions, solutions.

It is necessary to respect a pH level between 5 and 7 and to incorporate Nanospheres 100 Theophyllisilane C (SA) in emulsions at the end of the manufacturing process at a temperature below 30°C.

Ref.: 1

SCCS comment:
Nanospheres 100 Theophyllisilane C (SA)
The description is one for a final formulated product of which the nanomaterial (as encapsulating nano-entity) is only an ingredient (being 1% of the product). This final product may by itself also be used as an ingredient in another product. The function and uses are adequately described in which the nano-entities act as a reservoir for slow release and the theophyllisilane C is released as an active compound.

Nanosphere 100 Algisium C2
No information was submitted for the function and use of Algisium C2 (methylsilanol mannuronate). This information should be provided.

For Nanospheres 100 D.S.H. C.N. (SA), no information was submitted.

Information should be provided for all three nano-entities and the encapsulated substances (Theophylisilane C and Algisium C2 acid).

3.3 TOXICOLOGICAL EVALUATION

3.3.1 Acute toxicity

3.3.1.1 Acute oral toxicity

Nanospheres 100 Theophyllisilane C (SA)
DL 0 mouse: 20 mL/kg

Ref.: 2

Nanospheres 100 Algisium C

DL 0 mouse: 20 mL/kg

Ref.: 5

SCCS comment:
No protocol/information was submitted on performance and outcomes of the tests performed. This information should be provided. Information on Nanospheres 100 D.S.H. C.N is not provided. Study results and study reports on all three nano-entities and the encapsulated substances should be provided.

3.3.1.2 Acute dermal toxicity

No information provided.

SCCS comment:
Information for all three nano-entities and encapsulated substances should be provided.

3.3.1.3 Acute inhalation toxicity

No information provided.

SCCS comment:
If spray application is intended, a safety assessment on inhalation exposure would also be needed.

3.3.2 Irritation and corrosivity

Nanospheres 100 Theophyllisane C (SA)
Skin irritation, rabbits:
Index= 0. Non irritant.
Ocular irritation Draize test albino rabbits:
Index=0 at t=1, t=24, t=48 and t=72 hours. Non irritant.

Ref.: 2

Nanospheres 100 Algisium C
Skin irritation, rabbits

Index= 0. Non irritant.
Ocular irritation, Draize test albino rabbits:
Index = 0 at t=1, t=24, t=48 and t=72 hours. Non irritant.

Ref.: 5

SCCS comment:
No protocol/information was submitted on performance of the tests. Information on the protocol and results of tests need to be provided. Information on Nanospheres 100 D.S.H. C.N was not provided. Information for all three nano-entities and encapsulated substances should be provided.

3.3.3 Skin sensitisation

Nanospheres 100 Theophyllisilane C (SA)

Study Design

Guideline/method:	Maximization method of Magnusson and Kligman (Guinea pig maximization test, GPMT, OECD TG 406)
Species:	Guinea pigs
Strain:	Dunkin Hartley Ico: (HA) BR, IOPS.
Age:	1 – 3 months of age at start of study
Gender:	Females
Group size:	Negative control n=10, positive control n=10, test substance group n=20 animals
Test substance:	Nanosphere 100 SA a 100%.
Batch:	285.04
Particle sizes:	/
Dose applied:	See treatment schedule
Skin area:	dorsally in interscapular region
Route:	Intradermal injection
Exposure time:	24 days
Evaluation:	Determination of redness and swelling
GLP:	Study was performed according to GLP principles
Date of report:	Printed March 18, 2009.
Published:	No

Study schedule
Day 0
Three pairs of intradermal injections were given dorsally in the interscapular region of each animal..
Injection 1: Mixture of 1:1 mixture of Freund's Complete Adjuvant and NaCl 0.9% water
Injection 2: Undiluted vehicle (0.9% NaCl in water), or test substance at 12.5% in NaCl 0.9% water, or mercaptobenzothiazol at 1% in liquid paraffin (positive control)
Injection 3: Vehicle (0.9% NaCl in water) in a mixture 1:1 of Freund's Complete Adjuvant and NaCl 0.9% water, or Mercaptobenzothiazol at 1% in a mixture 1:1 ACF (Adjuvant Complet de Freund) and 0.9% NaCl water, or test substance at 12.5% in a mixture 1:1 ACF and 0.9% NaCl water.)
Day 7
All animals received a topical application of Sodium Lauryl Sulfate at 10% in liquid paraffin in order to induce local irritation.
Day 8
All animals received a topical application of the vehicle,or Mercaptobenzothiazol at 20% in liquid paraffin or the undiluted test substance.
Day 22

The challenge phase was performed by topical applications of the vehicle on the left flank of all animals. On the right flank, the undiluted test substance or Mercaptobenzothiazol at a concentration of 20% were applied.
24 and 48 hours after the dressing removal, both flanks of the treated and control animals were observed and the cutaneous reactions were scored.

