Scientific Committee on Consumer Safety

SCCS

OPINION ON

additional coatings for Titanium Dioxide (nano form) as UV-filter in dermally applied cosmetic products

The SCCS adopted this opinion by written procedure

on 7 November 2016

About the Scientific Committees

Two independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) and are made up of scientists appointed in their personal capacity.

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.).

Scientific Committee members

Contact

European Commission
Health and Food Safety
Directorate C: Public Health, country knowledge, crisis management
Unit C2 – Country knowledge and Scientific Committees
Office: HTC 03/073
L-2920 Luxembourg
SANTE-C2-SCCS@ec.europa.eu

ISSN ISBN

Doi: ND-

The Opinions of the Scientific Committees present the views of the independent scientists who are members of the committees. They do not necessarily reflect the views of the European Commission. The Opinions are published by the European Commission in their original language only.

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

ACKNOWLEDGMENTS

SCCS members
Dr U. Bernauer (Chairperson)
Dr L. Bodin
Dr L. Celleno
Prof. Q. Chaudhry (Rapporteur)
Prof. P.J. Coenraads
Prof. M. Dusinska
Prof. J. Duus-Johansen
Dr E. Gaffet
Prof. C. L. Galli
Prof. E. Panteri
Prof. V. Rogiers
Dr Ch. Rousselle
Dr M. Stepnik
Dr S. Wijnhoven

SCHEER Members
Prof. P.H.M. Hoet
Dr W.H. de Jong

External expert
Dr N. von Götz

The additional contribution for the drafting of the preliminary Opinion of former members of the SCCS, SCHENIR and external experts (term 2013-2016) listed below is gratefully acknowledged.

Former SCCS members:
Dr W. Lilienblum
Prof. Th. Platzek
Dr J. van Benthem

Former SCHENIR member:
Dr. K. Rydzynski

Former SCCS external experts:
Prof. A. Bernard
Dr O. Bussolati
Dr S. H. Doak
Dr T. Jung

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

Keywords: SCCS, scientific opinion, Titanium Dioxide, coatings, nano form, Regulation 1223/2009

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on additional coatings for Titanium Dioxide (nano form) as UV-filter in dermally applied cosmetic products, 7 November 2016, SCCS/1580/16

TABLE OF CONTENTS

1. BACKGROUND

Titanium Dioxide, TiO_2, (CAS/EC numbers 13463-67-7/236-675-5, 1317-70-0/205-280-2, 1317-80-2/215-282-2) is authorized both as colorant under entry 143 of Annex IV and as UV-filter under entry 27 of Annex VI to Regulation (EC) No 1223/2009.

In July 2013, the Scientific Committee on Consumer Safety (SCCS) delivered an Opinion on Titanium Dioxide (nano) (SCCS/1516/13[1]) to assess the safety of the nano form of Titanium Dioxide. In the Opinion, the SCCS concluded that the use of Titanium Dioxide (nano) as UV filter in sunscreens, with the characteristics indicated in the Opinion, and at a concentration of up to 25 %, can be considered not to pose any risk of adverse effects in humans after application on healthy, intact or sunburnt skin.

Among the characteristics reported in the SCCS Opinion (SCCS/1516/13), substances considered safe for use as coating for TiO_2 (nano) are indicated. Consequently as for the use of other coatings not covered in the Opinion, the SCCS concluded that: '*Other cosmetic ingredients applied as stable coatings on TiO_2 nanomaterials can also be used, provided that they can be demonstrated to the SCCS to be safe and the coatings do not affect the particle properties related to behaviour and/or effects, compared to the nanomaterials covered in this Opinion*'.

The SCCS conclusion clarifies that for the use of a substance as coating on TiO_2 nanomaterials, the applicant has to demonstrate that properties/behaviour of the particles with the new coating are not significantly different compared to those already covered in the SCCS Opinion. This would require provision of data on physico-chemical properties (in line with those provided in Tables 1-3 of the SCCS/1516/13 opinion), and data on dermal penetration.

In September 2015, the Commission' services received data from industry in order to assess the safety of the following additional coatings for Titanium Dioxide (nano form) used as UV-filter in dermally-applied cosmetic products:

- Cetyl Phosphate (CAS 3539-43-3)
- Manganese Dioxide (CAS 1313-13-9)
- Triethoxycaprylylsilane (CAS 2943-75-1)

2. TERMS OF REFERENCE

(1) In light of the data provided, does the SCCS consider safe the use of Cetyl Phosphate, Manganese Dioxide and Triethoxycaprylylsilane as coatings for Titanium Dioxide (nano) used as UV-Filter in dermally applied cosmetic products?

(2) Does the SCCS have any further scientific concerns regarding the use of the above-mentioned additional coatings for Titanium Dioxide (nano) used as UV-Filter in dermally-applied cosmetic products?

[1] http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_136.pdf

3. OPINION

This Opinion relates to three (3) nano-forms of TiO_2 materials coated with the following substances:

Material A: Eusolex® T- EASY coated with 16% silica + 6% cetyl phosphate
Material B: Eusolex® T-PRO coated with 7% alumina + 0.7% manganese dioxide
Material C: UV-Titan® M765 coated with 3% alumina + 9% triethoxycaprylylsilane

It is of note that nano-forms of the TiO_2 material coated with silica and alumina have already been evaluated in a previous SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014). Therefore this Opinion is concerned with the safety of the nano-TiO_2 materials with three coating substances (cetyl phosphate, manganese dioxide, and triethoxycaprylylsilane) for use as a UV filter in cosmetic products.

The accompanying files submitted by the Applicant provide data on size, shape, aspect ratio, and *in vitro* dermal penetration. Some parameters (e.g. photo-catalytic activity) have also been listed but relevant data files have not been provided.

Since the core TiO_2 materials along with silica and alumina coatings have previously been assessed by the SCCS, this Opinion has used relevant information on physicochemical and toxicological aspects of these materials from the previous Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014).

3.1 Chemical and Physical Specifications

3.1.1 Chemical identity

The Applicant has provided data on physicochemical properties of the TiO_2 materials coated with three coating materials in line with Table 1-3 of the SCCS Opinion on nano-forms of Titanium Dioxide (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014).