Results
During this study no mortality and no clinical observation occurred during the period of observation of 24 days. No statistical difference in body weight was noted in comparison to the negative control group.
For the negative control group there was an absence of cutaneous reactions after 24 and 48 hours. For the positive controls, a positive cutaneous reaction was observed after 24 and 48 hours for 100% of the animals, characterised by a discrete to moderate erythema on the exposed skin (Table 2). These results corresponded to the expected values generally observed at the laboratory, and the study can be considered to be valid.
For the animals treated by the test substance NANOSPHERE 100 SA, a 100% at the concentration of 100%, no positive cutaneous reaction was observed on the exposed skin after a period of 48 hours.
Conclusion: In our experimental conditions and in accordance with the maximization method of Magnusson and Kligman, the test substance NANOSPHERE SA a 100% undiluted can be considered as not sensitising by contact with the skin.

Ref.: 2

SCCS comment:
The report only contains 7 out of 33 pages. The applicants' claim that 100% concentration of the substance does not induce sensitisation is not correct. The initial induction/immunization was performed with a 12.5% concentration and not with a 100% concentration. The results for 24 hours are not mentioned. The final product was tested, not the separate ingredients or the composing nano-entities. Only results for 48 hours were mentioned. Table 2 was not present. A complete study report would be required.
For Nanospheres 100 Algisium C and Nanospheres 100 D.S.H. C.N no information was provided. Information on skin sensitisation should be provided for all three nano-entities and the encapsulated substances.

3.3.4 Dermal/percutaneous absorption

No information provided.

SCCS comment:
Information for all three nano-entities and encapsulated substances should be provided.

3.3.5 Repeated dose toxicity

3.3.5.1 Repeated dose (28 days) dermal toxicity

Nanospheres 100 Theophyllisilane C (SA)

Dermal toxicity absent as indicated in acute and subacute toxicity tests.

Ref.: 1

SCCS comment:
No data are provided to support statement on the absence of dermal toxicity. The study reports for the performed acute and subacute toxicity tests, including all study data, should be provided.

3.3.5.2 Repeated dose (28 days) oral toxicity

No information provided.

SCCS comment:
Information on repeated dose toxicity for all three nano-entities and encapsulated substances should be provided.

3.3.5.3 Sub-chronic (90 days) toxicity (oral, dermal)

No information provided.

SCCS comment:
In case of substantial systemic availability of the nano-entities, information for these nano-entities should be provided.

SCCS comments on repeat-dose toxicity:
Information on repeated dose toxicity should be provided covering information for all three products and encapsulated substances. For the dermal repeated dose toxicity study, no data were provided to support the statement on absence of toxicity. Protocols and results of the already performed studies should be provided.

3.3.6 Mutagenicity/genotoxicity

3.3.6.1 Mutagenicity/genotoxicity *in vitro*

Nanospheres 100 Theophyllisilane C (SA)
Negative genotoxicity in SOS Chromotest Kit.

Guideline/method:

Species:	Auxotrophic bacterias for histidine/tryptophane.
Strains:	S. typhimurium TA97, TA98, TA100, TA-102, TA1535, TA1537 E.coli WP2uvrA
Group size:	NA
Test substance:	Aqueous and organic solutions (suspensions) of Nanosphere 100 SA (21.7% nanospheres 100 SA)
Raw material:	Nanospheres 100 SA
Batch number:	0264.03
Solvent:	Tampon phosphate 0.2M pH 7.4 and DMSO
Particle sizes:	/
Dose applied:	Cytotoxicity test (CYC 03 004): 5000, 1667, 555, 185, 60 µL/box for each solution. Mutagenicity assays (MYC 0. 004):

5000, 1667, 555, 185, 60 µL/box for each solution.
Metabolic fraction: S9 mix (post mitochondrial fraction of rat liver induced by a blend of phenobarbital – beta naphtoflavone (S9) enhanced with cofactors (S9 mix) and used at 10% in the assays.
Route: in vitro.
Exposure time: 60 hours at 37°C.
Evaluation: after 60 hours of incubation colonies were counted.
GLP: No
Date of study: July 18, 2003 – October 24 2003.
Date of report:
Published: No

Cytotoxicity assay (CYC 03 004): realised using the method of direct incorporation (internal record SEDG-I09-005 EA) with or without the metabolic activator (S9 mix 10%). 5 doses of glutamyl-tryptamine were tested: 0, 0.061, 0.185, 0.555, 1.667, 5 µL per box.