Table 1: Form and Composition of TiO_2 nanomaterials

Material Code	TiO_2 Crystalline Form	Coating Material*	Doping Material	Form	Bulk density (g/cm^3)	VSSA (m^2cm^{-3})
Eusolex® T-EASY	> 98 % Rutile, < 2 % Anatase	16 % Silica, 6 % Cetyl Phosphate	None	Hydrophobic powder	0.2	150
Eusolex® T-PRO	> 95 % Rutile, < 5 % Anatase	7 % Alumina, 0.7 % MnO2	1000 ppm Fe	Hydrophilic powder	0.16	370
UV-Titan® M765	100 % Rutile	3 % Alumina, 9 %Triethoxycaprylylsilane	None	Hydrophobic powder	0.48	95

* the percentages of coating materials may vary slightly within the ranges given in the specification of the product

Table 2: Physicochemical properties of TiO_2 nanomaterials

Material Code	**Crystal Size (nm)**	**Aspect ratio**	**UV Absorption (Extinction coefficient)**			**Zeta potential**	**Photo-catalytic activity**		**Photo-stability**	**Coating stability**
	(XRD)	(L/W)	E308	E360	E400	(IEP)	△↓↑	% to Reference		
Eusolex® T-EASY	20	2.6	50.	14	6	2	0.4	1	Photostable	Stable**
Eusolex® T-PRO	13	4.1	41	12	5	9	1.3	4	Photostable	Stable**
UV-Titan® M765	50	1.7	26	22	15	N/A *	0.4	1	Photostable	Stable**

* Page 16, SCCS Opinion: "Zeta potential measurements have been provided for some materials, and not for others due to difficulties in measuring zeta potential for hydrophobic nanomaterials."

** The applicant has provided data to show stability of the coatings, showing no significant increase in photocatalytic activity of the coated nanomaterials during long term storage (up to 2 years).

Table 3: Particle size of TiO_2 nanomaterials

Material Code	**Particle Size Distribution**											
	Lower Cut Off level (nm)			**Volume weighted median, X50.3 (nm)**				**Number weighted median, X50.0 (nm)**				
CPS	**LUMI sizer**	**DLS**	**Average**	**CPS**	**LUMI sizer**	**DLS**	**Average**	**CPS**	**LUMI sizer**	**DLS**	**Average**	
Eusolex® T-EASY	30	-	-	n.a.	300	-	-	n.a.	70	-	-	n.a.
Eusolex® T-PRO	40	-	-	n.a.	978	-	-	n.a.	61	-	-	n.a.
UV-Titan® M765	30	-	-	n.a.	300	-	-	n.a.	100	-	-	n.a.

According to the Applicant: "The particle size measurement results of the products presented in the SCCS Opinion were measured with two different centrifuges (CPS and Lumisizer) and DLS. Both methods are suitable for Titanium Dioxide nanoparticles. As mentioned in the Opinion DLS provides higher Median, x50.0 values. Therefore we have chosen the Differential Sedimentation Analysis with CPS disc centrifuge for the new coatings because this provides results comparable to the Integral Sedimentation Analysis with LUMiSizer centrifuge."

3.1.1.1 Primary name and/or INCI name

Core material:
Titanium Dioxide

Coating materials:
Cetyl Phosphate
Manganese Dioxide
Triethoxycaprylylsilane

3.1.1.2 Chemical names

Core material: Titanium dioxide; Titanium (IV) oxide

Coating materials:

Cetyl phosphate:	Hexadecyl dihydrogen phosphate
Manganese dioxide:	Manganese oxide; Manganese (IV) oxide
Triethoxycaprylylsilane:	Triethoxycaprylylsilane

3.1.1.3 Trade names and abbreviations

Core material: COLIPA No. S75

3.1.1.4 CAS / EC number

Core material: TiO_2

CAS number: 13463-67-7, EC: 236-675-5

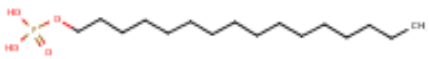
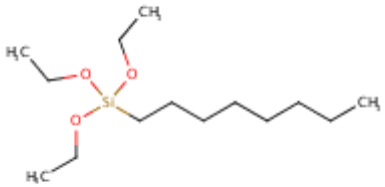
Coating materials:

Cetyl Phosphate:	CAS number 3539-43-3, EC number 222-581-1
Manganese Dioxide:	CAS number 1313-13-9, EC number 215-202-6
Triethoxycaprylylsilane:	CAS number 2943-75-1, EC number 220-941-2

3.1.1.5 Structural formula

Core material: TiO_2

Coating materials:

		
Cetyl phosphate	Manganese dioxide	Triethoxycaprylylsilane

3.1.1.6 Empirical formula

Core material: TiO_2

Coating materials:
Cetyl phosphate: C16-H35-O4-P
Manganese dioxide: Mn-O2
Triethoxycaprylylsilane: C14-H32-O3-Si

3.1.2 Physical form

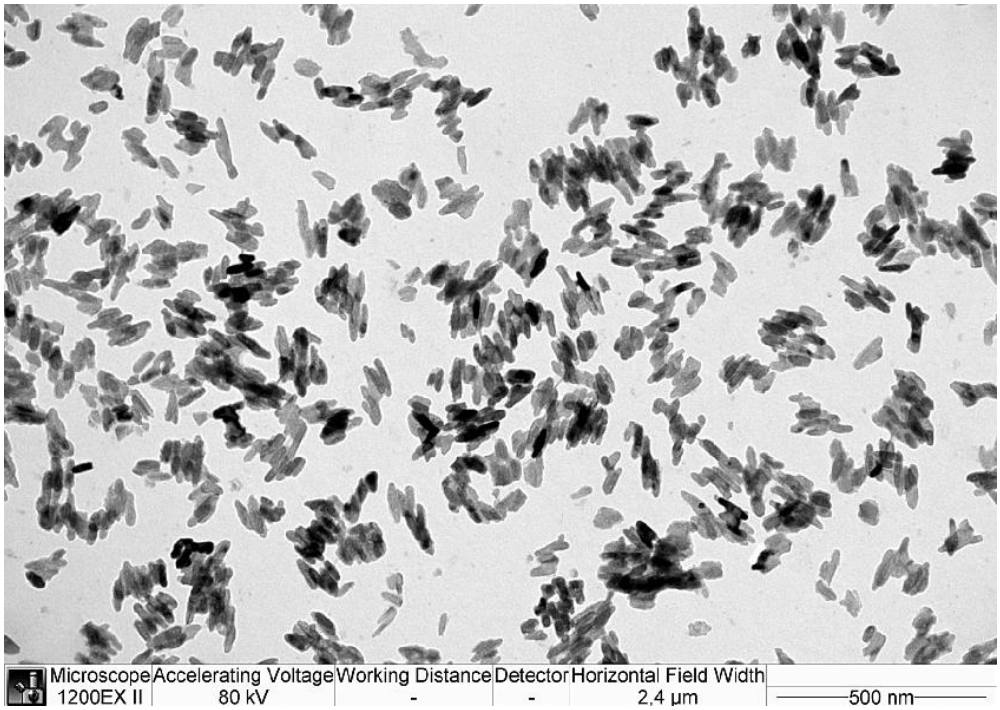
The following description for the core nanomaterial titanium dioxide is derived from the SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014):

Titanium dioxide (TiO_2, COLIPA No. S75, CAS No. 13463-67-7) is described as a solid, white, odourless powder. The TiO_2 materials used in sunscreen products are reported to be composed of two crystalline types: rutile and anatase or a mixture of the two. The materials have been reported to be needle, spherical, or lanceolate (longer than wide) in shape. The primary particle size of the TiO_2 nanomaterials has been reported to range from around 20 to 100 nm.