First assay on mutagenicity (MYC 03 004): realised using the method of direct incorporation (internal record SEDG-I09-007 EB) with or without the metabolic activator (S9 mix 10%). 5 doses of glutamyl-tryptamine were tested: 0, 0.061, 0.185, 0.555, 1.667, 5 µL per box.

Second assay on mutagenicity (MYC 03 004): realised using the method of direct incorporation (internal record SEDG-I09-007 EB) with or without the metabolic activator (S9 mix 10%). 5 doses of glutamyl-tryptamine were tested: 0, 0.061, 0.185, 0.555, 1.667, 5 µL per box.

Results: Under the selected experimental conditions, with or without treatment with a metabolic activator, the product "Nanospheres 100 SA" suspended in aqueous or in organic solutions did not demonstrate any mutagenic activity regarding the 7 strains of bacteria used in the Ames test.

Ref.: 2

SCCS comment:
Specific data regarding the outcome of the tests is missing (although the existence of internal records is indicated). Positive and negative controls are missing. In general the Ames test is considered not useful for the determination of genotoxicity of nanomaterials, unless uptake of the nanoparticles by the bacteria and nanomaterial exposure of bacterial DNA is demonstrated. Tests with mammalian cells are considered more appropriate to identify genotoxicity of nanomaterials. Only for one nano-entity (Nanospheres 100 SA) is information provided. Information on *in vitro* genotoxicity for all three nano-entities and encapsulated substances should be provided by using genotoxicity tests with mammalian cells, including different genotoxic endpoints as indicated in the SCCS Notes of Guidance.
In the absence of appropriate data, the SCCS cannot draw conclusions on the genotoxic potential.

3.3.7 Carcinogenicity

No information provided.

SCCS comment:
As described in the SCCS Nano Guidance (SCCS/1484/12), if significant systemic exposure is possible (based on tests above under heading 3.3.4 Dermal/percutaneous absorption), information on this endpoint should be provided.
"In cases where a considerable oral intake is expected, or when the data on dermal/percutaneous absorption indicate a considerable penetration of the ingredients through the skin (taking into account the toxicological profile of the substance and chemical

structure), further toxicological investigations (on carcinogenicity and reproductive toxicity) may become necessary, together with specific additional genotoxicity, and/or mutagenicity data".
The SCCS notes that no information has been provided that would make it possible to draw conclusions on the systemic availability via the relevant uptake route(s).

3.3.8 Reproductive toxicity

No information provided.

SCCS comment:
As described in the SCCS Guidance on the Safety Assessment of Nanomaterials in Cosmetics (SCCS/1484/12), if significant systemic exposure is possible (based on tests above under heading 3.3.4 Dermal/percutaneous absorption), information on this endpoint should be provided.
"In cases where a considerable oral intake is expected, or when the data on dermal/percutaneous absorption indicate a considerable penetration of the ingredients through the skin (taking into account the toxicological profile of the substance and chemical structure), further toxicological investigations (on carcinogenicity and reproductive toxicity) may become necessary, together with specific additional genotoxicity, and/or mutagenicity data".
The SCCS notes that no information has been provided that would make it possible to draw conclusions on the systemic availability via the relevant uptake route(s).

3.3.9 Photo-induced toxicity

3.3.9.1 Phototoxicity/photoirritation and photosensitisation

No information provided.

SCCS comment:
Information for all three nano-entities and encapsulated substances should be provided.

3.3.9.2 Phototoxicity/photomutagenicity/photoclastogenicity

No information provided.

SCCS comment:
Information for all three nano-entities and encapsulated substances should be provided.

3.3.10 Human data

No information provided.

SCCS comment:
When available, the information for all three nano-entities and encapsulated substances should be provided.

3.3.11 Special investigations

General SCCS comments:
Nanospheres 100 Theophyllisilane C (SA).
Submission containing toxicity data contains document of 7 pages with the last page indicating 7/33, so 26 pages are missing.
The information provided is not on Nanospheres 100 but on the interim product Nanospheres 100 Theophyllisilane C (SA) that is proposed to be used in final cosmetic formulations.
NOTE that the Material Data Safety Sheet contains a warning to avoid contact with skin and eyes for safe handling.
In general, the data submitted are insufficient to evaluate possible toxicity (or lack of toxicity) of the nano-entities. Appropriate data on toxicity should be provided.