Nanoparticles are generally known to have a tendency to stick together to form agglomerates and/or aggregates, and it is claimed that, in sunscreen products, TiO_2 is not present in the form of primary nanoparticles but as aggregates of between 30 to >150 nm.

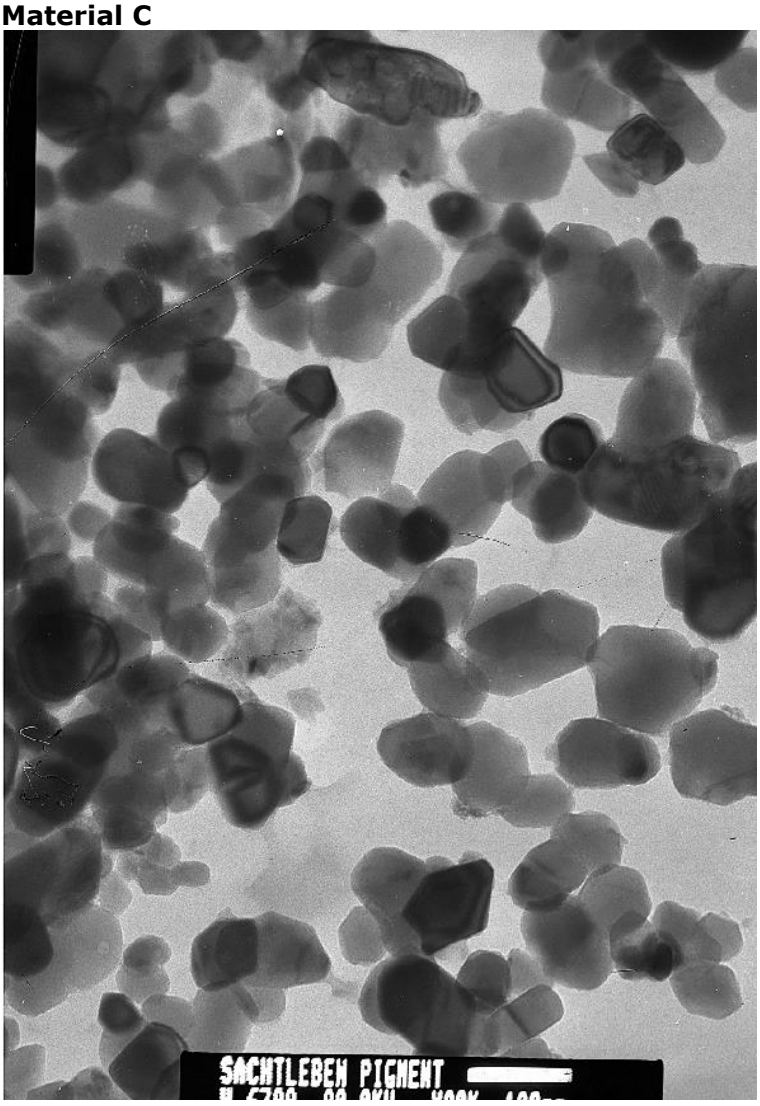
Electron Microscopy Images (provided in the current submission)

Material A



Material B

Material C



3.1.3 Molecular weight

Core material:
TiO_2: 79.9 g/mol.

Coating materials:

Cetyl phosphate: 322.4 g/mol.
Manganese dioxide: 86.9 g/mol.
Triethoxycaprylylsilane: 276.5 g/mol.

3.1.4 Purity, composition and substance codes

According to the description provided in the SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014), the TiO_2 materials are produced according to USP 31 specifications, in high purity, with concentration of the active material ≥99.0 %. It is also stated that the materials do not contain heavy metals (e.g., Hg, Cd, Pb, As or Sb) beyond the generally accepted limits.

3.1.5 Impurities / accompanying contaminants

Details not provided.

SCCS comment
Information on the impurities has not been provided for the nano-forms of TiO_2 materials.

3.1.6 Solubility

From SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014):

TiO_2 is insoluble in water and organic solvents. It also has a very low dissociation constant in water and aqueous systems, and thus can in practice be considered as insoluble, also under the physiological conditions.

(Numerous references in open literature)

3.1.7 Partition coefficient (Log P_{ow})

From SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014):

Log P_{ow}: Not applicable for uncoated TiO_2.

SCCS comment:
The partition coefficient only describes materials by and after their dissolution in octanol/water. However, the distribution between polar and non-polar phases should be described for the TiO_2 nanomaterials that are coated with organic substances.

3.1.8 Additional physical and chemical specifications

From SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014):

Melting point:	Not provided
Boiling point:	Not applicable
Flash point:	Not applicable
Vapour pressure:	Not applicable
Density:	Bulk densities reported as 0.2, 0.16 and 0.48 g/cm3 for materials A, B and C respectively (see Table 1 in the current Opinion).
Viscosity:	Not provided
pKa:	Not provided
Refractive index:	Not provided
UV_Vis spectrum (200-800 nm):	UV data only (see Table 2 in the current Opinion)

SCCS comment:
The dissociation kinetics of the materials in acidic media can be potentially modified by certain coatings. However, considering the physicochemical properties of TiO_2, it is agreed that, for TiO_2 nanomaterials, coatings are unlikely by definition to change the dissociation constant of TiO_2 in water.

3.1.9 Homogeneity and Stability

All 3 materials are reported to be photostable and have stable coatings.

The applicant has provided data to show stability of the coatings, showing no significant increase in photocatalytic activity of the coated nanomaterials during long-term storage (up to 2 years)).

SCCS comments on physicochemical characterisation

1. The physicochemical characterisation data provided relates to three (3) TiO_2 nanomaterials. The commercial names of the materials have been named by SCCS as material A, B and C.
2. One of the materials is composed of 100% rutile form, 2 materials are mainly rutile with 2-5% anatase form.
3. Primary crystal sizes (measured by XRD) range between 13 and 50 nm.
4. Particle size (measured by Lumisizer) range between 300-978 nm (volume weighted median), and 61-100 nm (number weighted median). The lowest size cut-off using this method is between 30 and 40 nm. This means that smaller sized nanoparticles (below 30 nm) were not measured by the method used.
5. The aspect ratios of the particles range between 1.7 and 4.1.
6. Zeta potential measurements have been provided for materials A and B (2 and 9 respectively), but not for material C due to difficulties in measuring zeta potential.
7. Material A is coated with 16% silica + 6% cetyl phosphate. Material B is coated with 7% alumina + 0.7% manganese dioxide. Material C is coated with 3% alumina + 9% triethoxycaprylylsilane.
8. Photocatalytic activity of the materials ranges between 1 and 4% (compared to reference).
9. All 3 materials are reported to be photostable, and with stable coatings.
10. UV absorption data for the materials have been provided.

3.2 Function and uses

From SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014):

Titanium dioxide is used as an UV-filter in a concentration up to 25% in cosmetic products. It is regulated in Annex VII, entry 27 of the Cosmetics Directive.

3.3 Toxicological Evaluation

The current submission did not provide any toxicological data. However, since the same core TiO_2 nanomaterials had been evaluated previously, the main conclusions drawn in the SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014) have been used in the current evaluation.

3.3.1 Acute toxicity

3.3.1.1 Acute oral toxicity

The following SCCS comment on acute oral toxicity has been taken from SCCS/1516/13, 22 July 2013, Revision of 22 April 2014:

From the limited data available, the acute oral toxicity of nano-TiO_2 (anatase and rutile mixtures) appears to be very low.

3.3.1.2 Acute dermal toxicity

The following SCCS comment on acute oral toxicity has been taken from SCCS/1516/13, 22 July 2013, Revision of 22 April 2014:

From the provided test data, acute dermal LD_{50} of TiO_2 has been derived at >2000 mg/kg (ultrafine material), and >10,000 mg/kg (natural colour material). However, the provided studies are of no value to the current assessment of nano forms of TiO_2.

3.3.1.3 Acute inhalation toxicity

The following SCCS comment on acute inhalation toxicity has been taken from SCCS/1516/13, 22 July 2013, Revision of 22 April 2014:

No study on acute inhalation toxicity was provided. Studies (including open literature) on acute and sub-chronic inhalation exposure to TiO_2 nanomaterials have indicated substantial inflammatory responses, and histologically clear indications of epithelial hypertrophy and hyperplasia at high exposure dose. In view of this, the SCCS does not recommend the use of nano TiO_2 in applications that would lead to any significant inhalation exposure (e.g. powder or sprayable products).

3.3.2 Irritation and corrosivity

3.3.2.1 Skin irritation

The following SCCS comment on skin irritation has been taken from SCCS/1516/13, 22 July 2013, Revision of 22 April 2014:

From the limited useful data presented in the dossier, it appears that the TiO_2 nanomaterials are either mild or non-irritant to skin.

3.3.2.2 Mucous membrane irritation / Eye irritation

The following SCCS comment on eye irritation has been taken from SCCS/1516/13, 22 July 2013, Revision of 22 April 2014:

From the limited useful data provided, eye irritation potential of nano-TiO_2 appears to be low.

3.3.3 Skin sensitisation

The following SCCS comment on skin sensitisation has been taken from SCCS/1516/13, 22 July 2013, Revision of 22 April 2014:

From the limited useful data, TiO_2 nanomaterials appear to be a weak or non-sensitiser for skin applications.

3.3.4 Dermal / percutaneous absorption

In vitro dermal/ percutaneous absorption Studies

Guideline/method:	OECD 428; SCCS/1501/12
Species:	Dermatomed pig skin (Back/flank skin from suckling pigs (aged 6-8 weeks)
Test substances:	Material A (Eusolex® T-EASY formulation)
Particle size:	Median particle size 300 nm (volume weighted), 70 nm (number weighted), lowest size cut off 30 nm.
Group sizes:	Two control and eight test cells
Dose applied:	24 hour, leave-on application of 10 µL /cm^2 of formulation (760 µg nano-TiO_2/cm^2), which is equal to 25.4 µL = 1930 µg nano-TiO_2
Skin area:	2.54 cm^2
Skin temperature:	32°C ± 1°C
Test chamber:	Static glass diffusion cell, receptor volume of approximately 4.5 mL.
Receptor fluid:	Physiological saline
Exposure period:	24 hours. A 0.5 ml sample of the receptor fluid was taken from the receptor chambers at 1, 2, 4, 8, 12 and 24 hours for analysis by ICP-MS. The volume of fluid in the receptor chamber was maintained by replacing with an equal volume after each sample).
GLP:	Yes
Published:	No
Study period:	2015
Reference:	Report Number: JV2342-REG

The penetration and distribution of titanium dioxide (nano form) from a Eusolex® T-EASY formulation was assessed in vitro through pig dermatomed skin. The formulation was applied at a rate of 10 µL/cm^2 to the skin surface mounted on static glass diffusion cell. Samples of physiological saline receptor fluid were taken at recorded intervals over a 24 hour contact period, during which time the applications remained unoccluded. At the end of the experiment, the dose was washed from the surface of the skin using cotton wool swabs soaked in 3% Teepol®L and layers of stratum corneum were removed using a tape stripping technique. Extracts of the donor chamber, the skin wash, tape strips, flange, heat separated epidermis and dermis were analysed for titanium dioxide by inductively coupled plasma - optical emission spectroscopy (ICP-OES) and/or inductively coupled plasma–mass spectroscopy (ICP-MS) to provide a full mass balance.
Membrane integrity was determined by measurement of the electrical resistance across the skin membrane. Membranes with a measured resistance of <3 kΩ (Davies et al, 2004) were regarded as having a lower integrity than normal and not used for exposure to the test materials.
The visualisation of titanium dioxide nano-particles in parallel treated skin samples exposed to the formulation for 24 hours was done with transmission electron microscopy (TEM).
The vast majority of the applied test material (mean of 92.5% ± 9.24%) was recovered from the skin wash at 24 hours. The proportions of the dose applied that were recovered from the donor chamber, stratum corneum (tape strips 1-20), epidermis, dermis and flange were 0.037% ± 0.040, 6.20% ± 7.52, 0.050% ± 0.060, 0.027% ± 0.030 and 0.183% ± 0.274.
The systemically available dose of titanium dioxide (epidermis, dermis and receptor fluid) was below 0.081% ± 0.071.

Applicant's conclusions
The results obtained in this study indicate that titanium dioxide present in this Eusolex® T-EASY formulation does not penetrate into or through the skin, as evidenced by the very low levels of detection in this study and the fact that minor traces of titanium are already present in the test system. The maximum systemically available dose is below 0.081%, representing worst case dermal exposure. The vast majority of the dose applied (92.5%) was washed from the skin surface 24 hours after application.
In addition, titanium dioxide particles were not observed by transmission electron microscopy in the regions beyond the uppermost layers of the stratum corneum such as the viable epidermis or dermis following application of Eusolex® T-EASY formulation.
Therefore, based on the results of this study, it can be concluded that titanium dioxide (nano form) in this representative formulation is not considered as systemically available.