Nanospheres 100 Algisium C2 (SA)
No data were provided on the toxicity of Nanospheres 100 Algisium C2 (SA). Appropriate data on toxicity should be provided.

Nanospheres 100 D.S.H. C.N
No data were provided on the toxicity of Nanospheres 100 D.S.H C.N. Appropriate data on toxicity should be provided.

Data on encapsulated substances were not provided. For all three nano-entities and the encapsulated ingredients (Theophylisilane C and Mannuronic acid), information on toxicity should be provided.

Exposure assessment

Nanospheres 100 Theophyllisilane C (SA)
Nanospheres 100 Algisium C2 (SA)
Nanospheres 100 D.S.H. C.N (SA)

No information provided.

SCCS comment:
Appropriate information on exposure should be provided covering information on possible human exposure in relation to product use. The information would be required for all three nano-entities (Nanospheres 100 Theophyllisilane C (SA), Nanospheres 100 Algisium C2 (SA), Nanospheres 100 D.S.H. C.N (SA)) and also for the encapsulated substances (Theophylosilane and Mannuronic acid).

3.4 SAFETY EVALUATION (INCLUDING CALCULATION OF THE MOS)

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SCCS comment:
In view of the limited information provided, calculation of the margin of safety is not possible.

3.5 DISCUSSION

All the information submitted by the Applicant was considered by the SCCS. In addition, a Call for Data was made by the European Commission. Information received on styrene acrylate copolymer as a result of this Call has also been considered by the SCCS. However, information received only concerned the encapsulating material and not the combination of encapsulating material and encapsulated substances. There are therefore major gaps in data and information regarding the physicochemical characterisation of encapsulating as well as encapsulated substances, toxicity, and exposure, making it impossible to produce a risk assessment regarding nano-entities that contain either Theophyllisilane C or Algisium C2.

Therefore, the SCCS considers that the information available at present is insufficient to allow drawing conclusions on the safety of the nano-entities that are made of styrene acrylate copolymer containing Theophyllisilane C or Algisium C2.

4. CONCLUSION

1. *In view of above, and taking into account the scientific data provided, the SCCS is requested to give its opinion on the safety of the nanomaterial Styrene/acrylates copolymer and Sodium styrene/Acrylates copolymer when used in leave-on cosmetics products with a maximum concentration limit of 0.06%, taking into account the reasonably foreseeable exposure conditions.*

The SCCS has not been able to conclude on the safety of any of the three styrene/acrylate copolymer nano-entities submitted by the Applicants. The data submitted are insufficient to allow evaluation of possible toxicity. Regarding use it was reported that the nano-entities as present in Nanospheres 100 Theophyllisilane C (SA), were used for encapsulation of a slimming agent Theophyllisilane C. According to the information provided by the Applicants, the formulation might be used in health products like milks, emulsions, creams, lotions and solutions. However, no data on the use frequency was provided, so, the potential exposure could also not be estimated based on a use scenario. In addition, the submitted information was based on a (nearly) finished product consisting of a nanomaterial shell (Nanosphere 100) and encapsulated active ingredients (Theophyllisilane C and Algisium C2 (SA) methylsilanol mannuronate). For the formulation Nanospheres 100 D.S.H. C.N (SA) no information on composition was submitted.
Data should be provided separately for all of the three styrene/acrylate nanospheres, including any encapsulated substances.

2. *SCCS is requested to address any further scientific concerns with regard to the use of Styrene/ acrylates copolymer and Sodium styrene/Acrylates copolymer in nano form in cosmetic products.*

For applications involving nano-scale materials as evaluated in this Opinion, it is imperative that safety assessment not only considers safety of the individual components (e.g. the encapsulating material and the encapsulated contents), but also safety of all the components when they are put together in the form of a nano-sized entity.

5. MINORITY OPINION

None.

6. REFERENCES

1. 16261_spec_file_2014-3-17-9-20-39
2. 16621_tox_profile_file_2014-3-17-9-20-39
3. 31453_spec_file_2014-4-18-11-37-43
4. 31453_spec_file_2013-5-22-15-23-46
5. 31453_tox_profile_file_2013-4-26-10-13-42
6. 31453_safety_file_2013-4-26-10-13-42