Guideline/method:	OECD 428; SCCS/1501/12
Species:	Dermatomed pig skin (Back/flank skin from suckling pigs (aged 6-8 weeks)
Test substances:	Material B (Eusolex® T-PRO formulation)
Particle size:	Median particle size 978 nm (volume weighted), 61 nm (number weighted), lowest size cut off 40 nm.
Group sizes:	Two control and eight test cells
Dose applied:	24-hour, leave-on application of 10 µL/cm^2 of formulation (816 µg nano-TiO_2) /cm^2, which is equal to 25.4 µL = 2072 µg nano-TiO_2
Skin area:	2.54 cm^2
Skin temperature:	32°C ± 1°C
Test chamber:	Static glass diffusion cell, receptor volume of approximately 4.5 mL.
Receptor fluid:	Physiological saline
Exposure period:	24 hours. A 0.5 ml sample of the receptor fluid was taken from the receptor chambers at 1, 2, 4, 8, 12 and 24 hours for analysis by ICP-MS. The volume of fluid in the receptor chamber

	was maintained by replacing with an equal volume after each sample).
GLP:	Yes
Published:	No
Study period:	2015
Reference:	Report Number: JV2343-REG

The penetration and distribution of titanium dioxide (nano form) from a Eusolex® T-PRO formulation was assessed in vitro through pig dermatomed skin. The formulation was applied at a rate of 10 µL/cm^2 to the skin surface mounted on static glass diffusion cells. Samples of physiological saline receptor fluid were taken at recorded intervals over a 24-hour contact period, during which time the applications remained unoccluded. At the end of the experiment, the dose was washed from the surface of the skin using cotton wool swabs soaked in 3% Teepol®L and layers of stratum corneum were removed using a tape-stripping technique. Extracts of the donor chamber, the skin wash, tape strips, flange, heat separated epidermis and dermis were analysed for titanium dioxide by inductively coupled plasma - optical emission spectroscopy (ICP-OES) and/or inductively coupled plasma – mass spectroscopy (ICP-MS) to provide a full mass balance.
Membrane integrity was determined by measurement of the electrical resistance across the skin membrane. Membranes with a measured resistance of <3 kΩ (Davies et al, 2004) were regarded as having a lower integrity than normal and were not used for exposure to the test materials.
The visualisation of titanium dioxide nano-particles in parallel treated skin samples exposed to the formulation for 24 hours was done with transmission electron microscopy (TEM).

Results
Background titanium dioxide was detected in varying amounts in each of the untreated control cell compartments and, in particular, in the tape strips. Therefore, the test data were adjusted by deducting the mean control values for background titanium dioxide for each test cell mass balance compartment.
All of the skin penetration data for titanium dioxide, that would be considered as dermally absorbed, was below the limit of quantitation (0.030 µg/cm^2 equivalent to 0.004% of the applied dose).
Mean recovery was very good at 101% ± 6.72 of the applied dose, with individual cell recovery values ranging from 92.3% to 111%. Two of the eight dosed cells (cells 39 and 94) had very low total recovery of the applied dose (42.6% and 16.8%) which was not typical of the other cells. The data from these cells were not included in the mean ± SD.
The vast majority of the applied test material (mean of 99.1% ± 6.29%) was recovered from the skin wash at 24 hours. The proportions of the dose applied that were recovered from the donor chamber, stratum corneum (tape strips 1-20), epidermis, dermis and flange were 0.023% ± 0.025, 1.47% ± 0.649, 0.030% ± 0.025, 0.015% ± 0.007 and 0.135% ± 0.184.
The systemically available dose of titanium dioxide (epidermis, dermis and receptor fluid) was below 0.048% ± 0.030.
Titanium dioxide levels in receptor fluid were below the limit of quantitation (0.030 µg/cm^2 equivalent to 0.004% of the applied dose) over the entire 24-hour exposure period.

Applicant's conclusions
The results obtained in this study indicate that titanium dioxide present in this Eusolex® T-PRO formulation does not penetrate into or through the skin, as evidenced by the very low levels of detection in this study and the fact that minor traces of titanium are already present in the test system. The maximum systemically available dose was below 0.048%, representing worst case dermal exposure. The vast majority of the dose applied (99.1%) was washed from the skin surface 24 hours after application.
In addition, titanium dioxide particles were not observed by transmission electron microscopy in the regions beyond the uppermost layers of the stratum corneum such as the viable epidermis or dermis following application of Eusolex® T-PRO formulation.

Therefore, based on the results of this study, it can be concluded that titanium dioxide (nano form) in this representative formulation is not considered as systemically available.

In vitro dermal/ percutaneous absorption

Guideline/method:	OECD Test Guideline 428; OECD Test Guideline 48; SCCS Guidelines (SCCS/1358/10; SCCS/1501/12 and SCCS/1484/12).
Species:	Dermatomed pig skin (Back/flank skin from suckling pigs (aged 6-8 weeks)
Test substances:	Material C (UV-TITAN M765 formulation)
Particle size:	Median particle size 300 nm (volume weighted), 100 nm (number weighted), lowest size cut off 30 nm.
Group sizes:	Two control and eight test cells
Dose applied:	24 hour, leave-on application of 10 µL /cm^2 (912 µg nano-TiO_2/cm^2), which is equal to 25.4 µL = 2316 µg nano-TiO_2
Skin area:	2.54 cm^2
Skin temperature:	32°C ± 1°C
Test chamber:	Static glass diffusion cell, receptor volume of approximately 4.5 mL.
Receptor fluid:	Physiological saline
Exposure period:	24 hours. A 0.5 ml sample of the receptor fluid was taken from the receptor chambers at 1, 2, 4, 8, 12 and 24 hours for analysis by ICP-MS. The volume of fluid in the receptor chamber was maintained by replacing with an equal volume after each sample).
GLP:	Yes
Published:	No
Study period:	2015
Reference:	Report Number: JV2344-REG

Method

The penetration and distribution of titanium dioxide (nano form) from a UV-TITAN M765 formulation was assessed in vitro through pig dermatomed skin. The formulation was applied at a rate of 10 µL/cm^2 to the skin surface mounted on static glass diffusion cell. Samples of the physiological saline receptor fluid were taken at recorded intervals over a 24-hour contact period, during which time the applications remained unoccluded. At the end of the experiment, the dose was washed from the surface of the skin using cotton wool swabs soaked in 3% Teepol®L and layers of stratum corneum were removed using a tape stripping technique. Extracts of the donor chamber, the skin wash, tape strips, flange, heat separated epidermis and dermis were analysed for titanium dioxide by inductively coupled plasma - optical emission spectroscopy (ICP-OES) and/or inductively coupled plasma – mass spectroscopy (ICP-MS) to provide a full mass balance.

Membrane integrity was determined by measuring the electrical resistance across the skin membrane. Membranes with a measured resistance of <3 kΩ (Davies et al, 2004) were regarded as having a lower integrity than normal and were not used for exposure to the test materials.

Membrane integrity was determined by measuring the electrical resistance across the skin membrane. Membranes with a measured resistance of <3 kΩ (Davies et al, 2004) were regarded as having a lower integrity than normal and not used for exposure to the test materials.

The visualisation of titanium dioxide nano-particles in parallel-treated skin samples exposed to the formulation for 24 hours was done with transmission electron microscopy (TEM).

Results
ICP-OES analysis of the formulation confirmed that the formulation was acceptable for use, i.e. with titanium dioxide being homogenously distributed and that the mean titanium dioxide concentration was 91.2 mg/g (9.12% w/w).
Background titanium dioxide was detected in varying amounts in each of the untreated control cell compartments and, in particular, in the tape strips. Therefore, the test data were adjusted by deducting the mean control values for background titanium dioxide for each test cell mass balance compartment.
All of the skin penetration data for titanium dioxide that would be considered as dermally absorbed was below the limit of quantitation (0.031 µg/cm^2 equivalent to 0.003% of the applied dose).
Mean recovery was very good at 101% ± 6.02 of the applied dose, with individual cell recovery values ranging from 91.6% to 107%. Two of the eight dosed cells (cells 49 and 59) had very low total recovery of the applied dose (56.6% and 34.1%) which was not typical of the other cells. The data from these cells were not included in the mean ± SD.
The vast majority of the applied test material (mean of 101% ± 5.91%) was recovered from the skin wash at 24 hours. The proportions of the dose applied that were recovered from the donor chamber, stratum corneum (tape strips 1-20), epidermis, dermis and flange were 0.018% ± 0.015, 0.730% ± 0.406, 0.009% ± 0.004, 0.009% ± 0.003 and 0.108% ± 0.154.
The systemically available dose of titanium dioxide (epidermis, dermis and receptor fluid) was below 0.021% ± 0.005.

Applicant's conclusions
The results obtained in this study indicate that titanium dioxide present in this UV-TITAN M765 formulation does not penetrate into or through the skin, as evidenced by the very low levels of detection in this study and the fact that minor traces of titanium are already present in the test system. The maximum systemically available dose was below 0.021%, representing worst case dermal exposure. The vast majority of the dose applied (101%) was washed from the skin surface 24 hours after application.
In addition, titanium dioxide particles were not observed by transmission electron microscopy in the regions beyond the uppermost layers of the stratum corneum such as the viable epidermis or dermis following application of UV-TITAN M765 formulation.
Therefore, based on the results of this study, it can be concluded that titanium dioxide (nano form) in this representative formulation is not considered as systemically available.

SCCS comment on dermal/percutaneous absorption

The 3 coated nano-TiO_2 materials under evaluation were tested in vitro for dermal/percutaneous absorption using dermatomed pig skin. The SCCS has accepted the results of the studies that have shown that none of the test materials penetrated in any significant amount through the dermatomed pig skin. Imaging of the skin sections using transmission electron microscopy also did not show any nanoparticles of TiO_2 beyond the uppermost layers of the stratum corneum.

The studies and literature information evaluated in the previous SCCS Opinion on coated and uncoated nano forms of TiO_2 (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014) also indicated that TiO_2 nanoparticles generally do not penetrate the healthy or (simulated) sunburnt skin. However, it was pointed out that such information on flexed or damaged skin was not available, and the evaluated studies were not directed towards hazard identification using either a dose response approach or a worst-case scenario (overdosing situation), and that there were certain knowledge gaps in relation to the possible dermal penetration of nano TiO_2 on repeated or long-term use of cosmetic products, which may not only be used on flexed healthy skin but also on skin that may have lesions or cuts.

3.3.5 Repeated dose toxicity

The following SCCS comment on repeated dose toxicity has been taken from SCCS/1516/13, 22 July 2013, Revision of 22 April 2014:

From the 60-day oral (gavage) study in mice, a LOAEL of 5 mg/kg bw/d may be derived.

3.3.5.1 Repeated Dose (14 days) oral toxicity

/

3.3.5.2 Sub-chronic (90 days) toxicity (oral)

/

3.3.5.3 Chronic (> 12 months) toxicity

/

3.3.6 Mutagenicity / Genotoxicity

The following SCCS comment on mutagenicity/genotoxicity has been taken from SCCS/1516/13, 22 July 2013, Revision of 22 April 2014:

From the studies discussed above, the potential to cause DNA damage has been clearly demonstrated for some TiO_2 nanomaterials. However, it is not clear how this relates to the other nanomaterials presented in the submission.

3.3.6.1 Mutagenicity / Genotoxicity *in vitro*

/

3.3.6.2 Mutagenicity / Genotoxicity *in vivo*

/

3.3.7 Carcinogenicity

The following SCCS comment on carcinogenicity has been taken from SCCS/1516/13, 22 July 2013, Revision of 22 April 2014:

Since TiO_2 particles have shown carcinogenic activity and since nano ncTiO_2 [non-coated TiO_2] also showed promoter activity after intra-pulmonary spraying, the use of nano TiO_2 in sprayable applications needs specific considerations.

3.3.8 Reproductive toxicity

The following SCCS comment on reproductive toxicity has been taken from SCCS/1516/13, 22 July 2013, Revision of 22 April 2014:

No relevant study on reproductive toxicity is provided. Overall information on this endpoint is as yet patchy and inconclusive.

3.3.8.1 Two-generation reproduction toxicity

/

3.3.8.2 Other data on fertility and reproduction toxicity

/

3.3.8.3 Developmental Toxicity

/

3.3.9 Toxicokinetics

The following SCCS comment on toxicokinetics has been taken from SCCS/1516/13, 22 July 2013, Revision of 22 April 2014:

The limited available evidence suggests that, if TiO_2 nanoparticles become systemically available, they may accumulate mainly in liver with a very slow clearance.

3.3.10 Photo-induced toxicity

The previous SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014) highlights the importance of surface coating for reduction of phototoxic activity of TiO_2 nanoparticles.

3.3.11 Human data

/

3.3.12 Special investigations

/

3.3.13 Safety evaluation (including calculation of the MoS)

The results of the dermal/percutaneous absorption studies submitted in the current dossier as well as the conclusions of the previous SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014) suggest that there is a very low, if any, dermal penetration of the nano-forms of TiO_2 when applied on healthy intact or sunburnt skin. When considered in conjunction with the low general toxicity of TiO_2, the calculation of a margin of safety (MoS) is not relevant for the dermally-applied formulations containing nano-forms of TiO_2.

Any exposure to nano-TiO_2 via oral route from a dermally applied product is also likely to be insignificantly low. Again, considering this together with the low toxicity of TiO_2, calculation of a margin of safety (MoS) for the oral route is also not relevant.

However, as concluded in the previous SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014), the use of nano-TiO_2 in applications that might lead to lung

exposure via the inhalation route (such as powders or sprayable products) is not recommended.

3.3.14 Discussion

The Applicant has sought the SCCS's opinion on three coatings on nano-forms of TiO_2 materials. Although these coating materials were not previously evaluated, the SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014) had a provision for the new coatings on nano-forms of TiO_2 as follows:

'Other cosmetic ingredients applied as stable coatings on TiO_2 nanomaterials can also be used, provided that they can be demonstrated to the SCCS to be safe and the coatings do not affect the particle properties related to behaviour and/or effects, compared to the nanomaterials covered in this Opinion.'

Chemical and Physical Specifications:

The physicochemical characterisation data provided in this submission relate to three (3) TiO2 nanomaterials. The commercial names of the materials have been named by SCCS as material A, B and C.

One of the materials is composed of 100% rutile form, 2 other materials are mainly rutile with 2-5% anatase form. The aspect ratios of the particles range between 1.7-4.1; zeta potentials range between 2-9; and photocatalytic activity between 1-4% (compared to reference). All 3 materials are reported to be photostable and have a relatively very low photocatalytic activity (1-4% compared to reference).

Primary crystal sizes (measured by XRD) range between 13-50 nm; particle sizes (measured by Lumisizer) range between 300-978 nm (volume weighted median), and 61-100 nm (number weighted median). The lowest size cut-off using this method is between 30 and 40 nm. This means that the majority of the smaller sized nanoparticles (below 30 nm) were not measured.

Material A is coated with 16% silica + 6% cetyl phosphate
Material B is coated with 7% alumina + 0.7% manganese dioxide
Material C is coated with 3% alumina + 9% triethoxycaprylylsilane

As highlighted in the previous SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014), there is a concern relating to the use of high proportions of coating materials, such as alumina. Although the current submission suggest that the coatings on all 3 materials are stable, it is important to know the concentration of any dissolved coating materials, e.g. aluminium ions, in the final formulation. A significant dissolution of the coating material (e.g. alumina) may require a separate safety assessment for the coating material.

Triethoxycaprylylsilane:

Triethoxycaprylylsilane is included in the CosIng database as a cosmetic ingredient. However it is not regulated as such in any of the Annexes of the Cosmetics Regulation, and therefore its safety has not been assessed either as a colorant, preservative, or UV-filter. Triethoxycaprylylsilane has been evaluated by the SCCS as a coating on nano-forms of zinc oxide (SCCS/1489/12, Revision of 11 December 2012). Furthermore, trimethoxycaprylylsilane, which is a close analogue of triethoxycaprylylsilane, has also been evaluated by the SCCS as a coating material for TiO_2 nanomaterials (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014).

A comparison of the $LogP_{ow}$ values (shown below) indicates that both trimethoxy- and triethoxy- caprylylsilane are hydrophobic compounds, although triethoxycaprylylsilane is

more hydrophobic and therefore less soluble in water than trimethoxycaprylylsilane (data derived from EChA and CIR.

Compound	**CAS number**	**Log Pow**	**Water solubility**
Trimethoxycaprylylsilane	3069-40-7	3.9	13.3 mg/L (at 20 °C)
Triethoxycaprylylsilane	2943-75-1	6.41	0.13 – 0.79 mg/L @ 20 - 22.8 °C and pH 5 - 7

Cetyl phosphate:

Cetyl phosphate is included in the CosIng database as a cosmetic ingredient. However, it is not regulated as such in any of the Annexes of the Cosmetics Regulation, and therefore its safety has not been assessed either as a colorant, preservative, or UV-filter. The material has not been evaluated by the SCCS as a coating on any nanomaterial.

Manganese dioxide:

Manganese dioxide is included in the CosIng database as a cosmetic ingredient. However, it is not regulated as such in any of the Annexes of the Cosmetics Regulation, and therefore its safety has not been assessed either as a colorant, preservative or UV-filter. The material has not been evaluated by the SCCS as a coating on any nanomaterial.

Toxicological evaluation

Coating materials

Triethoxycaprylylsilane:

Studies summarised in the Cosmetic Ingredient Review (CIR)'s tentative report (2016) indicate that triethoxycaprylylsilane is relatively non-toxic and is unlikely to be genotoxic. It is considered as a moderate to high irritant to the skin and a slight irritant to the eye. The CIR Expert Panel concluded that it is safe in the present practices of use and concentration in cosmetics at the concentration described in the safety assessment.

Cetyl phosphate:

Studies summarised in the CIR draft final report (2014) indicate that cetyl phosphate is relatively non-toxic and is unlikely to be genotoxic, a skin sensitiser or an eye irritant. It was not a sensitiser in GPMTs, but challenge concentrations of 10 and 40% cetyl phosphate were shown to be irritating. The CIR Expert Panel concluded that it is safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

Manganese dioxide:

According to Annex VI of CLP Regulation (1272/2008), MnO_2 has a harmonised classification as Acute Tox 4 H302 (harmful if swallowed).

CORE TiO_2 materials

Acute Toxicity: The previous SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014) considered that the core TiO_2 nanomaterials are likely to have low toxicity via oral or dermal application routes, but raised safety concerns over the inhalation exposure due to the substantial inflammatory effects in the lung.

Irritation and corrosivity: The previous SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014) considered that TiO_2 nanomaterials are likely to be mild- or non-irritant to skin; with a low potential for causing eye irritation; and weak or non-skin sensitisers.

Dermal absorption: The SCCS has accepted the results of the studies that indicated that none of the test materials under evaluation showed any significant absorption through the dermatomed pig skin and that nanoparticles of TiO_2 did not penetrate beyond the uppermost layers of the stratum corneum. The previous SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014) accepted that TiO_2 nanoparticles generally do not penetrate the healthy or (simulated) sunburnt skin, but also highlighted the knowledge gaps in regard to potential penetration of nanoparticles through cuts and bruises, or over repeated or long-term applications of a sunscreen formulation.

Repeated dose toxicity: The previous SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014) considered a 60-day oral (gavage) study in mice to derive a LOAEL of 5 mg/kg bw/d.

Inhalation toxicity: The previous SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014) considered that studies (including open literature) on acute and sub-chronic inhalation exposure to TiO_2 nanomaterials indicate substantial inflammatory responses in test animals, and histologically clear indications of epithelial hypertrophy and hyperplasia at high-exposure dose. In view of this, the SCCS does not recommend the use of nano TiO_2 in applications that would lead to any significant inhalation exposure of the consumer's lungs.

Mutagenicity/ Genotoxicity: The previous SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014) considered that the potential to cause DNA damage has been clearly demonstrated for some TiO_2 nanomaterials, whilst it is not clear how this relates to other TiO_2 nanomaterials.

Carcinogenicity: The previous SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014) considered that since TiO_2 particles have shown carcinogenic activity and since non-coated nano TiO_2 also showed promoter activity after intra-pulmonary spraying, the use of nano TiO_2 in sprayable applications (that may lead to inhalation exposure of the consumer lung) would need specific considerations.

Reproductive toxicity: The previous SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014) considered that overall information available on this endpoint is as yet patchy and inconclusive.

Photo-induced toxicity: This information was not required in the current submission in view of the photostable nature and the lack of any significant photocatalytic activity of the coated materials evaluated for this Opinion.

Toxicokinetics: The previous Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014) considered that, if TiO_2 particles become systemically available by the oral and/or inhalation uptake pathway, they are likely to accumulate mainly in the liver, followed by a very slow rate of clearance.

Special investigations: No relevant special investigations were provided as part of the current submission or were considered in the previous SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014).

4. CONCLUSION

(1) In light of the data provided, does the SCCS consider safe the use of Cetyl Phosphate, Manganese Dioxide and Triethoxycaprylylsilane as coatings for Titanium Dioxide (nano) used as UV-filter in dermally-applied cosmetic products?

In view of the above discussion, which indicates a general lack of dermal absorption and low general toxicity of nano-forms of titanium dioxide, the SCCS considers that the use of the three TiO_2 nanomaterials (A, B, C), coated with either cetyl phosphate, manganese dioxide or triethoxycaprylylsilane, can be considered safe for use in cosmetic products intended for application on healthy, intact or sunburnt skin. This, however, does not apply to applications that might lead to exposure of the consumer's lungs to the TiO_2 nanoparticles through the inhalation route (such as powders or sprayable products).

(2) Does the SCCS have any further scientific concerns regarding the use of the above-mentioned additional coatings for Titanium Dioxide (nano) used as UV-filter in dermally-applied cosmetic products?

The ingredients used in some type of products (e.g. in lipsticks) may be incidentally ingested. The potential harmful effects of manganese dioxide should therefore be taken into account if the MnO_2-coated nanomaterials are to be used for applications that could lead to oral ingestion.

This Opinion is based on the currently available scientific evidence which shows an overall lack of dermal absorption of TiO_2 nanoparticles. If any new evidence emerges in the future to show that the TiO_2 nanoparticles used in a sunscreen formulation can penetrate skin (healthy, compromised, or damaged skin) to reach viable cells, then the SCCS may consider revising this assessment.

As highlighted in the previous SCCS Opinion (SCCS/1516/13, 22 July 2013, Revision of 22 April 2014), there are certain knowledge gaps in regard to potential penetration of nanoparticles through cuts and bruises, or over repeated or long-term applications of a sunscreen formulation.

It should also be noted that the risk assessment of nanomaterials is currently evolving. In particular, the toxicokinetics aspects have not yet been fully explored in the context of nanoparticles (e.g. the size dependency). Also, long-term stability of the coatings remains unclear. At the moment, both the testing of nanomaterials and the present assessment are based on the methodologies developed for substances in non-nano form and the currently available knowledge on properties, behaviour and effects of nanomaterials. This assessment is, therefore, not intended to provide a blue-print for future assessments of other nanomaterials, where depending on the developments in methodological risk assessment approaches and nano-specific testing requirements, additional/different data may be required and/or requested on a case-by-case basis.

It is also important to note that the potential ecotoxicological impacts of nano TiO_2 when released into the environment have not been considered in this Opinion.

5. MINORITY OPINION

/

6. REFERENCES

1. 2008026826-1 DC Eusolex T-PRO number 41-275 US
2. 2015006390-1 UF PCS-Kurve Eusolex T-PRO
3. 2015006390-2 UF PCS-Kurve UV-Titan M765
4. 201504564-1 PCS-Kurve Eusolex T-EASY
5. B. Nair; Cosmetic Ingredient Review (CIR) Expert Panel: Final report on the safety assessment of stearoxy dimethicone, dimethicone, methicone, amino bispropyl dimethicone, aminopropyl dimethicone, amodimethicone, amodimethicone hydroxystearate, behenoxy dimethicone, C24-28 alkyl methicone, C30-45 alkyl methicone, C30-45 alkyl dimethicone, cetearyl methicone, cetyl dimethicone, dimethoxysilyl ethylenediaminopropyl dimethicone, hexyl methicone, hydroxypropyldimethicone, stearamidopropyl dimethicone, stearyl dimethicone, stearyl methicone, and vinyldimethicone; Int J Toxicol. 2003;22 Suppl 2:11-35.
6. CG11054 - B10 Stability test for coating after storage (Dossier S75, Ref 198) I
7. CG11054 - B10 Stability test for coating after storage (Dossier S75, Ref 198) II
8. CIR (2014) Safety assessment of alkyl phosphates as used in cosmetics, Draft Final Report for Panel Review, Cosmetic Ingredient Review, Washington, DC, Release Date: August 18, 2014: http://www.cir-safety.org/sites/default/files/alkyl%20phosphates_0.pdf
9. CIR (2016) Safety assessment of alkoxyl alkyl silanes as used in cosmetics, Scientific Literature Review for Public Comment, Cosmetic Ingredient Review, Washington, DC, Release Date: January 19, 2016: http://www.cir-safety.org/sites/default/files/alalsi122015Rep.pdf
10. CT14026 – excel table
11. Data on physicochemical properties of new coating materials (in line with Table 1-3 of the SCCS Opinion on Titanium Dioxide (nano form), SCCS/1516/13, 22 July 2013, Revision of 22 April 2014)
12. ECHA: https://echa.europa.eu/brief-profile/-/briefprofile/100.019.038
13. Eusolex T-AVO Aspect Ratio
14. Eusolex T-EASY number DC-Kurve (10880284)
15. Eusolex T-EASY weight DC-Kurve (10880284)
16. Eusolex T-PRO weight DC-Kurve (10880180)
17. Final report: Safety Assessment of Alkyl Phosphates as Used in Cosmetics; Cosmetic Ingredient Review; 2014
18. G.J. Nohynek and E.K. Dufour; Nano-sized cosmetic formulations or solid nanoparticles in sunscreens: A risk to human health? Arch Toxicol, DOI 10.1007/s00204-012-0831-5
19. Hombitec RM110 Aspect Ratio

20. In Vitro Penetration of Titanium Dioxide (nano form) from a Eusolex® T-EASY Formulation through Pig Dermatomed Skin - Final Report
21. In Vitro Penetration of Titanium Dioxide (nano form) from a Eusolex® T-PRO Formulation through Pig Dermatomed Skin - Final Report
22. In Vitro Penetration of Titanium Dioxide (nano form) from a UV-TITAN M765 Formulation through Pig Dermatomed Skin - Final Report
23. List of new coatings including its physicochemical properties – Comparison to approved coatings - table
24. Merck, 2014; Safety evaluation – Coating Materials for Titanium Dioxide (nano form)
25. Merck, 2008; Eusolex® T-PRO: Safety Evaluation of Manganese
26. Photocatalytic Activity of Titanium Dioxide (nano form) – additional coatings. Measurement of Photocatalytic Activity of additional Coatings
27. R. Graf et al; Titanium Dioxide Coated with Manganese Dioxide: A new radical defense line; IFSCC Melbourne, 2009
28. Sachtleben Chemie GmbH, 2011; Stability test for coating applied to titanium dioxide
29. UV-Titan M765 Lot 945001 Aspect Ratio
30. UV-Titan M765- number DC-Kurve (0803003)
31. UV-Titan M765 weight DC-Kurve (0803003)
32. Web page extract: RÖMPP - HLB-System - Georg Thieme Verlag KG